Contemporary Diabetes
Series Editor: Aristidis Veves

Jane E. B. Reusch
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Aristidis Veves *Editors*

Diabetes and Exercise

From Pathophysiology to Clinical Implementation

Second Edition

Humana Press

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To my wife Maria and son George

– Aristidis Veves

This book is dedicated to the hundreds of millions of people with and at risk for diabetes with appreciation to my family: Jay, Madeline, and Leah.

– Jane E.B. Reusch

This book is dedicated to my husband, Ken, my daughter, Allie and my mother, Dorothy, with love. You and your support mean the world to me!

– Judith G. Regensteiner

To my wife, Cherie, and children, Jordan and Rebecca and their families, for their support and encouragement for this book and for their patience over the years through many other academic journeys. Also, to the memory of my parents, who may have benefited 30 years ago if we knew then what we know now about preventing and treating diabetes and heart disease.

– Kerry J. Stewart

Preface

Diabetes is a major public health problem in the United States and worldwide. An estimated 29.1 million children and adults (1 in 11 people) have diabetes, although only about 21 million have been diagnosed. In addition, the estimated number of persons with prediabetes in the United States was 86 million in 2012. Worldwide there are currently an estimated 415 million people with diabetes and only half are diagnosed. Astronomical growth in the number of people with diabetes is predicted between now and 2040 – when 642 million individuals with diabetes are expected. Cardiovascular disease is the leading cause of death in people with type 1 diabetes and type 2 diabetes.

The pandemic of diabetes, not with standing the role of genetics, is largely preventable with meaningful changes in diet and physical activity. Exercise is recognized by leading authorities including the American Diabetes Association, the European Association for the Study of Diabetes, the American Association for Clinical Endocrinologists, the Endocrine Society, and the International Diabetes Federation and leading primary care groups as a cornerstone of diabetes prevention and treatment, yet still most people with or at risk for type 2 diabetes are not physically active. This is in part a societal issue, involving increased sedentary lifestyle (workplace, school, and home), a built environment that is not conducive to physical activity, and reduced norms for physical fitness plus physiological changes in people with diabetes that decrease exercise tolerance. In particular, women are more sedentary than men across the lifespan beginning with pubertal girls. Diabetes is also more common in people of color and low socioeconomic status among whom there is already a propensity toward lower physical activity. The prevalence of diabetes is higher among persons of Hispanic, African American, and Native American heritage than among persons of non-Hispanic white origins.

One reason people with type 2 diabetes are more sedentary than nondiabetic people is that there are some barriers which may be physiologic as well as socioeconomic. Persons with type 2 and type 1 diabetes have reduced exercise capacity, including lower maximal oxygen consumption and impairments in the submaximal measures of cardiorespiratory exercise performance. These exercise abnormalities appear early on in the course of type 2 diabetes and may be related to cardiac and hemodynamic abnormalities. Importantly, decreased physical fitness and increased sedentary activity correlate with cardiovascular and all-cause morbidity and mortality, which are already increased by diabetes. Implementation of safe and effective exercise programs for all

people with diabetes is essential for increased healthspan and prevention of cardiovascular disease.

The goal of our 2nd edition of *Diabetes and Exercise* is to give the researcher and practitioner in the area of diabetes evidence-based information that is both theoretically and clinically useful. We hope to facilitate further understanding of the importance of physical activity as part of the standard of care for diabetes management and prevention. We have invited experts in diabetes, diabetes prevention, integrative physiology, exercise physiology, and exercise implementation to inform the reader of the current state of the art. In addition, exercise guidelines and precautions are provided to maximize the benefits of activity and to minimize risk with physical activity interventions.

Part I: Epidemiology and Prevention This section sets the stage for the rest of the book. Drs. Ruegsegger and Booth highlight the current "state of fitness" and the implications of loss of fitness on the health of the individual and the population at risk for diabetes. Drs. Cusi and Sanchez-Portillo provide a sobering overview of the impact of obesity and sedentary behavior on fatty liver disease, and Drs. Nazare, Balkau, and Borel review the epidemic and physiology of metabolic syndrome. Prevention of diabetes is discussed by Dr. Perreault. In this section, the magnitude of the problems posed by diabetes are discussed to facilitate a deeper understanding of the compelling rationale for the use of exercise and increased physical activity in persons with and at risk for diabetes.

Part II: Physiological Effects of Exercise in Type 2 Diabetes In this section, the physiological interrelationships between diabetes, exercise capacity, and adaptations to exercise training are provided in seven chapters. We start with a synopsis of the current understanding of exercise performance in youth with diabetes by Drs. Nadeau, Baumgartner, and Gross. This is followed by an overview of the current knowledge on the impact of type 2 diabetes on exercise capacity in adults by Drs. Huebschmann, Reusch, Bauer, Regensteiner, and Schauer. In these two chapters, we provide a concerning picture of subclinical cardiovascular disease and diminished physical fitness even in youth and younger adults with apparently uncomplicated diabetes. Next, Drs. Kalyani, Quartuccio, Hill Golden, and Regensteiner highlight current knowledge on sex differences in diabetes and exercise, focusing on the worse impairments in women than men with diabetes. In order to inform the reader about the specific physiological effects of exercise and diabetes, the next few chapters examine the impact of exercise, in the context of diabetes, on mitochondrial function (Dr. Chow), endothelial function and inflammation (Drs. Roustit, Loader, and Baltzis), adiposity and regional fat distribution (Drs. Stewart and Dobrosielski), and muscle blood flow regulation (McClatchey, Bauer, Regensteiner, Reusch). This section presents a picture of how diabetes affects exercise capacity in women, youth, and adults and the multiple systems impacted by exercise training. We also highlight gaps in our current knowledge as to how diabetes changes exercise capacity and interferes with the adaptive responses to exercise training. This mechanistic information makes it possible to understand the reasons why

physical activity is especially important for people with diabetes. Thus, the concept of *exercise as medicine* has a strong scientific basis for prevention and treatment of diabetes.

Part III: Management and Treatment This section addresses practical issues that are essential in order to safely engage patients with diabetes in exercise-related research protocols and clinical programs. Drs. Barone Gibbs and Jakicic provide lessons learned and guidelines from Diabetes Prevention Program (DPP) and Action for Health in Diabetes (Look AHEAD) studies. Dr. Colberg discusses key concepts and guidelines on how to manage food intake with exercise to avoid low blood glucose and optimize safe, productive, and satisfying exercise programs. Critical behavioral issues that must be addressed to sustain exercise adherence in patients accustomed to sedentary behavior are reviewed by Drs. Bessesen and Bergouignan. This is followed by a chapter by Drs. Marcos Valencia and Florez on exercise, aging, and quality of life. Finally, Dr. Franklin discusses the medical evaluation and assessment that should be undertaken before beginning a program of exercise for persons with diabetes, including the value and limitations of exercise stress testing. Taken together, this section is a practical overview of the impact of exercise on diabetes prevention, treatment, and physical function along with some strategic advice on how to enable people with diabetes to incorporate sustainable and safe exercise practices into their lifestyles.

Part IV: Special Considerations for Exercise in People with Diabetes Throughout the previous sections, we highlight the excess premature mortality and cardiovascular disease common to people with diabetes. Diabetes is commonly associated with comorbid conditions that may interfere with exercise as reviewed by Drs. Mar, Herzlinger, Botein, and Hamdy. Drs. Schauer, Huebschmann, and Regensteiner present further detail on the interplay between exercise and macrovascular disease. New data on strategies to safely enable exercise and prevent hypoglycemia in people with type 1 diabetes are provided by Drs. Roberts, Forlenza, Maahs, and Taplin. Drs. Najafi, Patel, and Armstrong provide a pragmatic overview on how to facilitate safe exercise and optimal healing for individuals with diabetes-related lower extremity disease. Cardiac rehabilitation, absolutely critical for optimal outcomes in the contest of diabetes-related cardiovascular disease, is discussed by Drs. Squires and Stewart. Our closing chapter highlights the issue of peripheral artery disease in people with diabetes and exercise recommendations by Drs. Mays, Whipple, and Treat-Jacobson. The theme of this section is that there are real barriers to exercise in people with diabetes. These experts provide compelling, evidence-based data showing that people with diabetes and comorbid conditions will benefit from physical activity, and they review strategies to safely exercise with comorbidities to improve outcomes and quality of life.

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Part I

Epidemiology and Prevention

1 State of Fitness: Overview of the Clinical Consequences of Low Cardiorespiratory Fitness

Gregory N. Ruegsegger and Frank W. Booth

Less than one percentage (0.93%, or 1.58 million) of the 1958 US population was diagnosed with diabetes [1]. This was nearly six decades ago. Amazingly diabetes rates in the United States tripled from 1958 to 1991 [2.90% (or 7.21 million cases)] (Fig. 1.1). Nearly all of the three-decade increase was from non-insulin-dependent diabetes mellitus (NIDDM) [now called type 2 diabetes (T2D)], not in the juvenile form [now termed type 1 diabetes (T1D)]. In our opinion, the increase in T2D from 1958 to 1991 was relatively unnoticed. Since T2D is a noncommunicable chronic disease, we speculate that the increase of 5.63 million cases of diabetes over a three-decade period was less publicized than if 5 million people became infected with influenza, a communicable disease, in 1 week.

It wasn't until the mid-1990s that two landmark events began to garner limited attention to the T2D epidemic. First, over the roughly three-decade span from 1958 to 1991, the increase in diabetes prevalence linearly increased about 1% per decade, such that by 1991 it had tripled in percentage (Fig. 1.1). From the year 1991 onward, the diagnosed percentage of diabetes was 2.90%, 2.93%, 3.06%, 2.98%, 3.30%, and 2.89% for the years of 1991, 1992, 1993, 1994, 1995, and 1996, respectively. Then after 1996, an upward infliction in the percentage gain of diagnosed diabetes occurred. Data will next be presented as percentage gain, rather than as absolute percentage of total diabetes cases, in a given time period. Whereas a 1% gain per 10 years in total US population occurred in total diabetes cases from 1958 to 1991, the percentage rate doubled during the next 15 years. After 1996 a 1% gain in diabetes prevalence occurred approximately every fifth year. Starting from the end of 1996 to the end of 2001, the percentage of diagnosed diabetes in 5-year periods increased 1.86% from 1997 to 2001 (4.75–2.89%), rose 1.15% from 2002 to 2006 (5.90–4.75%), and rose 0.88% from 2007 to 2011(6.78–5.90%). To summarize, the percentage of the population diagnosed with diabetes drastically increased after 1996, compared to half the rate of percentage increases seen in the previous nearly four decades. This inflection in diabetes prevalence is shown in Fig. 1.1.

The second landmark began in the 1990s. T2D became a pediatric disease [2]. Historically, almost all youth diabetes was type 1 diabetes

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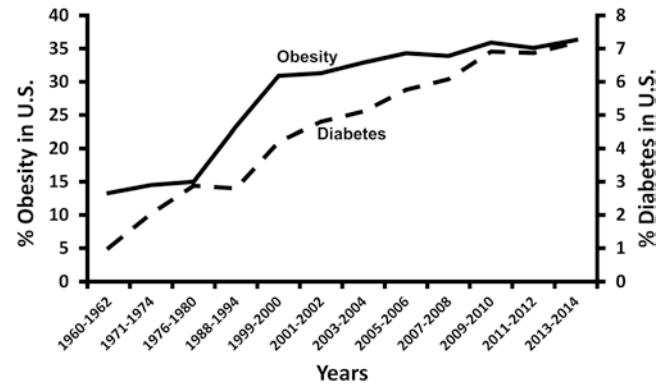

Fig. 1.1 Percentage of the US population with obesity or diagnosed with diabetes over the past ~50 years. Obesity data redrawn from [80] and diabetes data from the CDC [1]. Interestingly, diabetes' prevalence has an association that shows a slight lag in chronology with obesity's prevalence

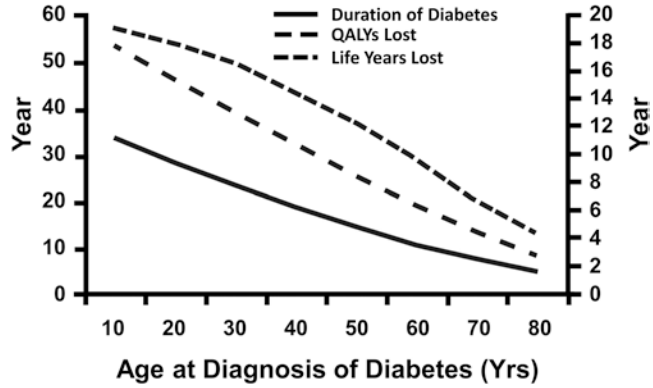

Fig. 1.2 Estimates of life-years lost and quality-adjusted life-years (QALYs) lost for a given age of diabetes diagnosis in women. Data are drawn from tabular data from Narayan et al. [81]. For example, for women diagnosed with diabetes at age 40, they will lose 14.3 life-years and 22.0 QALYs [81]. The "Year" axis on the left is for both "Duration of Diabetes" and "QALYs Lost," while the "Year" axis on the right is for "Life Years Lost"

(T1D). In the 1990s, prevalence of T2D was <3% of all new cases of adolescents [3]. However 15 years later, 45% of youth cases were T2D [3]. Taken together, it is reasonable to conclude that doubling in the rate of the rise in US diabetes occurring at the inflection year of 1996 was associated with T2D dropping into the age range formerly reserved to T1D prior to the turn of the century. The clinical consequences of T2D in children and adolescents are shown in Fig. 1.2.

The younger the age when T2D begins also increases lifetime medical spending. Diabetes diagnosed at the ages of 40, 50, 60, and 65 years is associated with excess-lifetime, discounted medical spending of $124,600 ($211,400 if not discounted), $91,200 ($135,600), $53,800 ($70,200), and $35,900 ($43,900), respectively [4].

Low Cardiorespiratory Fitness (CRF) Is Associated with Increased T2D

Importantly, T2D is highly associated with low cardiorespiratory fitness (CRF) [5], as mentioned for the next two studies. (1) In men with T2D, all-cause mortality was 2.1 × greater in the low-CRF group than in the fit group. Each MET decrease in CRF was associated with a 25% lower all-cause mortality risk [6]. (2) Compared with patients achieving ≥12 METs, patients achieving <6 METs had a 2.2 × higher risk of diabetes [7]. Furthermore, every 1 MET decrease was associated with an 8% higher diabetes risk. Low CRF is known to be a critical prognostic factor in patients with T2D and cardiovascular disease (CVD), and T2D is a comorbidity of CVD [5]. CRF independently predicts

mortality better than any other established CVD risk factor [8]. Hence, understanding the biological basis by which low CRF and physical inactivity contribute to T2D and other chronic diseases, many of which are inextricably lifestyle-dependent, is paramount to fighting our current T2D and obesity epidemic. In this chapter, we describe the importance of CRF as a prognostic marker of health and the clinical consequences associated with low CRF.

CRF: The Ultimate Morbidity and Mortality Risk Factor

Arguably, there is no outcome measure more important for health than cardiorespiratory fitness (CRF) [9]. CRF, which is commonly referred to as maximal aerobic capacity or VO_{2max}, has been defined by Warburton et al. [10] as, "a physiological state of well-being that allows one to meet the demands of daily living or that provides the basis for sports performance, or both." From the time living creatures began roaming the Earth and required oxygen for multicellular organisms, the ability to use oxygen has been critical for organismal survival [11]. The ability to integrate multiple physiological systems and efficiently deliver oxygen from the atmosphere to working skeletal muscle and other organs has been paramount for survival. Additionally, low CRF is well established as an independent risk factor of CVD morbidity [12] and mortality [13, 14]. To state it plainly, "no oxygen delivery/extraction: no life." While conventional risk factors, such as blood lipid panels, are regularly performed in disease screenings, due to the difficulties associated with directly measuring CRF, as well as the need for specialized exercise testing equipment, CRF's use as a clinical biomarker of cardiovascular, as well as other chronic, diseases is often underutilized [15]. Further, the lack of a standardized classification system used to classify CRF (such as for BMI and blood lipids for metabolic risk) has led to variation and discrepancies as to what constitutes "low" CRF.

In findings from Aerobic Center Longitudinal Study (ACLS) on CRF and mortality published in 1989, Blair et al. [9] categorized CRF for treadmill time to exhaustion during a maximal exercise test. In doing so, the authors defined low CRF as the lowest 20% of treadmill times in the standardized test. Strikingly, when adjusting CRF for sex, age, smoking, systolic blood pressure, fasting blood glucose level, and family history of coronary heart disease, greatest all-cause mortality rates were among individuals classified as having low CRF. Mortality rates declined across physical fitness quartiles from low to high CRF. Other absolute cutoffs to define low CRF using METs (1 MET = 3.5 ml O_2; fold-increase from resting metabolic rate) have defined low CRF as below 4 [16], 5 [8], and 6 [17] METs, respectively. Further, when the MET values in the previous sentence are expressed as percentiles of their respective populations, their respective cutoffs represent approximately the lower 20% [8] and 40% [16, 17] of CRF levels. However, it is worth noting that regardless of the classification system used, lower CRF is consistently associated with higher risk of mortality. Additionally, meta-analysis data compiled by Kodama et al. [12] shows that each 1 MET incremental increases in CRF (~1 km/h greater running/jogging speed) is associated with 13% and 15% decreased risk for all-cause mortality and CVD events, respectively. The authors also explain that a 1 MET increase in CRF is comparable to 7-cm, 5-mmHg, 1-mmol/L (88 mg/dL), and 1-mmol/L (18 mg/dL) reduction in waist circumference, systolic blood pressure, triglyceride level (in men), and fasting plasma glucose, respectively, in other studies.

As mentioned, direct measurements of CRF are often not feasible in most clinical examinations. However heart rate or exercise time to exhaustion in various exercise tests may be used as surrogates to estimate CRF. Submaximal exercise tests are less difficult and more convenient in terms of time, effort, cost, and patient fitness level yet still provide adequate estimates of CRF. Findings by Noonan and Dean [18] indicate that submaximal testing appears to have high correlation between maximal and submaximal testing (r = 0.7–0.9) in various tests, such as submaximal treadmill and cycle ergometer tests,

1-mile walk test, and 12-min run test. Many other reports have also recommended that CRF assessment be included in clinical settings for morbidity and mortality prevention [8, 12, 19, 20]. Thus, implementing CRF measurements, as a risk factor, is paramount in aiding in the detection of individuals at risk for developing chronic diseases and early death.

Determinants of CRF

Given the heavy involvement of neural, respiratory, cardiovascular, and skeletal muscle systems, CRF is a surrogate measure of an *integrative systemic function*. Many modifiable and non-modifiable factors influence CRF. As listed by Lee et al. [15], non-modifiable factors of CRF include genetic factors, age, and sex, while modifiable factors include some medical conditions, smoking, obesity, and physical activity. The seminal work of Bouchard and colleagues on more than 700 men and women in the HERITAGE Family Study provides perhaps the most well-known findings on the influences of human genetics on CRF [21–23]. In healthy, sedentary subjects, 20 weeks of exercise training improved CRF on average 15–18% in both sexes and generations (mothers, fathers, daughters, and sons). However, the variation in CRF response to exercise training was 2.5-fold greater between families than within families. From this observation, it was estimated that, at its maximum, the heritable component to CRF response to exercise training is 47%. Findings from the HERITAGE Family Study also concluded the maximal heritability of CRF as 51%, further suggesting that genetic factors can greatly influence CRF, as well as physical activity levels.

To further understand the genetic basis, Britton and Koch [24] employed selective breeding experiments in rats based upon a single, volitional/behavioral forced-running test until they do not wish to further run, providing experimental evidence that natural selection of genes for high aerobic capacity by distance of run-time to exhaustion is a feasible concept. The selection criteria of selecting rats based on longest or shortest running distances during a single exercise test resulted in selection of a 58% greater CRF in the high-distance line compared to the short-distance line over 11 generations. Further, rats with high CRF had healthier cardiovascular systems (12% lower mean 24-h blood pressures and 48% better acetylcholine-induced vasorelaxation) and healthier metabolic risk factors (16% less fasting plasma glucose, 39% less visceral adipose tissue, 63% lower plasma triglyceride levels, and increased mitochondrial protein concentrations). Together, with findings from the HERTIAGE Family Study, the rat selective breeding data provides strong evidence of a genetic role in determining CRF that is correlated with better health outcomes.

Likewise, aging has profound influences on CRF. Data from longitudinal studies [25, 26] suggests that after reaching its maximal value prior to 20–30 years of age, CRF begins to decline with increasing age in healthy populations. The rate of decline is dramatically accelerated at advanced age. Authors of these studies also conclude the pattern of CRF decline with age is accelerated by physical inactivity or weight gain. Given the severe clinical consequences associated with low CRF, as we will continue to discuss, future efforts should be made to find the "molecule triggers" causing the age-related decline in CRF to potentially delay and/or prevent multiple chronic diseases associated with low CRF that is associated with T2D.

Physical Activity and Inactivity Are Primary Determinants of CRF

As mentioned above, physical activity is a modifiable, lifestyle factor associated with CRF [15]. Notably, among modifiable factors, the American College of Sports Medicine suggests physical activity may be one of the principle determinants of CRF [27]. Controlled, clinical trials show a positive dose-dependent relationship between increases in physical activity and increases in CRF [28, 29]. The authors of these studies also infer that increases in either intensity or volume of physical activity (caloric expenditure) have additive effects on CRF after controlling for one and other. Importantly,

these improvements in CRF were observed with low-volume, moderate-intensity exercise. The inverse effects of physical inactivity on CRF have been well documented, as highlighted next.

Perhaps the most eloquently noted example of the effects of physical inactivity on CRF is the 1966 Dallas Bedrest and Training Study and its subsequent 30- and 40-year follow-up studies [30–33]. In 1966, Saltin et al. [33] took five 20-year-old men and carried out comprehensive physiological evaluations assessing the cardiovascular systems ability to respond to 20 days of bed rest, followed by 8 weeks of heavy endurance training. In doing so, the authors demonstrated that 20 days of bedrest significantly decreased CRF. While this finding alone may not seem remarkable, the magnitude of the drop in VO_{2max} (28% drop), total heart volume (11% drop), maximal stroke volume (29% drop), and maximal cardiac output (26% drop) proved the rapidness of the severity with which near complete physical inactivity compromises the cardiorespiratory system. Equally remarkable, the subjects then underwent supervised endurance training and showed that all of the aforementioned CRF parameters were recovered following 8 weeks of training. Furthermore, the results of 20 days of bedrest on CRF were later compared 30 and 40 years of free-living in the same five subjects. In these follow-up studies, it was remarkably determined that 3 weeks of bedrests resulted in a greater decline in CRF than did 30 years of free living from ages 20 to 50 years old in the same subjects [31]. It was not until monitoring the same subjects 40 years after the initial study did the authors observe a comparable decline in CRF from the 1966 baseline value when compared to 3 weeks of strict bedrest (27% vs 26% reduction, respectively, which included one subject who had a major decrease in CRF due to disease). The aforementioned are truly remarkable findings and confirm the detrimental influences physical inactivity can have on CRF. Remarkably, another study [34] shows that a physically inactive lifestyle from 40 to 80 years of age speeds the aging of CRF by four decades (Fig. 1.3).

Also of importance is to identify which genes fix a decline in CRF beginning as early as adolescence.

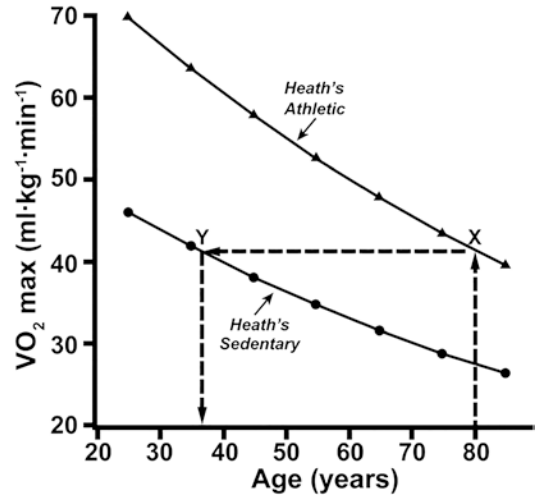

Fig. 1.3 CRF, as determined by maximal oxygen uptake, declines as a function of age when measurements are first made in the third decade of life. At any age, with continued activity (Heath's Athletic line), CRF is greater by ~20 ml/kg/min. Remarkably, at the age of 80, CRF of the athletic line is equivalent to that of the sedentary line at ~age 40 (Redrawn with permission from Heath [34])

Clinical Implications Associated with Low CRF

As stated above, CRF is a useful, if not objective, prognostic and diagnostic of health outcomes in clinical settings. The 1996 US Surgeon General's Report [35] concluded that high CRF decreases the risk of CVD mortality and is associated with "positive health" while low CRF is associated with "negative health." Maintaining the highest possible CRF is a primary preventer of morbidity and mortality from CRF (discussed later). Not only is CRF an independent predictor of mortality but CRF has important clinical implications with relevance to T2D and CVD, as well as hypertension, metabolic syndrome, obesity, and cancer. Indeed, physical inactivity is upstream of both CRF and chronic diseases, lowering the prior and increasing the latter. In this section of the chapter, we will break down unique attributes of several highly prevalent diseases and conditions and the how these conditions associate with CRF.

Low CRF, Physical Inactivity, and Glucose Control

One mechanism leading to decreased risk of T2D following increases in CRF and habitual physical activity is the maintenance of normal glucose levels [36]. It is well established that both low CRF and obesity have been shown to associate with elevated fasting glucose levels [37]. Interestingly, low CRF may potentiate age-related increases in fasting glucose. In a study of 10,092 healthy men, low CRF, as measured by maximal treadmill testing, was associated with greater age-related increases in fasting glucose (0.25 mg/dl per year) as compared to average-CRF (0.15 mg/dl per year) and to high-CRF (0.13 mg/dl per year) individuals [38]. Sui et al. [38] state that aging-related increases in fasting glucose were halved in high-fitness compared to low-fitness subjects. These results suggest like many other maladies associated with aging, improvements in CRF can delay the onset of age-related impairments in fasting glucose.

Step-reduction studies also highlight the strong association between CRF, physical activity/inactivity, and glucose control and insulin sensitivity. When ten healthy young men reduced their daily mean physical activity level from 10,501 steps to 1344 steps for 2 weeks, declines in (1) VO_{2max} of 7%, (2) peripheral insulin sensitivity, and (3) decreased insulin-stimulated ratio of pAktthr308/total Akt, in part, led to a 17% reduction in the glucose infusion rate during a hyperinsulinemic-euglycemic clamp following step reduction [39]. Similarly, lean muscle was reduced, and visceral adipose tissue increased after step reduction. Importantly the 7% decline in CRF in the 2-week period demonstrates the strong association between CRF and diabetes risk factors. The above functional decrements in metabolism help explain a part of the link between the risks associated with the progression of chronic disorders and premature mortality with reduced physical activity [39] and highlight the benefits of using physical activity prescriptions to help maintain functional capacities.

Low CRF Outcomes on T2D and Metabolic Syndrome

Metabolic syndrome is commonly a precursor to T2D, if not appropriately treated. Metabolic syndrome is described by the presence of hyperinsulinemia, impaired fasting glycemia, and at least two of the following: adiposity (waist-to-hip ratio >0.90 or BMI >30 mg/m^2), dyslipidemia (triglyceride level >1.70 mmol/l or HDL level <0.9 mmol/l), and hypertension (blood pressure >140/90 mmHg or current use of antihypertensive medication) [40].

In recent decades, the global prevalence of T2D and glucose intolerance has skyrocketed to where, in 2014, ~29 million Americans had T2D, and 86 million were estimated to be a high risk for developing T2D, which totals about one-third of the US population [1]. Physical inactivity is one factor linked with the high occurrence of T2D and glucose intolerance [41]. Several reports have described CRF as an objective marker of the relationship between habitual physical activity and T2D [37, 42, 43]. The 15-year longitudinal Coronary Artery Risk Development in Young Adults (CARDIA) study concluded that a person's risk for developing metabolic syndrome, or T2D, was inversely associated with his or her CRF, when measured with a maximal treadmill test [42]. In the report, the authors concluded that risk of developing T2D, metabolic syndrome, and hypertension was three- to sixfold greater for individuals with low (less than 20th percentile) compared to high (greater than 60th percentile) CRF after adjusting for covariates. Equally striking is the age range, 18–30 years of age, within which the study was completed, suggesting poor CRF is associated with metabolic disorders and diabetes at relatively young ages. However, the same report also concluded that improvements in CRF over 7 years, in a subset of subjects, significantly reduced the risk of developing T2D and metabolic syndrome. Importantly, the improvement in CRF provides evidence for health improvement with increased CRF in people 18–30 years of age.

Laaksonen et al. [44] examined the relationship between leisure-time physical activity (LTPA), CRF, and the risk of metabolic syndrome. When classifying the 1038 male subjects into low and high CRF categories, the authors showed that, even when adjusting for major confounders, men with low CRF and who engaged in low levels of LTPA were sevenfold more likely to develop the metabolic syndrome compared to men with high CRF and who engaged in vigorous LTPA. Further, these findings suggest that men complying with the CDC-ACSM recommendations (>3 h/week of structured or lifestyle physical activity of >4.5 METs) decrease their risk of developing the metabolic syndrome. Taken together, the three- to sevenfold better risk-factor profiles for T2D with high CRF imply emphasizing avoidance of low CRF.

Findings from animal studies also display similar trends and suggest that low CRF is not only associated with but may independently lead to metabolic diseases and T2D. The selective breeding for the phenotype of low run-times in a forced run-time on a motor-drive treadmill by Britton and Koch [24], as described above, co-selected low-running-capacity rats for the inherent phenotypes of (1) low aerobic capacity; (2) increased fasting plasma glucose and insulin; (3) decreased insulin-stimulated glucose transport, glucose oxidation, intramuscular glycogen, and complete and partial lipid oxidation; and (4) less skeletal muscle fatty acid transporter CD36 [45, 46]. Importantly, many of the above measurements were improved with exercise training by the low-capacity rats, highlighting the plasticity of these systems to physical activity, even when CRF was artificially reduced by selective breeding [45]. Together with findings in humans, these data provide an indispensable link between low CRF and increased prevalence of diabetes and metabolic disorders. Furthermore, the preclinical data highlight the *power of physical activity to prevent, or reverse, these negative clinical consequences*.

Low CRF Is Predictive of CVD

Low CRF is associated with increased T2D [37, 38, 42, 47]. T2D is associated with a higher rate of complications related to CVD [48]. Physical inactivity and low CRF confer an attributable risk for death due to coronary heart disease that is similar to that of other major modifiable risk factors [49]. Similarly, CRF is a stronger predictor of risk for increased CVD events as compared with self-reported physical activity levels [50, 51], and a single measurement of low CRF in midlife is strongly associated with increased CVD risk and mortality decades later [14, 50]. Taken together, the likely major comorbidity of T2D is CVD. Low CRF is associated with increased T2D further endorsing the need for clinical screening for CRF.

Using data from the Cooper Center Longitudinal Study (CCLS), Gupta et al. [14] assessed the influence of low CRF of CVD risk when added to traditional risk factors. After modeling to estimate the risk of CVD mortality with a traditional risk factor model (age, sex, systolic blood pressure, diabetes, total cholesterol, and smoking) with and without the addition of CRF measurements, the addition of CRF to the traditional risk factor model resulted in reclassification of 10.7% of the men, with net reclassification improvement for both 10-year and 25-year risk of cardiovascular mortality. Similar findings were observed for women for 25-year risk [14].

Improvements in CRF are associated with reductions in heart failure risk in people with and without diabetes [52]. Diabetes patients are at high risk of developing and then dying of heart failure [53]. The protective benefits by which high CRF prevents the development of heart failure may be due to its associations with reduced prevalence of standard cardiovascular risk factors, inhibiting pathological cardiac remodeling, promoting physiological remodeling, and improving cardiac, neurohormonal, skeletal muscle, pulmonary, renal, and vascular performance [52]. Higher levels of CRF in midlife are protective against future risk for non-fatal CVD events, such as myocardial infraction and heart failure hospitalization based on data from the CCLS [54]. Further, every 1 MET increase in CRF achieved in midlife was associated with ~20% decreased risk for heart failure hospitalization after the age of 65 in men [54]. Likewise, a dose-dependent inverse association

between CRF and heart failure risk has been reported in a cohort of middle-aged Finnish men [55]. Taken together, these studies highlight the possible role of low CRF as an important causal risk factor for heart failure.

Similarly, CRF is directly associated with CVD risk factors themselves. Hypertension affects ~20–60% of diabetic patients [56]. The association between hypertension incidence and low CRF was documented from participants in the ACLS, as mentioned previously [57]. A total of 4884 women performed maximal treadmill testing and completed a follow-up health survey. After an average follow-up time of 5 years and 157 incident cases of hypertension, the authors reported that the cumulative incidence rate of hypertension was highest in woman with low CRF and significantly less in woman with moderate and high CRF. These findings suggest that CRF is an independent predictor of incident hypertension in women. A second cohort of individuals from the ACLS was analyzed for associations between CRF and incident hypertension and was published in 2007 and referred to as the HYPGENE study [58]. The study's goal was to address hypotheses regarding the genetic basis of hypertension while taking CRF level into account. From a total of 1234 subjects, 629 developed hypertension, while 605 remained normotensive, during a follow-up period of 8.7 and 10.1 years. The authors present the risk of hypertension across quartiles of CRF using METs as a marker of CFR. Being unfit (METs <11.2 for men, <9.0 for woman) translated into a 2.7-fold greater risk of hypertension compared to the fit (METs <13.8 for men, <11.4 for women) group. The overall conclusion from the above-mentioned studies is that strong associations exist between hypertension and low CRF.

Low CRF, Rather Than Obesity, May Drive Disease Risk

Obesity is a common, serious, and costly condition that continues to increase in prevalence in our country and around the world. According to the CDC, more that 78.6 million (34.9%) Americans are obese. Obesity-related conditions include T2D, as well as heart disease, stroke, and certain types of cancer. Potentially more alarming is the economic cost of obesity, costing US $147 billion in 2008. Evidence from large observational studies suggests that CRF attenuates obesity-related health risk [59, 60], and obese persons have ~10–15% lower CRF than non-obese [51]. In a 2004 study of 397 Caucasian men ranging in age from 30 to 76 years of age and in BMI from 21.2 to 34.9, the authors tested the hypothesis that men with a high CRF have a lower waist circumference and less total abdominal, abdominal subcutaneous, and visceral adipose tissue compared to men with low CRF. The authors' primary finding was that for a given BMI, men with high CRF display significantly lower levels of abdominal adipose tissue compared to those with low CRF [61]. Similar findings argue that low CRF, rather than excess body fat, is a partial culprit behind the negative metabolic and cardiovascular consequences associated with obesity, which has been coined the "obesity paradox" [62]. For example, Goel et al. [63], who followed 855 coronary artery disease patients, found low CRF (<21.5 mL O_2 kg^{-1} min^{-1} for men and <16.8 mL O_2 kg^{-1} min^{-1} women) was associated with a ~ threefold increase in mortality, even after adjusting for BMI and waist-to-hip ratio. However after stratifying into subgroups, mortality risk for patients with high CRF in the subgroups of overweight and obese did not differ from the normal-weight reference subgroup. Other similar findings have also been reported [64, 65]. Likewise, several findings suggest overweight and obese patients with high CRF have lower mortality compared to their normal-weight patients [8, 66], further highlighting the important clinical features associated with high CRF.

Low CRF Increases Multiple Risk Factors for Increased Mortality

As mentioned repeatedly throughout this chapter, physical inactivity lowers CRF. CRF is a strong independent predictor of mortality, independent of other established CVD risk factors [8]. Thus, understanding the independent effect of CRF on mortality may lead to benefits for those who are obese or at increased risk for complications

associated with low CRF such as T2D, leading to early death. Myers et al. [8] followed 6213 male subjects classified by normal or abnormal exercise-test performance and history of having, or not having, CVD. Remarkably, low CRF was a stronger predictor of death than all established risk factors or clinical variables, such as hypertension, smoking, and diabetes, as well as other exercise-test variables, including the peak heart rate, ST-segment depression, or the development of arrhythmias during exercise in both healthy subjects and those with CVD. Specifically, subjects 60 years of age and older with low CRF had notably higher mortality risk from all causes than those with high CRF [67]. Further, Myers et al. [8] determined that each 1-MET increase in exercise-test performance conferred a 12% improvement in survival and ultimately concluded that "VO_{2max} is a more powerful predictor of mortality among men than other established risk factors for CVD." One relationship between CRF and mortality risk is shown in Fig. 1.4. The important public health message is that maintaining CRF >10 METs for as long as possible can lengthen your health span and life span.

Several biological mechanisms may account for inverse relationship between CRF and CVD plus all-cause mortality, these will be briefly explained here [see the following reviews for additional detail: [15, 49, 68]]. CRF may play an important role with concern for insulin resistance and sensitivity. In a cross-sectional study on 369 subjects, lower CRF was correlated with impaired insulin sensitivity when assessed by homeostasis model assessment of insulin resistance (HOMA-IR) [69]. However, whether the influence of CRF on insulin sensitivity is independent from, or at least partially a reflection of, adiposity remains unclear [69]. Low CRF is associated with unhealthier blood lipid and lipoprotein profiles, body composition, inflammation, blood pressure, and autonomic nervous system functioning; each of which is a risk factor for greater mortality [70]. In healthy, nondiabetic men, low CRF was associated with increased triglyceride, apolipoprotein B (a strong predictor of coronary heart disease), and total cholesterol-HDL cholesterol ratio, after adjusting for BMI [71]. Similar findings of increased plasma saturated fatty acids associate with low CRF [72]. Higher CRF also appears to be an important predictor of future lower rates of weight gain, adiposity, and obesity [73]. Similarly, studies have shown

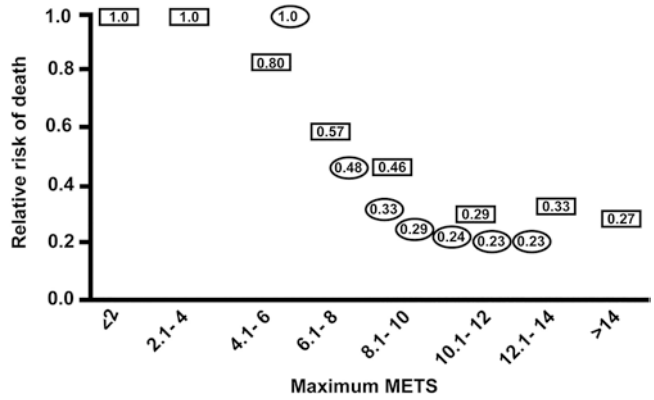

Fig. 1.4 Relative risk of death is a function of estimated maximal METs. Data is replotted from two separate publications. For the first publication from Fig. 41.4 of Blair et al. [9], male and female data are replotted for METs ≥6 (shown within ovals), and data is rescaled for relative death risk relative maximal MET values. Data from the second study of Kokkinos and Myers [82] is replotted in maximal METs ranging from <2 to >14 (shown in rectangles). In a note of importance, the dose-response relationship only occurs between METs of 4 and 9–10, with a lack of dose-response for METs <4 and >9–10. Interestingly, both studies have an overlap of data between 6 and 14 METs. One suggested lifetime strategy to minimize risk of death is to maintain the highest possible maximum METs at each life stage (Redrawn with permission from Heath [34])

an inverse association between low CRF, the CVD predictor C-reactive protein that is higher even after corrections for BMI, and other CVD risk factors, suggesting that low CRF may increase disease risk via increases in inflammation regardless of body composition [74–76]. High mortality is associated with low CRF and also with (1) high oxidative stress or (2) low antioxidative enzyme levels [77]. However, many of these data are from cross-sectional studies, and thus prospective studies, as well as randomized controlled trials, are needed to show the relative contributions of CRF for each factor. Nonetheless, these studies highlight the detrimental, far-reaching comorbidities associated with low CRF and stress the importance of preserving, or increasing, CRF throughout the life course. Finally, it must be mentioned that only ~40–60% of impact of CRF on the relative risk of CVD and coronary heart disease can be explained by impact on traditional risk factors [78, 79].

Concluding Remarks

T2D and other chronic diseases are stealth pandemics affecting millions of people with a great economic cost. Remarkably, nine out of ten cases of T2D can be prevented by lifestyle modification, such as decreasing time spent being physically inactive. Physical inactivity is associated with low CFR, which in turn is associated with the pandemic of T2D, as well as mortality, regardless of age, body composition, smoking, and other risk factors. Despite its powerful predictive and diagnostic power, CRF measurement is often underutilized in clinical settings. If we hope to curb our current T2D pandemic, strategies to minimize physical inactivity and increase or maintain high CRF must be implemented to prevent or to delay the onset of T2D.

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Prevention of Type 2 Diabetes

2

Leigh Perreault

Introduction

As the human and economic cost of type 2 diabetes has surged, focus on its prevention has intensified. Clinical trials across the globe have demonstrated that diabetes can be prevented in high-risk populations over a wide range of cultures and ethnicities [1–12]. Further, reduction in diabetes onset is observed beyond the time of the interventions, albeit attenuated [13, 14]. Waning benefit post-intervention has been attributed to lack of long-term adherence to lifestyle changes or drug therapy. An alternate explanation, however, may be that lack of progression to diabetes rather than the restoration of normoglycemia has been our goal. All of the landmark trials for diabetes prevention to date have enrolled participants with untreated prediabetes due to their exceptionally high risk for acquiring diabetes [1–12]. Even when overt diabetes is delayed or prevented, both micro- and macrovascular diseases appear more prevalent in those with prediabetes compared to their normoglycemic peers [15–18]. Thus, there is reason to believe that true prevention of diabetes and its complications likely reside in the reversal of prediabetes and the restoration of normoglycemia. New evidence supports this speculation [19] and guidelines are changing accordingly [20]. Nevertheless, there is much to be considered in identifying the people at highest risk for diabetes and determining when and how to institute preventive measures.

Through the combination of known and emerging risk factors, the worldwide burden of type 2 diabetes continues to rise. National statistics estimate roughly 29 million Americans – 9.3% of the population – currently have diabetes, reflecting an approximate tripling in the prevalence over the past 25 years [21]. Even more staggering are the 415 million people around the world with diabetes – a number that is expected to increase by more than 50% by 2040 [22]. And although these numbers include all diabetes, >90% have type 2. Fortunately, a number of clinical trials have demonstrated that early intervention can prevent or delay type 2 diabetes [1–12] and newer evidence has shown that prevention of diabetes can also prevent microvascular complications [13].

Diabetes Prevention: Clinical Trials

A broad array of approaches has been employed in prospective, randomized clinical trials for the prevention of diabetes. These have included a variety of glucose-lowering medications, weight

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loss medications, and intensive lifestyle modification. Collective results demonstrate that diabetes incidence can be reduced by 20–80% over 2.4–6 years in a wide range of ethnic groups. Non-randomized prospective and cross-sectional data allude to even higher rates of diabetes prevention using bariatric surgery.

Clinical Trials Using Glucose-Lowering Medication

Glucose-lowering therapy has been repeatedly shown to decrease/delay the onset of diabetes in high-risk populations. Metformin has demonstrated comparable efficacy for prevention in both the USA (−31% risk reduction with metformin 850 mg twice daily) and Indian (−26% with metformin 250 mg twice daily) Diabetes Prevention Programs (DPP) despite considerable disparity in the dosing [6, 9]. Low-dose metformin (500 mg twice daily) in combination with low-dose rosiglitazone (2 mg once daily) also proved an effective strategy in the CANOE study (−27%) [12] but paled in comparison to the robust reductions in diabetes onset seen with the full-strength thiazolidinediones (TZDs) observed in the US DPP (−75% with troglitazone 400 mg once daily), DREAM (−60% with rosiglitazone 8 mg once daily), and ACT NOW (−72% with pioglitazone 45 mg once daily) [2, 5, 23]. Similar results were generated using rosiglitazone in women at high risk due their history of gestational diabetes in the TRIPOD study (−55%) [24]. Nevertheless, safety concerns have dampened enthusiasm for widespread dissemination. Acarbose also diminished diabetes incidence in the STOP NIDDM trial (−25%) despite participants only tolerating approximately two-thirds of the prescribed dose (192 vs. 300 mg daily) [1]. Tolerance of both metformin and acarbose was far higher, as was the reduction in diabetes incidence (−77% and 88%, respectively), in the non-randomized Chinese DPP [25]. Lastly, basal insulin lowered diabetes onset in the ORIGIN study (−20%) albeit with a threefold increase in hypoglycemia [4]. Only the NAVIGATOR study (nateglinide 60 mg three times daily) failed to mitigate diabetes risk using glucose-lowering medication, and, in this case, diabetes risk actually increased (2.1%) [26]. Altogether, there is clear evidence that a number of glucose-lowering medications with distinct mechanisms of action can safely and effectively prevent diabetes (Fig. 2.1). Nevertheless, no prescription glucose-lowering medication to date has been approved by the Food and Drug Administration (FDA) for this indication.

Clinical Trials Using Weight Loss Medication

As glucose-lowering medications were proving their value in diabetes prevention, orlistat became the first prescription medication to show the same by virtue of its ability to induce weight loss [10]. Participants randomized to orlistat (120 mg three times daily) in the XENDOS trial demonstrated a 37% decline in diabetes incidence – an effect size commensurate with what was observed with acarbose, insulin, or metformin in their respective clinical trials (Fig. 2.1). Since this time, the reinvigorated pipeline of anti-obesity medications has performed key post hoc analyses of their pivotal trials showing the utility of these new medications not only for weight loss but for the prevention of diabetes. Pooled data from the lorcaserin (20 mg once daily) trials BLOSSOM and BLOOM boasted a 62% reduction in development of diabetes [27], whereas the combination of low-dose topiramate (92 mg once daily) with low-dose phentermine (15 mg once daily) revealed an even more impressive 79% reduction in the SEQUEL study [28]. Most recently, prospective results from the SCALE study program were released, highlighting an 80% lower rate of diabetes over 3 years in participants with prediabetes randomized to high-dose liraglutide (3 mg once daily) [29]. Not only do these emerging data rival the efficacy of the TZDs for diabetes prevention (Fig. 2.2), but they do so with the pleiotropic benefits of weight loss.

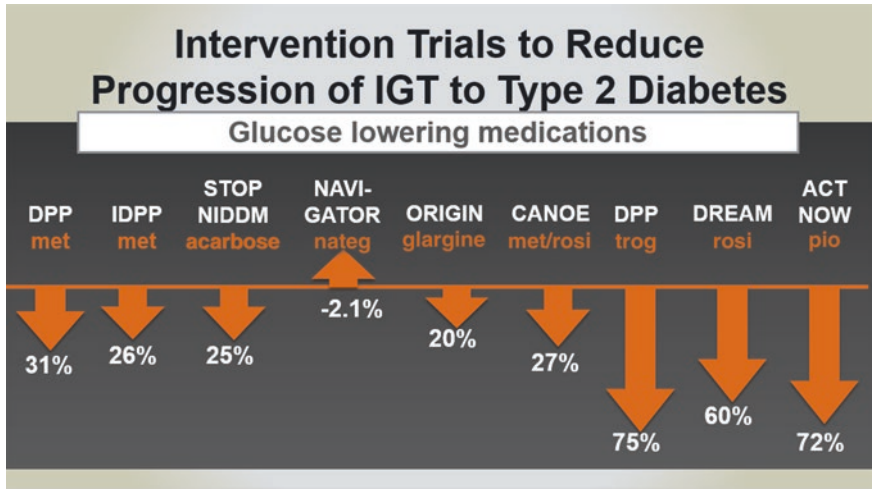

Fig. 2.1 Intervention trials to reduce progression from IGT to diabetes using glucose-lowering medication [1, 2, 4–6, 9, 12, 24, 26]

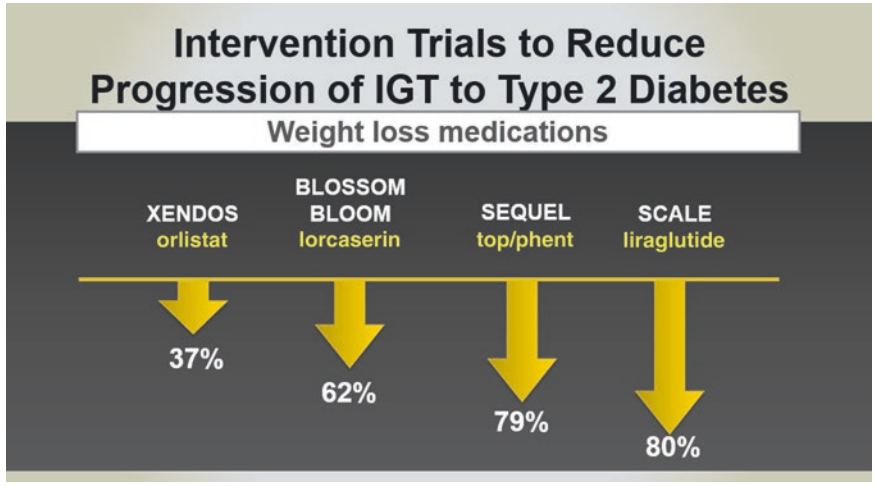

Fig. 2.2 Intervention trials to reduce progression from IGT to diabetes using weight loss medication [10, 27–29]

Evidence with Bariatric Surgery

Extrapolating diabetes prevention observed with anti-obesity medication (5–10% mean weight loss) to bariatric surgery (15–50% mean weight loss), one may imagine total obliteration of diabetes risk. And although no randomized controlled trials have specifically tested this hypothesis, increasing evidence supports this speculation. Both gastric bypass [30, 31] and laparoscopic banding [32] have revealed a consistent 30-fold reduction in diabetes onset during the postsurgical follow-up. The number needed to treat (NNT) in the Swedish Obesity Study (SOS) was only 1.3 people with prediabetes to prevent one case of diabetes over 10 years [30]. Further, a recent meta-analysis compared multiple intervention strategies for diabetes prevention, highlighting the 84% risk reduction with bariatric surgery, suggesting that this may be the most effective single approach to long-term diabetes prevention [33].

Clinical Trials Employing Intensive Lifestyle Modification

Intensive lifestyle modification has been employed in Sweden, China, Finland, the USA, India, and Japan for the prevention of diabetes (Fig. 2.3) [3, 6–9, 11]. Lifestyle interventions, for the most part, have utilized a low-fat (<30% calories from fat, <10% from saturated fat) hypocaloric diet and moderate intensity exercise ~150 min per week for the purpose of 5–7% weight reduction. Interestingly, even where weight loss was not significantly achieved, diabetes incidence was still reduced. This has been largely observed in Asia where starting body mass indices were much lower than in the west [7–9, 25]. Positive results from the Asian studies implicate physical activity and dietary changes, specifically, as responsible for the reduction in diabetes risk. In contrast, the US DPP attributed the entire success of the intensive lifestyle modification group to weight loss with every 1 kg loss translating into a 16% lower risk for diabetes [34]. The Finnish DPP conducted a useful analysis to individually assess the beneficial impact of weight loss, dietary changes, and increased physical activity on the outcome. This analysis revealed an increasing reduction in diabetes for the increasing numbers of goals achieved [11]. The particular goals included >5% weight loss, dietary fat <30% daily calories, dietary saturated fat <10% daily calories, dietary fiber intake ≥15 g/1000 kcal, and/or moderate exercise ≥30 min/day. Although weight loss appeared the most potent protective factor, the participants derived benefit from meeting each of the individual goals [35]. Importantly, the US and Finnish studies continue to demonstrate reduction in diabetes incidence well beyond the duration of the intensive intervention periods [13, 14]. These latter observations should underscore clinical messaging for patients who may cycle through periods of adherence and nonadherence to a healthy lifestyle.

Durability and Hard Outcomes

Continued observation of clinical trials' participants following the randomized intervention periods has afforded us the ability to determine durability of the interventions and their impact on hard outcomes – most notably micro- and macrovascular disease and mortality. After 20 years of follow-up, participants randomized to the active lifestyle interventions in the Da Qing study maintained a 51% reduction in diabetes incidence compared to the control group [36]. Further, they reported a three-fold lower rate of all-cause mortality, largely attributable to fewer

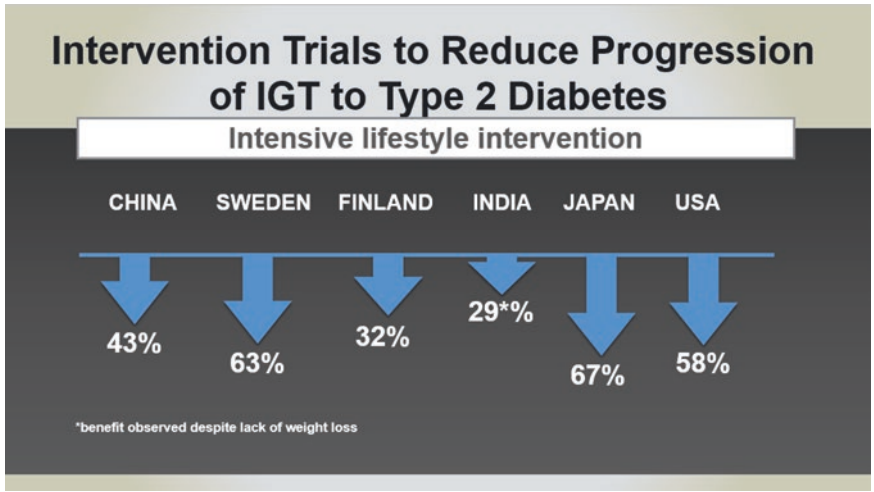

Fig. 2.3 Intervention trials to reduce progression from IGT to diabetes using intensive lifestyle modification [3, 6–9, 11]

cardiovascular and cerebrovascular events, in participants who regressed to normoglycemia compared to those who had progressed from impaired glucose tolerance (IGT) to diabetes in the 23-year follow-up [37]. It should be noted that results remained significant after adjustment for age and traditional cardiovascular risk factors implicating diabetes status, specifically, on the mortality outcome. Both Finnish and US DPPs also continue to follow their participants. The 58% reduction in diabetes onset observed in the active lifestyle participants of the Finnish study has declined to 33% during the 13-year post-intervention observational period [14], but remains highly statistically significant with a high level of residual adherence to the lifestyle curriculum. Similar results were reported from the US DPP where the intervention-mediated reduction in diabetes incidence of 58% and 31% in the lifestyle and metformin groups, respectively, has since declined to 27% and 18%, respectively, over the 15-year observational follow-up [13]. Although no treatment-specific effects on the composite microvascular outcome (retinopathy, nephropathy, and/or neuropathy) have yet to be observed, where diabetes can be prevented, risk of microvascular disease is reduced 28% [13].

Diabetes Prevention: Translation of Clinical Trials to the Real World

Widespread success of clinical trials aimed at diabetes prevention has led to cautious optimism that their recapitulation in a real-world setting is possible. Hence is the charge of the National Diabetes Prevention Program (NDPP). With support from the Centers for Disease Control (CDC), the NDPP provides a free online curriculum for lifestyle coaches and organizations dedicated to lifestyle change programs, as well as training and resources for delivering the curriculum (www.cdc.gov/diabetes/prevention/). The NDPP has been most widely disseminated through the YMCA (http://www.ymca.net/diabetes-prevention/about.html) [38]. The 12-month group-based program consists of 16 1-h, weekly sessions, followed by monthly sessions led by a trained lifestyle coach who facilitates a small group of people with similar goals. Education around healthy eating, increasing physical activity, reducing stress, and problem solving is coupled with strategies to maintain motivation. Success of the YMCA's translation of the NDPP is the subject of great anticipation [38–43].

Much ado has been made about the cost-effectiveness of the DPP lifestyle intervention and whether its translation to the real world would be hindered because of the associated expense. Analyses conducted within the DPP have demonstrated its cost-effectiveness within the confines of a clinical trial [44, 45]. The use of the "community health-care worker" for the translation of the DPP lifestyle intervention has also demonstrated consistent positive results and cost-effectiveness in a variety of non-trial settings [46, 47]. These efforts appear particularly efficacious when delivered in a culturally appropriate manner [48] and are achievable regardless of socioeconomic status [49]. Lastly, there is evidence to support the use of the DPP lifestyle model in routine clinical care. A recent study demonstrated that 7% weight loss was achieved in ~36% of intensively treated patients (vs. 14% in the usual care group) 1 year after a 3-month intervention delivered in a primary care setting [50].

Diabetes Prevention: In Clinical Practice

As we ponder the notion of early intervention to prevent diabetes, strategic allocation of resources to do so is critical. Obesity has long been touted as the number one risk factor for diabetes, and although roughly two-thirds of people with diabetes are overweight or obese, only 2–13% of people who are simply obese will acquire diabetes [51]. Likewise, the 50 or so known genes associated with type 2 diabetes explain only a small fraction of the risk and are dwarfed by modifiable risk factors [52]. To reconcile our seeming inability to readily identify the highest-risk people – the people most likely to benefit from early preventive therapy – the American Diabetes Association

(ADA) publishes a list of risk factors [53], and a number of groups have developed diabetes risk calculators based on these risk factors [54, 55]. Collectively, these tools lend guidance for who should be screened for diabetes.

Approximately 50% of people with diabetes remain undiagnosed, in part, because they have never been screened. According to ADA, all adults ≥45 years old without additional risk factors or adults of any age who are overweight (BMI>25 kg/m^2) and have at least one other risk factor should receive a screening test for diabetes [53]. The screening test should be HbA_{1c}, fasting glucose, or 2-h glucose and repeated at least at 3-year intervals, once yearly in those diagnosed with prediabetes [53]. The European Society of Cardiology and the European Association for the Study of Diabetes (EASD) stated in 2007 that stepwise screening for type 2 diabetes using a noninvasive risk score [54] as first step and then an oral glucose tolerance test (OGTT) for those with high score values is more efficient than performing invasive testing in all people [56]. However, the efficiency of a stepwise screening strategy may be counterbalanced by the observation that many high-risk individuals fail to complete first step of the screening program unless they are in contact with a doctor for other reasons [57]. Therefore, *opportunistic*, stepwise screening for diabetes and prediabetes may be the most cost-effective approach for identifying individuals at risk [58].

Opportunities to Improve Diabetes Prevention

A Closer Look at Prediabetes

Adoption of any of the proposed approaches to screening people for diabetes may result in a diagnosis of normoglycemia, diabetes, or an intermediate dysglycemic state termed "prediabetes." Diagnostic criteria for "impaired glucose tolerance" (IGT, one subtype of pre-diabetes) were introduced by the National Diabetes Data Group in 1979, concurrent with the first ever proposed criteria for diabetes itself [59]. Interestingly, criteria for IGT have remained steadfast over the past three decades, whereas the introduction and refinement of criteria for impaired fasting glucose (IFG, a second subtype of prediabetes that can be seen in isolation or in combination with IGT) have been far more moveable [60, 61]. The latter observation stems from the explicit expectation that people with IFG would also have IGT, a notion repeatedly debunked over the past decade [62, 63]. IFG and IGT are indeed discreet prediabetic states (Table 2.1).

Unlike diagnostic criteria for diabetes that are based on their predictive value for retinopathy [60], diagnostic thresholds for prediabetes are based on the likelihood of developing overt diabetes [62–66]. However, discussion regarding the existing cut points is ongoing. Longitudinal data from a cohort of Israeli soldiers suggest that a fasting glucose above 87 mg/dl (~4.8 mmol/L) is associated with an increased risk of future diabetes [67]. Further, misclassification is common given the day-to-day variability in the fasting

Table 2.1 Overview of the metabolic defects in IFG and IGT

	Isolated IFG	Isolated IGT	Combined IFG+IGT
Insulin resistance			
Reduced peripheral glucose disposal	–	+	+ +
Increased hepatic glucose production	+	–	+
Beta cell dysfunction			
Defective absolute insulin secretion	+	–	+ +
Defective relative insulin secretion	+	+ +	+ +
Ectopic fat accumulation			
Increased fat content in liver	+	+ +	+ + +
Increased fat content in skeletal muscle	+	+	+

The symbols (+ and –) illustrate whether the condition is present in the different prediabetic subtypes seen in relation to individuals with NGR. The number of symbols illustrates the severity of the conditions
References: [81–87]
IFG impaired fasting glucose, *IGT* impaired glucose tolerance

(15%) and 2-h (46%) glucose concentrations [68]. The use of the 1-h glucose value (post-OGTT), fructosamine, 5-androhydroglucitol, and others has also been proposed [69]. With the standardization and widespread use of the HbA_{1c}, in 2010, the American Diabetes Association (ADA) advocated its use in the screening and diagnosis of prediabetes (e.g., 5.7–6.4%) [70]. It should be noted, however, the HbA_{1c} does not discriminate between IFG and IGT. Furthermore, the World Health Organization (WHO) only supports the use of HbA_{1c} for diagnostic use if stringent quality assurance tests are in place, assays are standardized to criteria aligned to the international reference values, and no clinical conditions are present which preclude its accurate measurement [71].

Much discussion remains over the term "prediabetes" because not all people with prediabetes will develop diabetes, but many will. A recent meta-analysis showed that the yearly progression rate to diabetes in individuals with prediabetes is 3.5–7.0% (vs. 2%/year in their normoglycemic counterparts [64]), with highest rates in those with combined IFG and IGT and the lowest in those with IFG by ADA (vs. WHO) definition [72]. Increasing HbA_{1c} is also associated with increased risk of diabetes with yearly incidence rates approximating 5% for those with an HbA_{1c} of 5.7–6.0% and up to 10% for those with an HbA_{1c} of 6.1–6.4% [73]. Adding non-glycemic risk factors (e.g., obesity, hypertension, and family history of diabetes) to the diagnosis of prediabetes markedly increases risk for diabetes, approaching 30% per year [74]. Large clinical trials for diabetes prevention around the globe have universally enrolled participants with untreated prediabetes due to their high risk for acquiring overt diabetes [1–12]. Altogether, the prediabetic state, especially when enriched with other risk factors, should be our target population for diabetes prevention.

Altogether, strong evidence supports the notion that we can prevent or delay the onset of diabetes in people with prediabetes using lifestyle modification or drug therapy. Not uncommonly, however, the question is posed as to whether these trials prevented diabetes or simply treated prediabetes. Although seemingly rhetorical, the answer has implications that could change treatment goals and guidelines for people with prediabetes.

Targeting Defects Specific to the Subtypes of Prediabetes

Elegant human clinical research has delineated the pathophysiology of IFG vs. IGT (Table 2.1). Liver insulin resistance, as measured using stable isotopes, has been reported to be 8–25% higher in people with IFG vs. normoglycemic controls in some studies [75, 76], or "inappropriately" comparable to people with normoglycemia (given the higher circulating glucose and insulin levels in IFG) in others [77, 78]. In contrast, skeletal muscle, not liver, has been implicated in the insulin resistance of IGT. Muscle insulin sensitivity has been shown to be 42–48% lower in IGT vs. normoglycemic controls [77, 78] with only minimal impairments seen in IFG [76]. Because of the larger contribution of muscle (vs. liver) to whole body insulin sensitivity, people with isolated IGT demonstrate on average 15–30% greater whole body insulin resistance compared to those with isolated IFG [79–81]. Additionally, aspects of beta cell dysfunction are discreet in isolated IFG vs. isolated IGT with impaired first-phase insulin release noted in the former and diminished second phase in the latter [78, 80]. To date, no intervention aimed at diabetes prevention has considered the clear physiologic differences in IFG vs. IGT, a matter not likely to be resolved as we move increasingly to the use of A1c or the diagnosis of both diabetes and prediabetes.

Restoration of Normoglycemia in People with Prediabetes

Despite the various strategies employed, only intensive lifestyle modification has been universally advocated (whereas metformin can be considered) for the treatment of prediabetes [82]. The rationale for this decision has included the questionable risk/benefit ratio, cost-effectiveness, and reduction in complications, such as cardiovascular disease, in people with prediabetes using medications for glucose lowering or weight reduction. Nevertheless, any intervention appears to diminish in effectiveness over the long-term [13, 14]. Waning benefit post-intervention has been attributed to lack of long-term adherence to lifestyle changes or drug

therapy. An alternate explanation, however, may be that lack of progression to diabetes rather than the restoration of normoglycemia has been our goal.

In clinical trials to date, interventions were deemed successful if diabetes was prevented or delayed, yet many participants remained with prediabetes. Arguably, prevention of diabetes and its complications lies in the restoration of normoglycemia rather than in the maintenance of prediabetes. This was confirmed by a recent post hoc analysis from the Diabetes Prevention Program Outcomes Study (DPPOS) [19]. This analysis demonstrated a 56% lower risk of diabetes 10 years from randomization among those who were able to achieve normoglycemia during DPP vs. those who remained with prediabetes. The concept that diabetes risk can be significantly reduced over the long term through the pursuit of normoglycemia represents a major shift in our current thinking and has quickly gained consensus as the goal for people with prediabetes [20, 83]. Exactly how normoglycemia should be achieved is far less clear. Data from the DPP would contend that only lifestyle modification (OR = 2.05), not metformin, is useful in achieving normoglycemia in people with prediabetes [84]. Nevertheless, the use of low-dose metformin in combination with low-dose rosiglitazone in the CANOE trial (OR = 1.50) was able to attain normoglycemia [12]. Full-strength TZDs have also been shown to do the same in both the DREAM and ACT NOW studies (OR = 1.71 for both) [2, 5]. High-dose liraglutide boasted a robust and sustained ability to restore normoglycemia in the SCALE studies (OR = 4.9) [29], an effect that rapidly declined off treatment in the 12 weeks that followed the 160-week active treatment period (Table 2.2). Collectively, there is mounting interest in learning if normoglycemia should be the goal for people with prediabetes and, further, if they should be monitored for relapse to prediabetes with escalating and earlier intervention instituted as needed to maintain normoglycemia [85].

Table 2.2 Regression to normoglycemia in people with prediabetes

	N = Population		Follow-up (years)	Regression in controls	Treatment	Regression
US DPP	1990	IGT+IFG	10	37	Lifestyle	2.05 (1.66–2.53)
					Metformin	1.25 (0.99–1.58)
Indian DPP	531	IGT	2.5	24.1	Lifestyle	1.48 (0.99–2.22)
					Metformin	1.27 (0.85–1.89)
					Both	1.31 (0.87–1.95)
ACT NOW	602	IGT	2.4	28	Pioglitazone	1.71 (1.33–2.19)
DREAM	5269	IGT+/−IFG	3.0	30.3	Rosiglitazone	1.71 (1.57–1.87)
					Ramipril	1.16 (1.07–1.27)
CANOE	207	IGT	3.9	53.1	Rosi+Met	1.50 (1.21–1.86)
STOP NIDDM	1429	IGT+IFG	3.3	31	Acarbose	1.14 (0.98–1.33)
SCALE	2254	IGT+/−IFG	3.1	36	Liraglutide	3.60 (3.40–4.40)

References: [1, 2, 5, 6, 9, 12, 30]
IFG impaired fasting glucose, *IGT* impaired glucose tolerance

This shift in our clinical approach may be justified considering the higher incidence of diabetic complications seen in people with prediabetes, independent of their conversion to overt diabetes [15–18]. Nevertheless, enthusiasm for the medical treatment of prediabetes is currently tempered by cost and risk/benefit ratio, especially in light of the many clinical trials failing to demonstrate CVD risk reduction from glucose lowering in frank diabetes [86–89]. Most surprising, however, are data to the contrary in prediabetes. The rate of progression of carotid intima media thickening has been slowed in women with a history of gestational diabetes [90], as well as people with prediabetes [2], using glucose-lowering therapy for ≤3 years. More convincing still was the 49% CVD event reduction in prediabetic participants of the STOP NIDDM trial who underwent glucose-lowering medical therapy [91]. Together, these data suggest that glucose lowering has a disproportionate benefit in CVD risk reduction in prediabetes vs. diabetes – possibly because CVD is less established – providing some of the most vital support for the pursuit of normoglycemia.

Conclusions

As the human and economic cost of type 2 diabetes has surged, focus on its prevention has intensified. Clinical trials across the globe have demonstrated that diabetes can be prevented in high-risk populations over a wide range of cultures and ethnicities [1–12]. Further, reduction in diabetes onset is observed beyond the time of the interventions, albeit attenuated [13, 14]. Waning benefit post-intervention has been attributed to lack of long-term adherence to lifestyle changes or drug therapy. An alternate explanation, however, may be that lack of progression to diabetes rather than the restoration of normoglycemia has been our goal. All of the landmark trials for diabetes prevention to date have enrolled participants with untreated prediabetes due to their exceptionally high risk for acquiring diabetes [1–12]. Even when overt diabetes is delayed or prevented, both micro- and macrovascular diseases appear more prevalent in those with prediabetes compared to their normoglycemic peers [15–18]. Thus, there is reason to believe that true prevention of diabetes and its complications likely reside in the reversal of prediabetes and the restoration of normoglycemia. New evidence supports this speculation [19], and the American Association of Clinical Endocrinologists (AACE) has changed its guidelines accordingly [20]. Nevertheless, there is much to be considered in identifying the people at highest risk for diabetes and determining when and how to institute preventive measures.

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The Metabolic Syndrome

3

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Introduction

Metabolic syndrome defines a group of risk factors underlying cardiovascular and metabolic diseases. These risk factors are related with the development of atherosclerotic diseases: abdominal obesity, atherogenic dyslipidemia, elevated blood pressure, insulin resistance with or without glucose intolerance, pro-inflammatory state, and prothrombotic state [1]. The epidemiological association between these multiple risk factors points to the possibility of a unifying underlying pathophysiology. There has been controversy regarding the concept of a metabolic syndrome and whether it is clinically useful in terms of predicting cardiovascular diseases beyond the risk resulting from the sum of risks associated with each component [2]. However, the criteria used to define this syndrome identify a larger phenotype which is related to a higher risk of developing cardiovascular and metabolic diseases than the simple addition of risks associated with each criterion. The metabolic syndrome is typically under-recognized in the clinical setting. To encourage its use, efforts have been made to unify its definition, with the aim of implementing a comprehensive care approach to address the specific needs of people with the metabolic syndrome.

This chapter recalls the current definition to clinically diagnose the metabolic syndrome and covers the related epidemiological and pathophysiological knowledge. Finally, its link with metabolic and cardiovascular diseases, as well as with cancer, is reported.

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Definition

In 1998, the World Health Organization (WHO) became the first organization to introduce the term metabolic syndrome, with a primary focus on insulin resistance and hyperglycemia [3]. In 2001, the National Cholesterol Education Program's Adult Treatment Panel III (NCEP-ATP III) released its own definition, adding abdominal adiposity, specifically an increased waist circumference, as a major component of the syndrome [4]. Several definitions followed, issued from different societies, that mainly diverged on the clinical evaluation of abdominal adiposity (Table 3.1).

In 2009, the International Diabetes Federation Task Force on Epidemiology and Prevention; the National Heart, Lung, and Blood Institute; the American Heart Association; the World Heart Federation; and the International Atherosclerosis Society joined to release a statement harmonizing the criteria for defining the metabolic syndrome. This is the definition that is in use today, and it takes into account population-specific cutoffs for waist circumference [5]. This definition is reported in Table 3.2.

The term metabolic syndrome remains and includes the previous "syndrome X," "insulin resistance syndrome," and "cardiometabolic syndrome" that covered the same concept. In 2015, a group of experts, representing more than 20 organizations, clearly stated the three fundamental axioms that sustain this concept: (1) the metabolic syndrome is a chronic and progressive pathophysiological state, (2) it represents a clustering of risk factors that form a complex syndrome defined by a unifying pathophysiology, and (3) it is associated with an increased risk for cardiovascular diseases, type 2 diabetes, and other related disorders [1]. The criteria retained for the clinical diagnosis of the metabolic syndrome allow the identification of a phenotype that not only covers the summed risk of its individual risk components but also the residual risk markers that associate with cardiovascular and metabolic disease risk. These residual markers are part of the pathophysiology of the syndrome, but they are not measured in routine clinical practice. It includes elevated levels of apolipoprotein B and small, dense LDL particles, microalbuminuria, and prothrombotic and pro-inflammatory states indicated by high levels of circulating inflammatory markers, such as C-reactive protein and fibrinogen [6].

Epidemiology

The prevalence of the metabolic syndrome has been increasing worldwide for several decades together with obesity, affecting both developed and developing countries [10, 11]. Although the true figures remain difficult to evaluate due to the varying definitions used, the prevalence ranges from 10 to 84% across ethnic groups, age, genders, and countries [12–16]. Epidemiologic studies have shown that the metabolic syndrome occurs in a wide variety of ethnic groups including Caucasians, African-Americans, Mexican-Americans, Asian-Indians, and Chinese, with varying prevalences of both the metabolic syndrome and its components [16–21].

The comparison of US data from NHANES 1999–2000 with NHANES 2009–2010, using the 2009 harmonized definition of the syndrome (Table 3.2) [5], showed that the metabolic syndrome prevalence decreased over the decade, from 25.5 to 22.9%, in US adult men and women [22]. This decrease was particularly seen in Caucasians and may be attributable to drug therapy used for hypertension and dyslipidemia. Even higher rates (almost 40%) emerged when using the IDF definition of the syndrome and the NHANES 1999–2002 data [23] that requires central obesity to be one of the three criteria; further the thresholds for waist circumference were substantially lowered. Specifically, the prevalence of abdominal obesity increased from 45.4% in 1999 to 56.1% in 2010, together with an increase in hyperglycemia from 12.9% to reach 19.9%, whereas for the other parameters, there were decreases from 32.3 to 24.0% for elevated blood pressure and from 33.5 to 24.3% for hypertriglyceridemia, with a parallel increase in the use of lipid-lowering agents [22]. With the lower thresholds of waist circumference, new estimates of prevalence are especially increased for Mexican-Americans and Asians [23–27]. In the USA in 2009–2010, the highest

Table 3.1 Previous criteria for clinical diagnosis of metabolic syndrome

Organization (year) (Ref.)	MetS definition	Insulin resistance or hyperglycemia	Body weight abdominal adiposity	Dyslipidemia	Elevated blood pressure	Other/comments
WHO (1998) [3]	Insulin resistance +2 other criteria	Impaired glucose regulation: fasting glucose ≥110 mg/dl or 2-h glucose ≥140 mg/dl or lowered insulin sensitivity	WHR >0.90/0.85 men/women or BMI >30 kg/m^2	TG ≥150 mg/dl or HDL-C<35/39 mg/dl men/women	≥140/90 mmHg	Microalbuminuria included
EGIR (1999) [7]	Insulin resistance +2 other criteria	Plasma insulin >75th percentile, fasting glucose ≥110 mg/dl	WC ≥94/80 cm men/women	TG >180 mg/dl or HDL-C <40 mg/dl or therapy	≥140/90 mmHg or therapy	Only defined in people without diabetes
NCEP-ATP III (2001) [4]	3 of 5 criteria	Fasting glucose ≥110 mg/dl (modified in 2004 to ≥100 mg/dl), diabetes	WC>102/88 cm men/women	TG ≥150 mg/dl, or HDL-C <40/50 mg/dl men/women	≥130/85 mm Hg	
AACE/ACE (2003) [8]	Clinical judgment, too little known to make a score	Fasting glucose ≥100 mg/dl or 2-h glucose ≥140 mg/dl (but not diabetes)	BMI a risk factor not a criterion	TG >150 mg/dl, HDL-C <40/50 mg/dl men/women	>130/85 mmHg	
IDF (2005) [9]	WC + 2 other criteria	Fasting glucose ≥100 mg/dl, diabetes	Increased WC (population specific)	TG >150 mg/dl, or therapy HDL-C <40/50 mg/dl men/women or therapy	≥130/85 mmHg or therapy	
AHA/NHLBI (2005) [6]	3 of 5 criteria	≥100 mg/dl or on therapy	WC ≥102/88 cm men/women	TG ≥150 mg/dl or therapy HDL-C <40/50 mg/dl in men/women or therapy	≥130/85 mmHg or therapy	

AACE American Association of Clinical Endocrinologists, *ACE* American College of Endocrinology, *AHA* American Heart Association, *NCEP-ATP III* National Cholesterol Education Program's Adult Treatment Panel III, *BMI* body mass index, *EGIR* European Group for the Study of Insulin Resistance, *HDL-C* high-density lipoprotein cholesterol, *IDF* International Diabetes Federation, *MetS* metabolic syndrome, *NHLBI* National Heart, Lung, and Blood Institute, *TG* triglycerides, *WC* waist circumference, *WHC* waist-hip ratio, *WHO* World Health Organization

Table 3.2 Uniform criteria for clinical diagnosis of the metabolic syndrome

MetS definition	Insulin resistance or hyperglycemia	Body weight or abdominal adiposity	Dyslipidemia	Elevated blood pressure
3 of 5 criteria with dyslipidemia being 2 criteria	Fasting glucose ≥100 mg/dL or therapy	WC: Caucasian[a]: Men ≥94 or 102 cm	TG ≥150 mg/dl and/or HDL-C <40/50 in men/ women or therapy	≥130/85 mmHg or therapy
		Women ≥80 or 88 cm		
		Other ethnicities: Men ≥94, 90, 85 cm		
		Women ≥90, 80 cm		

HDL-C high-density lipoprotein cholesterol, *MetS* metabolic syndrome, *TG* triglycerides, *WC* waist circumference
aFor Caucasians, both thresholds could be used until more data are available

age-standardized prevalence was encountered in Hispanic men (34.8%) compared to Caucasian (22.9%) and Black (19.0%) men and in Hispanic women (28.5%) compared to Black (24.5%) and Caucasian (20.3%) women [22]. In AusDiab, an Australian population-based survey, the prevalences of the metabolic syndrome were found to be 29.1% and 19.3%, according to the IDF and NECP-ATP III definitions, respectively [28]. In Brazil, in a systematic review of published studies, the mean prevalence was 30%, using various definitions of the metabolic syndrome [29].

Similar findings come from European and Asian cohorts [16]. In Europe, the prevalence of metabolic syndrome ranges from 10 to 30% and from 24 to 78% for the obese [10, 18, 30]. In the Norwegian HUNT 2 study, the metabolic syndrome prevalence (IDF) was 29.6% compared to 25.9% using the 2005 NCEP-ATP III criteria [31]. The prevalence of metabolic syndrome in France was evaluated in a population-based cohort of subjects evaluated between 1994 and 1996. Using the NCEP-ATP III definition, the metabolic syndrome was found in 16% and 11% men and women, respectively [32].

In a recent meta-analysis in China including more than 220,000 individuals, the prevalence of metabolic syndrome was 19.2% in men and 27.0% in women and substantially higher with increasing age and in urban areas [33]. Of note, hypertension was the most prevalent metabolic syndrome component in men (52.8%) and abdominal obesity (46.1%) in women. In India, the prevalence using the NCEP-ATP III definition was 18.3% and 25.8% according to IDF [34] and was even higher in urban settings [11]. The prevalence reaches even higher levels in Indian immigrants in USA [35]. Rates were lower in Japan, 8% in men and 10% in women [36]. Concurrently, it has also been well documented that Asians population present with higher intra-abdominal fat for a given BMI [17, 37, 38].

A study in 2006 by Harzallah et al. examining the metabolic syndrome in Arab men and women found that the prevalence was 45.5% using the new IDF criteria, 55.8% in women and 30.0% in men [39], and much lower when using WHO or NCEP-ATP-III criteria. Regardless of which definition is used, the reported prevalence tends to be higher in women than in men predominantly because of significant differences in the prevalences of central obesity and HDL-C and, to a lesser extent, hypertension. The prevalence of the metabolic syndrome in Tunisia was 50%; 27% and 39% in men and women, respectively, in Turkey; and 33.1% in Iran [18, 40, 41].

A family history of type 2 diabetes or cardiovascular disease increases the risk of insulin resistance and the risk of subsequently developing the metabolic syndrome [42]. Metabolic syndrome phenotypes also vary across countries and ethnic groups with different clusters of components [43, 44].

The prevalence of the metabolic syndrome increases with age, regardless of gender [16, 18]. In the NHANES 2003–2006 cohort, it rose from 20% in men and 16% in women at age 20–39 to 41% and 37%, respectively, in individuals of ages 40–59 to 52%, and 54%, respectively, for individuals >60 years old [45]. These data have been replicated in several ethnic groups and countries [23, 25, 31, 41, 46].

Importantly, an increase in the prevalence of obesity/overweight and type 2 diabetes has been reported in children [47, 48], and along with this, the prevalence of the metabolic syndrome has also increased, paralleling the degree of obesity. It has been underlined that the diagnosis of the metabolic syndrome remained unstable [44]. In a sample of US adolescents who were included in NHANES III (1988–1994), the prevalence of the metabolic syndrome was 6.8% among overweight adolescents and 28.7% among obese adolescents [49]. In NHANES 2001–2006, the prevalence of metabolic syndrome was 8.6%, higher in boys and lower in Black adolescents compared to Caucasian and Hispanic individuals [50]. A recent review reported that the median prevalence of the metabolic syndrome was 3.3% in children, 11.9% in the overweight, and 29.2% in the obese. The prevalence of the metabolic syndrome was higher in boys and older children [47].

Pathophysiology

Excess visceral adipose tissue may be a primary driver of the cardiometabolic complications of obesity [51]. Ectopic fat deposition in the liver, muscles, and other organs is directly linked to the amount of visceral adiposity. An increase in visceral adiposity is thought to reflect the relative inability of the subcutaneous adipose tissue depot to sufficiently expand its clearance and storage capacity in response to caloric excess [1]. The specific characteristics of visceral adiposity, as opposed to subcutaneous adiposity, and the consequences of ectopic fat deposition drive the altered glucose homeostasis, pro-inflammatory adipocytokines release, and endothelial dysfunction that appear to be a primary cause of the metabolic syndrome. Insulin resistance, which is closely related to ectopic fat deposition and low-grade inflammation, holds therefore a central role in the pathophysiology of the syndrome [52]. Indeed, many of the diseases, detailed below, which aggregate around the metabolic syndrome, include insulin resistance among their likely causal mechanisms: for example, atherogenic dyslipidemia, including elevated levels of triglycerides and low concentrations of HDL-C, increased sympathetic nerve activity and sodium retention predisposing to hypertension, androgen excess and polycystic ovarian syndrome, sleep-disordered breathing, and some cancers. Owing to the many intermediary mechanisms associated with its phenotype, this syndrome is likely to identify groups of individuals with a residual risk beyond the addition of risks associated with each included individual parameter. The metabolic syndrome allows the identification of individuals who can be provided with comprehensive healthcare strategies covering several chronic diseases, giving a common answer to a common underlying pathophysiology [1].

Associations and Complications of the Metabolic Syndrome

Type 2 Diabetes

The metabolic syndrome is an especially strong predictor of incident type 2 diabetes mellitus [53–56]. It has proven as good as the oral glucose tolerance test to predict incident diabetes [57]. The insulin resistance associated with increased visceral adiposity explains much of this strong association [51]. Further progression from insulin resistance to type 2 diabetes implies a relative impairment in insulin secretion, which is related to genetic predisposition, pancreatic glucose and lipid toxicity, and oxidative stress [51].

The increased cardiometabolic risk associated with the metabolic syndrome is linked with a higher prevalence of cardiovascular diseases in people with type 2 diabetes. In the International Study of Prediction of Intra-abdominal Adiposity and its Relationships with Cardiometabolic Risk/Intra-Abdominal Adiposity (INSPIRE ME IAA), the prevalence of cardiovascular disease was not different between people with or without type 2 diabetes, but was strongly associated with the amount of visceral fat accumulation [58].

Lifestyle interventions in viscerally obese men or people with glucose intolerance have proven that addressing visceral fat accumulation and its related cardiometabolic risk is efficient to prevent incident type 2 diabetes [59–61].

Atherogenic Dyslipidemia

Higher abdominal adiposity, more particularly visceral adiposity, is associated with increased triglycerides, LDL-cholesterol, reduced LDL particle size leading to an increase in apolipoprotein B, and decreased HDL-C [62, 63]. This atherogenic dyslipidemia is present in the majority of people with the metabolic syndrome [64].

Whether LDL particle size is an independent risk factor for cardiovascular diseases or merely reflects other changes in the lipid profile associated with the metabolic syndrome is debated [65]. Smaller and denser LDL particles may be more atherogenic as they are more easily able to transit through endothelial basement membrane, have reduced binding affinity to the LDL receptor, are more toxic to the endothelium through enhanced potential interaction with the arterial wall, and have increased susceptibility to oxidation [65, 66]. Importantly, the increased cardiovascular risk attributed to the presence of small, dense LDL particles is partly mediated by LDL particle number, as reflected by elevated apolipoprotein B concentrations [65, 67]. Apolipoprotein B-rich lipoproteins are more prone to macrophage phagocytosis at the origin of plaque genesis that could be disrupted, leading to thrombosis and cardiovascular events [68]. On the other hand, high HDL-C levels have been shown to be independently associated with lower cardiovascular disease risk [69].

There is evidence that individuals with the metabolic syndrome may benefit from more aggressive lipid-lowering therapy, and intensive Apolipoprotein B-rich-lipoprotein-lowering treatment such as statins has been shown to reduce cardiovascular risk in patients with the metabolic syndrome [70–72].

Hypertension

The relationship between hypertension and risk for cardiovascular diseases is well documented [10, 73]. Hypertension is one of the key features of the metabolic syndrome, with a large proportion of people with the metabolic syndrome being hypertensive, with ethnic variations in prevalence. The association appears to be multifactorial with contributions of both obesity and insulin resistance. In an analysis of the NHANES data on trends in hypertension, about 2%, which is more than half, of the increase in the prevalence of hypertension could be attributed to increases in BMI in the population [74]. The links between obesity and insulin resistance with hypertension may be mediated through several pathways. Insulin stimulates vasodilator nitrite oxide (NO) production, a mechanism that is impaired in insulin-resistant conditions, leading to hypertension [75]. Obesity also enhances renal absorption of sodium, activation of the renin-angiotensin-aldosterone system, and the sympathetic nervous system [76, 77]. In addition, hypertension results from the metabolic syndrome through other potent mechanisms such as endothelial dysfunction, increased free fatty acids that may contribute to vasoconstriction, increased levels of inflammatory cytokines, and high leptin levels [10, 78, 79].

Hypertension management is highly linked to caloric restriction [80]. Accordingly, the DASH (Dietary Approach to Stop Hypertension) diet, designed for people with hypertension, with reduced caloric, saturated fat, and salt intake was efficient in those with the metabolic syndrome [81].

Whatever the etiology, individuals with the metabolic syndrome should be closely monitored with aggressive management of hypertension. In individuals with type 2 diabetes, the goal of therapy is a blood pressure <130/80 mmHg [82]. In persons with hypertension (blood pressure above 140/90 mmHg), drug therapies are required according to the Joint National Committee 7 recommendations [83]. The choice of blood pressure-lowering drugs is still debated as some of them may improve other metabolic factors (e.g., ACE inhibitors), whereas others are neutral or could even be deleterious, by enhancing insulin resistance (e.g., beta-1 receptor blockers, thiazide diuretics) [80].

Sleep Apnea Syndrome

Obstructive sleep apnea (OSA) is a condition characterized by recurrent episodes of obstruction of the upper airway, leading to sleep

fragmentation and intermittent hypoxia during sleep. This alteration of sleep quality is associated with excessive daytime sleepiness, an increase in the risk of road traffic accidents, deterioration in quality of life, and long-term cardiovascular morbidity and mortality. Obesity predisposes to OSA due to fat infiltration at the level of the neck, leading to upper airway collapse and increased abdominal pressure, and to lung volume reduction. Adipose tissue accumulation might also alter the neuromechanical control of the upper airway via the specific effects of leptin on central respiratory command [84]. Overall, it is estimated that 50–60% of people with the metabolic syndrome have OSA [85, 86]. OSA is a mechanical and biochemical consequence of abdominal obesity, and patients having OSA share the increased cardiometabolic risk associated with abdominal obesity. Indeed, people with OSA have higher prevalent and incident hypertension, type 2 diabetes, and cardiovascular events [87]. However, evidence suggests that OSA by itself leads to an increase in cardiometabolic risk. Indeed, OSA is associated with the sympathetic activation [88], systemic inflammation, endothelial dysfunction [89], and insulin resistance [90–92], independently of obesity.

Regarding surrogate markers of atherosclerosis and arterial stiffness, it was found that people with both the metabolic syndrome and OSA had higher carotid intima-media thickness, pulse wave velocity, and carotid diameter than those with the metabolic syndrome without OSA. The apnea-hypopnea index was independently associated with impairments in these three vascular parameters [93]. Finally, in a preliminary single-arm study, Oyama et al. [94] reported that continuous positive airway pressure (CPAP) therapy improved endothelial dysfunction and decreased markers of oxidative stress in people with the metabolic syndrome and OSA. Thus, abdominal obesity appears to have a causal role in the development of sleep apnea, and people with the metabolic syndrome are prone to present with OSA. In addition, OSA by itself has a deleterious effect on several intermediary mechanisms that further increase the cardiometabolic risk of patients having both conditions [85].

Therapeutic approaches should address these cumulative risks and propose comprehensive interventions treating both conditions. For instance, Chirinos et al. have treated people with OSA by CPAP, weight loss intervention, or both combined. When both were cumulated, the cardiometabolic risk profile improved, through weight loss intervention with an additional effect on blood pressure and to some extent insulin resistance and triglycerides [95]. It has been demonstrated that lifestyle interventions improve both the metabolic syndrome and OSA in people presenting with both conditions. More specifically, diet and exercise have led to body weight loss but also to an improvement in sympathetic peripheral sensitivity and ventilatory central chemoreflex [96].

Polycystic Ovary Syndrome

Polycystic ovary syndrome (PCOS) is diagnosed by a combination of oligoovulation, clinical and/or biochemical signs of hyperandrogenism, or ultrasound findings consistent with polycystic ovaries. PCOS is associated with central obesity, and the prevalence of the metabolic syndrome in adult premenopausal women with PCOS is approximately 40% [97]. However, PCOS is a heterogeneous disease with many different phenotypes and metabolic aspects. Women with PCOS and an androgen excess are at a higher risk of metabolic and cardiovascular comorbidities compared to women with PCOS and normal androgen levels [98]. It was recently demonstrated that testosterone-to-dihydrotestosterone ratio was a good marker identifying women with PCOS and the metabolic syndrome [99].

How best to achieve pregnancy and improve health in these women is uncertain. Lifestyle interventions have proven successful in improving their cardiometabolic risk profile [100]. A recent randomized controlled trial demonstrated that a combined weight loss and exercise lifestyle intervention, as a preconception infertility treatment, was successful in increasing live births, after ovulation induction [101].

Nonalcoholic Fatty Liver Disease

People with the metabolic syndrome frequently have an increase in fat (triglyceride) accumulation in the liver and hepatic insulin resistance. This increase in liver fat, which is associated with insulin resistance but not with other known causes of steatosis (e.g., alcohol, viruses, drugs), is called nonalcoholic fatty liver disease (NAFLD) [102]. The spectrum of fatty liver disease includes NAFLD and nonalcoholic steatohepatitis (NASH), with and without fibrosis, cirrhosis, and hepatocellular carcinoma [103]. NAFLD is now the most common cause of liver disease in the western world, accounting for an increasing proportion of people with this condition who undergo liver transplantation (15–20%) [104]. NAFLD is largely underdiagnosed owing to the lack of a simple, sensitive method of screening. In addition, there are no clear algorithms to predict the development of more severe manifestations such as cirrhosis or hepatocellular carcinoma. In cross-sectional studies, components of the metabolic syndrome or the syndrome itself have frequently been identified as risk factors for hepatic fibrosis and NASH. In a cross-sectional analysis of 976 liver biopsy samples taken from adults in the NASH Clinical Research Network, the metabolic syndrome was significantly more common (1.43-fold) in patients with NASH than in those without [105]. Although people with NAFLD can die from liver-related diseases, their main cause of mortality is cardiovascular diseases [106]. Beyond the risk related to the metabolic syndrome itself, the Korean Genome Epidemiology Study has shown that NAFLD is associated with early alterations of the cardiovascular system, independent of established cardiovascular risk factors and the metabolic syndrome [107].

Finally, in people with NAFLD, the ability of insulin to normally suppress production of glucose and VLDL is impaired. The liver is the site of production of two key components of the metabolic syndrome, fasting plasma glucose and VLDL, which contains most of the triglycerides present in serum. The liver, once fatty, also overproduces many other markers of cardiovascular risk such as C-reactive protein, fibrinogen, and coagulation factors. Thus, NAFLD has, by itself, an important role in the pathogenesis of the metabolic syndrome [102].

Cardiovascular Diseases

Many prospective cohort studies have evaluated and demonstrated the risk of cardiovascular disease in individuals with the metabolic syndrome, irrespective of the definition used [44, 108–116]. However, the NCEP-ATP III definition presented a higher predictive power than the IDF definition for cardiovascular risk [16]. The 2009 harmonized definition provides similar cardiovascular disease predictive capacity [117].

As observed for the metabolic syndrome, the risk of cardiovascular disease appears to differ between races and ethnic groups [63, 118]. Moreover, the relative hazard ratio outcomes in men and women with the metabolic syndrome range between 2 and 5 in most studies [44, 112, 113, 118]. If each individual component independently increases cardiovascular risk [73], the presence of multiple components further intensifies it [16, 111] and the progression of risk [5]. Whether the predictive potential of the metabolic syndrome exceeds the one associated with the sum of its individual components is still debated [116].

The risk for atherosclerotic cardiovascular disease and stroke is doubled in the metabolic syndrome, for both men and women [6, 113], with a major role of dyslipidemia and inflammation [119]. Moreover, insulin resistance, low HDL-C, hypertension, and hypertriglyceridemia are all independently associated with the risk of myocardial infarction (MI) and stroke [113]. Obesity is an independent risk factor for coronary artery diseases [120], through adipokine and inflammation pathways, and more particularly abdominal obesity as seen in the INTERHEART study [121, 122]. High BMI also doubles the risk for heart failure, independently of other risks factors [119, 123], and is associated with the risk of stroke [124]. Insulin resistance, adipokine release, and inflammation may also contribute to

the increased risk associated with the metabolic syndrome [119]. In addition to cardiovascular disease, the metabolic syndrome also appears to be a significant risk factor for cardiovascular and total mortality, beyond established risk factors for cardiovascular disease [110, 111, 116].

Cancer

It has been shown that many types of cancer are more common in people who have the metabolic syndrome: breast cancer in women after menopause, bowel cancer, colon cancer, esophageal cancer, gastric cancer, and pancreatic, kidney, and liver cancer [125]. Esposito et al. [126] analyzed the relationship between the metabolic syndrome and cancer in a meta-analysis including 38,940 people. The metabolic syndrome is associated with an increased risk of several cancers, but associations often differ between sexes. In men, the metabolic syndrome was strongly associated with liver (RR 1.43, $P < 0.0001$) and colorectal (RR 1.25, $P < 0.001$) cancers and weakly associated with bladder cancer (RR 1.10, $P = 0.013$). In women, the presence of the metabolic syndrome was associated with endometrial (RR 1.61, $P = 0.001$), pancreatic (RR 1.58, $P < 0.0001$), breast (in particular postmenopausal, RR 1.56, $P = 0.017$), colorectal (RR 1.34, $P = 0.006$), and ovarian cancers (RR 1.26, $P = 0.054$).

Furthermore, the presence of the metabolic syndrome is significantly associated with increased cancer mortality, at least in men. Using the NCEP-ATP III criteria, men with the metabolic syndrome had a 56% higher risk of cancer mortality compared with those without. Moreover, people with three or more metabolic factors had an 83% higher risk of cancer death compared to men without metabolic factors [127].

Physical Activity, Diet, and Metabolic Syndrome

It is well documented that metabolic syndrome is associated with sedentary behaviors and lack of physical activity. For example, in 960 men, the SCAPIS pilot study found that time spent sedentary (OR: 2.38, 95% CI, 1.54–4.24 for T3 vs T1), in light-intensity (OR: 0.50, 95% CI, 0.28–0.90) and in moderate-to-vigorous activity (OR: 0.33, 95% CI, 0.18–0.61), and cardiorespiratory fitness (OR: 0.24, 95% CI, 0.12–0.48) were all independently related to the prevalence of metabolic syndrome [128].

Westernized dietary patterns, characterized by a high consumption of meat or meat products, snacks, baked desserts, and sugar-sweetened beverages, which provide high amounts of saturated fatty acids and simple carbohydrates as added sugars, have been associated with higher risk of metabolic syndrome. In contrast, more traditional dietary patterns, including the Mediterranean dietary pattern, characterized by a high consumption of vegetables, fruits, whole cereals, and fish are associated with a reduced risk of metabolic syndrome. The main characteristics of the Mediterranean dietary pattern include a high consumption of nuts and olive oil, resulting in a relatively fat-rich pattern that provides high amounts of mono- and polyunsaturated fatty acids, bioactive polyphenols, and dietary fiber. Strong evidence is accumulating to support that a closer conformity with the Mediterranean dietary pattern is inversely associated with the incidence of Mediterranean dietary pattern, cardiovascular risk factors, diabetes, and cardiovascular disease [129].

A meta-analysis has been conducted, including randomized clinical trials of lifestyle interventions longer than 6 months in subjects having metabolic syndrome [130]. Nine studies were included, five with diet interventions alone and four with diet and exercise combined interventions. Metabolic syndrome resolution was double in the lifestyle intervention arm of the meta-analysis compared to the controlled arm ($n = 2839$).

Beyond body weight loss reduction that results from combined diet and physical activity interventions, physical activity *per se* could have a beneficial role in metabolic syndrome. Ross et al. [131] have nicely demonstrated that exercise could induce a visceral adipose tissue reduction independent of the caloric cost of

exercise. Their study compared the visceral adipose tissue change of subjects assigned to three different intervention groups: (1) a 700-Kcal/day dietary restriction, (2) a 700-Kcal/day deficit produced by exercise with a maintained caloric intake, and (3) exercise inducing an expenditure of 700-Kcal/day which was totally compensated for by an increased caloric intake. Regardless of the group assignment, subjects showed a significant visceral adipose tissue reduction, including subjects assigned to exercise treatment without a caloric deficit. This observation suggests that exercise may promote a visceral adipose tissue loss independent of the related energy deficit. The American College of Sports Medicine recommends that most adults engage in moderate-intensity cardiorespiratory exercise training for ≥30 min/day on ≥5 day/week for a total of ≥150 min/week, vigorous-intensity cardiorespiratory exercise training for ≥20 min/day on ≥3 day/week (≥75 min/week), or a combination of moderate- and vigorous-intensity exercise to achieve a total energy expenditure of ≥500–1000 MET/min/week [132]. Numerous studies and systematic reviews have reported the benefits of aerobic exercise training or resistance training on components of metabolic syndrome, such as abdominal obesity, blood pressure, blood lipids, and insulin resistance [133].

Conclusion

The metabolic syndrome allows the identification of people at high cardiometabolic risk, with a residual risk that exceeds the summed risks of each of its components. Presenting with the metabolic syndrome is likely to raise awareness in the physicians to screen for chronic metabolic diseases that are often clinically silent for a long time. In addition, whatever the presence or absence of chronic diseases aggregated around the syndrome, these people should benefit from comprehensive, healthy eating, and physical activity interventions that address the modifiable risk factors included in the metabolic syndrome and so reduce their cardiometabolic risk.

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4 Diagnosis and Treatment of Nonalcoholic Fatty Liver Disease (NAFLD) in Type 2 Diabetes

Kenneth Cusi

Abbreviations

^{1}H-MRS	Proton magnetic resonance spectroscopy
Adipo-IR	Adipose tissue insulin resistance
ALT	Alanine aminotransferase
AST: ALT	Aspartate aminotransferase
BMI	Body mass index
CT	Computed tomography
CVD	Cardiovascular disease
DNL	De novo lipogenesis
DPP-4	Dipeptidyl peptidase-4
GLP-1RA	Glucagon-like peptide-1 receptor agonist
HbA_{1C}	Hemoglobin A1c
HCC	Hepatocellular carcinoma
IHTG	Intrahepatic triglycerides
NAFLD	Nonalcoholic fatty liver disease
NAS	NAFLD activity score
NASH	Nonalcoholic steatohepatitis
PPAR	Peroxisome proliferator-activated receptor
PUFAs	Polyunsaturated fatty acids
RCT	Randomized controlled trials
SGLT2	Sodium-glucose co-transporter 2
T2DM	Type 2 diabetes mellitus
TZDs	Thiazolidinediones

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Introduction

Nonalcoholic fatty liver disease (NAFLD) is a growing problem likely to worsen worldwide with the epidemic of obesity. Insulin resistance in obesity drives a constellation of metabolic abnormalities that create a state known as "lipotoxicity," in which the liver is uniquely posed to be affected [1, 2]. Additional factors that appear to play a role are chronic hyperglycemia and subclinical inflammation. As the vast majority of patients with type 2 diabetes mellitus (T2DM) are obese, they are particularly susceptible to develop NAFLD and to have a worse long-term prognosis. The disease can present itself as a quiescent condition with hepatic triglyceride accumulation with minimal or no inflammation or adopt a more aggressive phenotype associated

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with hepatocellular injury, marked inflammation, and fibrosis (known as nonalcoholic steatohepatitis or NASH) [3]. These patients are at a much higher risk of cirrhosis, as well as of hepatocellular carcinoma [4].

Both endocrinologists and primary care physicians often are unaware of the health risks associated with NAFLD/NASH in obese patients with diabetes. Moreover, the relationship between NAFLD and diabetes is complex and incompletely understood. It is likely bidirectional, with many longitudinal studies reporting a two- to fivefold increase in the prevalence of T2DM in nondiabetic patients with NAFLD. For instance, Sung et al. [5] reported in a study involving 11,091 patients assessed for NAFLD with a liver ultrasound and restudied after 5 years that only 0.7% of individuals without NAFLD at baseline developed diabetes compared to 4% of those with steatosis. Even after multivariate adjustment, the hazard ratio (HR) remained twofold higher in individuals with NAFLD at baseline. In a larger study in 38,291 subjects without diabetes at baseline who were followed for 5.1 years, the HR for developing diabetes in a multivariate-adjusted model ranged from 2.0 (if only mild NAFLD at study entry) compared to 4.7 if moderate-severe NAFLD was present [6]. Similar results have been reported in other large longitudinal studies [1].

Conversely, having diabetes carries a much higher risk of progression from NASH to cirrhosis. A number of studies have identified ethnic, genetic, metabolic, and other factors in disease progression [7–9]. However, to this day, the natural history of NASH remains incompletely understood. Poor knowledge of the diagnostic and treatment options, and certain disregard by clinicians to screen patients for NASH, remains a major obstacle for early intervention and prevention of long-term hepatic and extrahepatic complications associated with the disease. The recent positive results by Cusi et al. [10] with pioglitazone in a long-term randomized clinical trial (RCT) in patients with prediabetes or T2DM and biopsy-proven NASH suggest that modifying dysfunctional, insulin-resistant adipose tissue may change the natural history of the disease. Early screening will become as important as it is today for microvascular complications such as retinopathy, nephropathy, and neuropathy in T2DM [11–13]. Soon NAFLD will be recognized as a common complication of T2DM that deserves early treatment to prevent hepatic [11, 14, 15] and extrahepatic complications [11, 16, 17], including cardiovascular disease that is the leading cause of mortality in patients with NAFLD.

The Epidemic of NAFLD

The current definition of nonalcoholic fatty liver disease (NAFLD) is liver triglyceride concentration ≥5.6% on imaging when performed by the gold-standard magnetic resonance imaging and proton (^{1}H) spectroscopy [MRS], or triglycerides present in >5% of hepatocytes on histology [18]. This is obviously in the absence of other secondary causes of liver steatosis (see Table 4.1) such as viral disease, medications, alcohol abuse, autoimmune hepatitis, and other identifiable causes [7, 8]. Its histological severity varies greatly from patient to patient. It can range from isolated steatosis with only minimal (or without any) inflammation to its more severe presentation with hepatocyte injury (ballooning) and inflammation (nonalcoholic steatohepatitis or NASH). Cirrhosis or hepatocellular carcinoma can develop in patients with more active and/or longstanding disease [19–22]. Excess adiposity is a major driving factor [1, 2]. In the United States, about two-thirds or more of the population are either overweight or obese with similar trends affecting most countries across the globe [23]. As recently reviewed by Bril and Cusi [24], the prevalence of NAFLD depends on the population studied and the test used for its diagnosis (Table 4.2), being lower with the rather insensitive measurement of plasma aminotransferases (5–10%), between 17 and 46% by liver ultrasound and higher with the gold-standard ^{1}H-MRS with an estimated prevalence of 34% in the general population. In a landmark study in ~400 middle-aged individuals randomly selected, the prevalence of hepatic steatosis on ultrasonography was 46% and the prevalence of biopsy-proven NASH was 12% [25].

Table 4.1 Secondary causes of hepatic steatosis that must be considered in the differential diagnosis of patients with NAFLD

• Alcohol abuse
• Autoimmune hepatitis
• Primary biliary cirrhosis
• Alpha-1 antitrypsin deficiency
• Lipodystrophy
• Wilson's disease
• Abetalipoproteinemia
• Hepatitis C genotype 3
• HIV infection
• Acute fatty liver of pregnancy (microvesicular steatosis)
• Parenteral nutrition or chronic starvation
• Drugs (most relevant): corticosteroids, tamoxifen, diltiazem, amiodarone, methotrexate, valproic acid, anti-retroviral therapy

Table 4.2 Diagnosis of steatohepatitis (NASH)

(a) Clinical and laboratory considerations
• Usually gives few clinical symptoms
• Most common: right upper quadrant discomfort
• Most frequently ALT > AST (except if advanced end-stage liver disease)
• At least 50% of patients with NASH may have normal liver AST and ALT
(b) Plasma biomarker panels for the diagnosis of NASH or fibrosis
• Several biomarker panels are commercially available that combine clinical parameters of risk for NASH (obesity, T2DM) with clinical and liver-specific laboratory testing
• The best clinically validated are Fibrotest[196], NAFLD fibrosis score[197], BARD score[198], NAFIC score[199], Hepascore[200], and FIB-4 index[201]
(c) Imaging
• *Ultrasonography and controlled attenuation parameter (CAP):* elpful and simple approaches for the diagnosis of steatosis at point of care (in the clinic). However, operator dependent and with moderate sensitivity in very obese patients
• *Vibration-controlled transient elastography (VCTE):* utilized to measure liver fibrosis. Present in the same device with CAP (similar limitations)
• *Magnetic resonance imaging and spectroscopy (^{1}H-MRS):* the gold-standard research technique for the diagnosis and monitoring of hepatic triglyceride content
• *Magnetic resonance imaging-estimated proton density fat fraction (MRI-PDFF):* an alternative MRI-based imaging technique for liver triglycerides used in research
• *Magnetic resonance elastography (MRE):* MR-based technique for the assessment of liver fibrosis
• *(d) Liver biopsy*
• Needed for definitive diagnosis (gold standard for the diagnosis of NASH)
• Allows staging of the disease and monitoring of treatment
• Required in research settings to establish efficacy of new agent

The prevalence of NAFLD and NASH is higher in high-risk groups, that is, obese patients and those with T2DM. For instance, some studies suggest that the prevalence of NAFLD in patients undergoing bariatric surgery may be as high as ≥90% [2, 3]. In the setting of T2DM, the prevalence of NAFLD is at least twofold higher than in obesity alone, with a range that goes from 43 to 70%, depending on the population studied and diagnostic test used for screening [25–31]. It should be noted that having T2DM makes more likely that steatosis is associated with hepatocyte necrosis and liver inflammation, as well as progression to fibrosis and hepatocellular carcinoma [1–4, 21, 28].

Diabetes and NAFLD

T2DM is a common comorbidity in NAFLD, but estimates of the prevalence of prediabetes in patients with NAFLD are unknown. Initially it was believed that a minority of patients with NAFLD had abnormal glucose metabolism based only on self-reporting or a fasting plasma glucose concentration [2]. More recent studies assessing glucose metabolism in a more sensitive manner by means of an OGTT report much higher rates [1]. Recently, Ortiz-Lopez et al. [32] reported a threefold increase in the rate of prediabetes and T2DM (or about 85% versus 30%) of overweight or obese patients with NAFLD compared to healthy controls without the disease. As discussed above, NAFLD often precedes and may predispose individuals to develop T2DM [5, 6, 33]. This is even more important in high-risk subgroups prone to diabetes such as individuals with a family history of T2DM or presence of the metabolic syndrome [34].

Another reason why NASH should be kept in mind in patients with T2DM is that their risk of hepatic and extrahepatic complications is much higher than in the general population [1–3, 7, 8]. A chronically increased plasma glucose concentration can have toxic effects on a broad spectrum of molecular pathways and cells, such as endothelial cells, retinal pericytes, mesangial cells in the renal glomerulus, neurons, pancreatic β-cells, and many others, with glucose-sensing pathways that may translate into proapoptotic signals [35, 36]. Hyperglycemia is a known risk factor for microvascular complications, but it is not clear whether the combination of hyperglycemia per se and NAFLD worsens outcomes. Only a few cross-sectional studies have looked at microvascular complications in relation to NAFLD [37]. At the level of the liver, hyperglycemia can cause oxidative stress by several mechanisms. Glucose may increase oxidative stress by stimulating the formation of hydrogen peroxide and hydroxyl radicals that cause hepatocyte lipid peroxidation [36]. The mitochondrial membrane is especially susceptible to lipid peroxidation-derived products like malondialdehyde. Advanced glycosylation end-products (AGEs), also known as glycotoxins, also play an important role as they are the final reaction products of protein with sugars produced through a Maillard reaction [38]. Their interaction with cell surface receptor (RAGE) is associated with the development of inflammation. Both Kupffer and hepatic stellate cells have RAGE receptors [39]. Hepatocytes from patients with steatohepatitis stain much more positive for glyceraldehyde-derived AGE compared to those from patients with simple steatosis or healthy controls [40].

Fructose is a simple carbohydrate found in fruits, but excess intake in modern diets in the form of corn syrup in processed foods and soft drinks may be an important contributor for the development of NAFLD [41]. Some studies report that patients with NAFLD have up to a threefold higher consumption of fructose when compared to matched controls and much higher fructokinase gene expression, which promotes lipogenesis through fatty acid synthase [42]. Others have reported a correlation between fructose intake and higher fibrosis stages in NASH [43]. However, the issue of fructose intake and steatohepatitis remains controversial. Chiu et al. [44] performed a meta-analysis from 13 trials and found no effect of fructose in isocaloric-diet trials, but a positive effect for fructose to increase plasma ALT levels and steatosis with fructose-enriched hypercaloric diets, suggesting a greater role to excess energy than fructose itself. The concern about fructose comes from evidence suggesting that a high-fructose diet stimulates de novo lipogenesis (DNL) and activates inflammatory pathways (i.e., c-jun N-terminal kinase (JUN)-signaling pathway) that induce hepatocellular injury (ballooning) and apoptosis. As proof of concept, DNL and hepatic steatosis can be prevented if the cell surface glucose and fructose transporter GLUT8 (Slc2A8), highly expressed in liver and other oxidative tissues, is abolished in mice lacking GLUT8 [45]. Future studies will help understand the role of fructose in NASH.

The molecular mechanisms by which hyperglycemia may worsen hepatic insulin resistance in NAFLD or exacerbate steatohepatitis have not been carefully examined. However, the activation of glucose-6-phosphatase (G6Pase), a key enzyme of endogenous glucose production, is a well-established defect in diabetes. Hyperglycemia appears to induce the production of reactive oxygen species (ROS) and, in parallel, induce G6pc promoter activity. In one study, this was abolished with small interfering RNAs that targeted either the hypoxia-inducible factor (HIF)-1α or the CREB-binding protein (CBP) [46]. An experimental elevation of glucose increased the interaction of HIF-1α with CBP and the recruitment of HIF-1 to the G6pc promoter, exacerbating hepatic glucose production and hyperglycemia. Glucose also regulates the transcription of many genes encoding important lipogenic/glycolytic pathways, such as the transcription factor carbohydrate-responsive element-binding protein (ChREBP) [47]. Glucose can contribute to lipotoxicity by stimulating ChREBP and increasing the activity of liver-pyruvate kinase (L-PK) [48]. This enzyme is fundamental for the conversion of pyruvate to citrate in the mitochondria, in order to then be transported to the cytosol to feed fatty acid synthesis.

At the clinical level, there is a modest but significant relationship between hyperglycemia and

worse steatohepatitis in patients with T2DM and NASH [32], but it appears to be less than the role of insulin resistance and lipotoxicity. Future work will determine the role of improved glycemic control per se, independent of changes in insulin resistance or weight loss, on steatohepatitis. However, that patients with T2DM have a more rapid progression to advanced fibrosis is an observation that has been consistent in the literature [1, 7, 8, 17, 26–31]. In a report from Brazil by Leite et al. [30], 78% of patients with T2DM had biopsy-proven NASH and fibrosis developed in ~50%. In a larger study in 458 patients by Fracanzani et al. [49], T2DM was the main risk factor for NASH and advanced fibrosis, consistent with work by Neuschwander-Tetri et al. [20] in 698 patients with NASH in whom advanced disease was much more likely if they had diabetes and insulin resistance. Moreover, three recent large population-based studies have confirmed that the presence of fibrosis is also associated much more common in patients with diabetes [20, 50, 51]. Paired-biopsy studies confirm the associations reported in the cross-sectional data discussed above. Several investigators [52–58] have reported that patients with NAFLD have a much higher rate of advanced fibrosis and cirrhosis compared to controls without T2DM. Other prospective studies have arrived to a similar conclusion about the high risk of aggressive steatohepatitis and end-stage liver disease, even increased mortality in the presence of T2DM [55–58]. There is also a large body of literature on the link between T2DM, cirrhosis, and hepatocellular carcinoma [4, 53]. In general, epidemiological studies agree that having diabetes increases the risk of cirrhosis and hepatocellular carcinoma by two- to fourfold although the reasons for this remain elusive and have been reviewed in depth elsewhere [1–3, 7, 8]. However, there is a growing consensus that progression from NASH to HCC requires development of the carcinogenic pathways that develop in cirrhosis [21], although not all agree [59].

Another important question is whether NAFLD in diabetes worsens microvascular disease. The strongest evidence in this regard comes from studies assessing the association between NAFLD and chronic kidney disease and/or proteinuria. An early study reported in a cohort of 2103 middle-aged patients with T2DM that NAFLD was associated with an increased prevalence of chronic kidney disease and retinopathy [26], even after adjusting for key cardiovascular risk factors. Musso et al. [12] found a significant association between NAFLD and kidney disease in both cross-sectional and longitudinal studies. Moreover, the presence of NASH and advanced fibrosis was linked with worse CKD when compared to patients with isolated steatosis or those without fibrosis, respectively. This effect remained when adjusted for diabetes status or other classic risk factors of CKD. Future studies are needed for a better understanding of the role of NAFLD, if any, on microvascular complications in T2DM are very much needed. In summary, the above data emphasizes the need for clinicians to be proactive and establishes an early diagnosis and long-term follow-up strategy for high-risk patients, especially those that are obese and have diabetes. If cirrhosis is present, frequent HCC surveillance is needed [60].

Role of Insulin Resistance and Lipotoxicity in the Pathophysiology of NAFLD

The pathways that lead to hepatocellular injury and fibrosis in NASH are poorly understood, and most current knowledge at the molecular level arises from in vitro or animal models that often do not resemble the conditions seen in human disease. However, an aspect that appears consistently in animal models and at the clinical level is the key role of insulin-resistant adipose tissue in promoting ectopic triglyceride deposition, and in a broad sense, "lipotoxicity" across tissues poorly adapted to such a chronic insult [1, 2]. This was well illustrated in a recent report by Lomonaco et al. [17]. The investigators recruited 154 obese patients and divided them in four groups of carefully matched subjects: controls without T2DM or NAFLD, T2DM without NAFLD, T2DM with isolated steatosis, and T2DM with NASH. The authors found that adipose tissue and hepatic insulin resistance were much worse when NASH was present compared to matched obese controls with only isolated steatosis or without NAFLD. Why steatohepatitis is associated with worse

hepatic and adipose tissue insulin resistance remains unclear, but a logical interpretation is that increased fatty acid flux from dysfunctional, insulin-resistant adipose tissue may trigger the series of events that lead to hepatic steatosis, inflammation, and hepatocyte injury over time [1]. This work followed an earlier study by our group that demonstrated that even across patients matched for BMI, the severity of liver disease on histology (i.e., triglyceride accumulation, inflammation/necrosis, and fibrosis) followed not that much the increase in BMI but how insulin-resistant and dysfunctional adipose tissue was in these patients with steatosis [61]. The source for 60–70% of the total triglycerides made by the liver is from adipose tissue [1, 2, 62]. Excess dietary intake of nutrients and newly synthesized triglycerides from DNL contribute the rest. Insulin resistance promotes hyperinsulinemia (from chronic over secretion of insulin and impaired insulin clearance) [63] which drives hepatic DNL and steatosis. Ethnicity is believed to be another factor, accounting primarily for modest differences in fibrosis between Caucasians and Hispanics but not so much for steatohepatitis when adiposity is matched across ethnic groups [64].

Mitochondrial dysfunction is believed to play a central role in the development of hepatocyte "lipotoxicity" and steatohepatitis [65]. Recent studies from our laboratory [66, 67], as well as from others [68–70], support a key role for mitochondrial dysfunction in NAFLD. In C57BL/6 mice fed a high-trans-fat, high-fructose diet for 24 weeks (a validated mice model of NASH), hepatic mitochondrial fluxes are increased to adapt to the insult of chronic substrate excess [67]. However, this response is inadequate to avoid activation of inflammatory pathways in this model and hepatocyte injury/death from chronic accumulation of lipid peroxidation products and other toxic lipid metabolites such as ceramides, diacylglycerols (DAGs), and acylcarnitines [67]. This inefficient disposal of excess energy through the tricarboxylic acid (TCA) cycle has also been reported in obese patients with hepatic steatosis [70, 71] and associated with reduced oxidative capacity, activation of intracellular inflammatory pathways and macrophage (Kupffer cell) recruitment, and an overall loss of the mitochondria to have the "metabolic flexibility" needed to up- and downregulate its function to changing metabolic conditions. As a proof of concept, amelioration of mitochondrial demand by either weight loss [1], hormonal manipulation [72], pharmacological therapy [73, 74], or controlled mitochondrial uncoupling with protonophore 2,4-dinitrophenol (DNP) [68] prevents steatohepatitis.

In summary, the pathophysiology of steatohepatitis is closely linked to the chronic energy/fatty acid supply and mitochondrial oxidation reaching a breaking point where harmful intracellular pathways activate dell death and fibrogenesis. The good news is that to a certain extent this damage requires a long time to be permanent and that current therapies may halt or cause significantly regression in the vast majority of patients, although most patients remain undiagnosed and untreated [24].

Cardiovascular Impact of NAFLD

Development of NAFLD is associated with increased cardiovascular disease [1, 3, 7–9, 13, 24]. The presence of NAFLD appears to promote atherogenic dyslipidemia [62]. This is at least in part because in patients with hepatic steatosis, inhibition of hepatic VLDL secretion by insulin is impaired [75]. Bril et al. [16] recently reported in 188 middle-aged patients that NAFLD was associated with a worse atherogenic lipoprotein profile, regardless of being matched with controls without NAFLD for body mass index and other relevant clinical parameters. The observed worse atherogenic profile was largely associated with increased hepatic fat alone and not by the severity of steatohepatitis. Patients with NAFLD had a significantly higher plasma apolipoprotein B to apolipoprotein A1 ratio and smaller LDL particle size. These lipid profile changes happen in NAFLD independently of the presence or not of T2DM [17].

Other mechanisms at play in patients with NAFLD include chronic subclinical inflammation and endothelial dysfunction. It is known that increased plasma free fatty acids can impair insulin signaling and nitric oxide production by endothelial cells in a dose-dependent manner [76]. Our group has reported that this can be achieved

within 2–3 days of lipid infusion under experimental conditions and with plasma FFA levels increasing within the physiological range observed in obesity or T2DM [77, 78]. Another factor may be an increased myocardial triglyceride accumulation in patients with NAFLD and obesity and T2DM [79]. There is a close association between hepatic steatosis and myocardial insulin resistance, impaired ventricular metabolism, presence of diastolic dysfunction, and even coronary artery disease [80–82].

As reviewed elsewhere [1, 3, 9, 24, 81], while there is significant controversy about NAFLD as an independent risk factor for CVD, support for this notion comes from many cross-sectional [26, 83–85] and longitudinal [55–58] studies. The association between NAFLD and CVD persists even after adjusting for traditional cardiovascular risk factors. The limitations of most studies include one or more of the following:

(a) In many studies, the diagnosis of NAFLD is solely based on liver aminotransferases or ultrasonography (not on gold-standard tests like a liver biopsy or at least ^{1}H-MRS).
(b) Inadequate controls, so that patients with NAFLD have a much worse phenotype already from just assessing traditional CV risk factors. It is unclear if adjustment for traditional CV variables can truly account for the tangled web of factors present in NAFLD (in some the risk attributed to NAFLD disappeared when correcting for traditional CV risk factors).
(c) Short follow-up or few CV events [1, 11, 86]. In conclusion, more work is needed to include NAFLD as an independent CV risk factor, but it appears to be reasonable to have a high degree of suspicion of CVD in obese patients with NAFLD.

Diagnosis of NAFLD

Clinicians must become more aware about the health risks linked to NAFLD and develop accordingly a screening and treatment strategy. This has become even more imperative given the long-term safety and efficacy of pioglitazone in patients with prediabetes or T2DM [10], which, combined with its relative low cost as a generic medication and its potential to modify the natural history of the disease, offers the potential to be a disease-modifying intervention for many patients.

Table 4.1 summarizes many conditions associated with NAFLD that must be considered in the evaluation of these patients. Plasma aminotransferase concentration is still today the first step in the diagnosis of NASH. This is primarily because they are routinely measured in clinical practice. However, the sensitivity of plasma AST and ALT is rather low. Many patients with elevated plasma ALT levels do not have NASH as well as patients with NASH may have a normal plasma ALT concentration. Its sensitivity can be improved if lower cutoffs are chosen based on epidemiological evidence so that one may consider normal ALT in women to be $\leq$19 IU/L and $\leq$30 IU/L in males [8, 9]. However, to some degree, worse hepatic steatosis may often correlate often with the severity of ALT elevation [87]. But also severe liver disease on histology is observed with normal liver aminotransferases. In patients without diabetes, Verma et al. [88] reported that the predictive value of ALT levels for NASH and advanced fibrosis was very low. In one of the few studies focusing in patients with T2DM, Portillo-Sanchez et al. [89] examined the presence of NAFLD or NASH in those with normal plasma AST and ALT. They reported that 56% of overweight or obese patients with T2DM had NAFLD and 26% had NASH. Taken together, the current consensus is that plasma aminotransferase concentration, while to some extent useful, is an insensitive test alone to base a screening strategy in NAFLD.

Table 4.2 recapitulates the available approaches for the diagnosis of liver steatosis, steatohepatitis, and fibrosis. Liver ultrasonography is widely available and frequently used test for the diagnosis of hepatic steatosis, but again, its sensitivity/specificity is also poor in the presence of severe obesity or when liver triglyceride content is not very high (lower than 12.5%) [90]. The gold standard is a test for liver triglyceride measurement based on nuclear magnetic reso-

nance, either ^{1}H-MRS or MRI-proton density fat fraction (MRI-PDFF). Currently used regularly in clinical trials and other research settings, they are posed to become more widely available in the near future. This will limit the need for a liver biopsy to just a subset of patients with very specific indications. More recently, a useful noninvasive approach being tested to quantify liver fat is controlled attenuation parameter (CAP) that is present in the same device with vibration-controlled transient elastography (VCTE, which is utilized to measure liver fibrosis) [91–93]. It is often used in hepatology clinics, but not yet by endocrinologists or PCPs, who are still less aware about diagnosing NAFLD and establishing their risk of cirrhosis. As with ultrasonography, severely obese individuals make more difficult the diagnosis by CAP (and of fibrosis by VCTE), although newer probes may reduce this diagnostic gap [24]. The importance of VCTE, and of the more costly but more accurate technique known as MR elastography [94], is to screen patients at risk of having liver fibrosis. The presence of liver fibrosis identifies a subset of patients that will progress more rapidly to cirrhosis and who carry the worse long-term prognosis [3, 7, 8]. It also helps to determine the need for a liver biopsy and hepatology referral. Currently, a liver biopsy is indicated to (a) confirm a presumable diagnosis and determine the severity of steatohepatitis; (b) establish the severity of fibrosis and long-term prognosis; (c) be able to monitor response to treatment, especially at a time when safe and effective treatments are becoming available; and (d) learn about the above to enroll a potential patient into a clinical trial.

While today the diagnosis of NASH remains elusive other than by liver biopsy, in the not so far future, it will likely be replaced by plasma biomarkers and clinical scores [1, 7–9, 24, 95, 96]. The ones most widely used at present, having been better validated in larger cohorts of patients (some can be ordered commercially in the clinic) [187–192], are summarized in Table 4.2. However, the reader must be aware that they still require further validation in larger cohorts of patients across different ethnic groups. More importantly, while they have overall a good negative predictive value (NPV) to rule out patients with cirrhosis (≥0.90), their positive predictive value (PPV) is much lower depending on the test (0.60–0.70) and often misclassifies patients with intermediate disease severity, which are most of the patients not attending hepatology clinics. Among the many single biomarkers tested, plasma keratin-18 fragment levels appeared to be the most promising but let to disappointing results as a stand-alone test when tested in a relatively large cohort of patients [97]. In short, none of the available biomarkers or noninvasive tests based on a combination of clinical parameters and blood tests can yet replace a liver biopsy [7, 8]. In the end, clinicians must keep a high degree of clinical suspicion for NAFLD in patients that are obese or have T2DM because the combination of the above tests and a candid discussion of the likelihood of having NASH will determine the need for a liver biopsy to confirm the diagnosis.

Treatment of NASH

Role of Lifestyle Intervention in NAFLD

Lifestyle modification and weight loss can ameliorate NAFLD, but evidence in this field is not robust in terms of long-term outcomes. Most studies have been short-term efforts in small cohorts of patients, lacking proper controls and/or not using liver histology but noninvasive endpoints instead (i.e., plasma aminotransferases, liver ultrasound, or ^{1}H-MRS) [1, 3, 7–9, 98]. Overall, one can summarize a large body of literature by saying that even a modest weight reduction of ~5% with lifestyle modification can decrease liver triglyceride content by about ~30 to 40% [1, 7, 8, 99]. A greater weight loss, in the range of ≥10%, usually offers greater benefit with amelioration of hepatocyte injury and necrosis and even of fibrosis. Promrat et al. [100] conducted a 48-week randomized control trial (RCT) in obese patients with and without T2DM and biopsy-proven NASH. The average weight loss in the intensive arm was 9.3% and versus 0.2% in the control group that received only basic educa-

tion on diet and exercise. This weight loss was associated with significant histological (NAS) improvement in 72% of patients versus 30% in control subjects ($p = 0.03$). The magnitude of weight loss was an important factor in determining improvement in NAS, with consistent histological benefit if weight loss ≥7%. Both diabetics and nondiabetics benefited to a comparable degree. Lazo et al. [101] reported similar results in a 12-month dietary and exercise intervention study in 102 obese patients with T2DM compared to a control group given only general nutrition and exercise information. The intensive lifestyle intervention arm lost more weight (–8.5 vs. –0.05%; $p < 0.01$) with 51% versus 22% of patients having a decrease in hepatic steatosis, respectively ($p = 0.04$). Reduction in weight and hepatic triglycerides was associated, as expected, with better glycemic control with intensive lifestyle intervention (A1C: –0.7% vs. –0.2%; $p = 0.04$), and both variables were closely correlated. In another recent study [102], the cutoff reported from earlier studies appeared to be confirmed in among 293 patients with biopsy-proven patients who underwent lifestyle changes for 52 weeks, but the goal of losing ≥5% was reached by just 30% and ≥10% by only 10% of patients. The study suffered from being uncontrolled, but 25% achieved resolution of steatohepatitis and 19% had regression of fibrosis (although with a large variability in the response). Bacchi et al. [103] compared 4 months aerobic or resistance training on insulin resistance, hyperglycemia, and hepatic steatosis in patients with T2DM, as reported in 31 sedentary adults with T2DM and NAFLD. Training by both approaches improved all three parameters similarly with hepatic triglycerides decreasing by –32.8% vs. –25.9%, respectively (NS between groups, both $p < 0.001$ vs. baseline). We refer the reader to additional reviews that have examined the effects of lifestyle and/or exercise alone in NAFLD/NASH and of bariatric surgery in NAFLD [1, 3, 7–9, 104, 105].

The response of hepatic fibrosis to weight loss is more unpredictable than to steatosis and necroinflammation [1, 7, 8, 104]. This is also true even for the large histological improvement expected following bariatric surgery [106, 107]. Reversal of fibrosis is subject to a large variability and not as directly proportional to the amount of weight loss as with steatosis. In conclusion, much more remains to be learned about the role of lifestyle intervention in NAFLD. There is a need for large multicenter controlled trials of longer duration (>12 months). No large RCTs of >12 months comparing different lifestyle and/or exercise programs in NASH have ever been conducted in this field. It also remains to be established what the minimal degree of weight loss or exercise intensity that will successfully reverse NASH in the long term and what are the effects of discontinuing lifestyle changes on histology. Other knowledge gaps include establishing the optimal dietary macronutrients for weight loss vs. long-term weight maintenance in patients with NASH and which approach can be more sustainable to patients over time.

Insulin Sensitizers in NASH: Role of Pioglitazone

Restoring insulin action is a major goal of therapy given the central role of insulin resistance, dysfunctional fat, and "lipotoxicity" in the pathogenesis of NASH [1, 2, 10]. In this setting, insulin sensitizers have been often tested for the treatment of NASH. While early small and uncontrolled open-label clinical trials with metformin suggested benefit [108, 109], benefits were likely from weight loss and not specific to metformin per se. More recent RCTs have all been negative, as reviewed elsewhere [1, 3, 7, 8, 104]. This is also true for studies in pediatric patients with biopsy-proven NASH treated with metformin [110].

Pioglitazone is a thiazolidinedione (TZD) that modifies the response of transcription factor peroxisome proliferator-activated receptor (PPAR)-γ and enhances glucose and lipid metabolism in obesity and T2DM [1, 73], restoring adipose tissue insulin sensitivity and rising by two- to threefold plasma adiponectin levels [10, 74, 111, 112]. Preliminary data from a long-term RCT in pioglitazone-treated NASH patients [10] suggests that hepatic histological response can be predicted by the magnitude of the early increase in plasma adiponectin levels. The early study by Belfort et al.

[74] established that patients with NASH and prediabetes or T2DM treated with pioglitazone improved within 6 months hepatic steatosis and necroinflammation. The NAFLD activity score (NAS) improved with pioglitazone in 73% compared to 24% of placebo-treated patients ($P < 0.001$). Liver fibrosis improved compared to baseline ($p = 0.002$) although the small sample size ($n = 55$) made is not significant versus placebo ($p = 0.08$).

Recently, a 3-year study in 101 patients with NASH, and either prediabetes or T2DM, confirmed its long-term safety and efficacy in this population [10]. Patients had either prediabetes ($n = 49$) or T2DM ($n = 52$). All received instruction on a hypocaloric diet (a 500-kcal/day deficit from weight-maintaining caloric intake) and prescribed pioglitazone, 45 mg/day, or placebo for 18 months. This was followed by an 18-month open-label phase of pioglitazone treatment for all patients. As shown in Fig. 4.1a (*left panel*), the primary outcome of a reduction of at least two points in the NAS (in two different histologic categories) without worsening of fibrosis was achieved by 58% of pioglitazone-treated patients (treatment difference, 41% [95% CI, 23–59%]), $p < 0.001$). Figure 4.1a (*right panel*) shows another important outcome of the study: pioglitazone therapy led to a resolution of NASH in 51% of patients (treatment difference, 32% [CI, 13–51%], $p < 0.001$). Treatment improved every aspect of histology, including the fibrosis score ($p = 0.039$), as summarized in Fig. 4.1b. These benefits reflected in a normalization of plasma AST (Fig. 4.2a) and ALT (Fig. 4.2b) concentrations improved insulin resistance as expressed by the homeostatic model assessment (HOMA) which largely reflects hepatic insulin resistance (Fig. 4.2c) and restoration of normal adipose tissue insulin function with near normalization of adipose tissue insulin resistance (Fig. 4.2d). The improved adipocyte biology with PPARγ agonism markedly increased plasma adiponectin concentration (Fig. 4.2e). Finally, treatment led to a decrease in keratin-18 levels as a reflection of reduced caspase activity/apoptosis and a reduction liver fibrogenesis (Fig. 4.2f). Pioglitazone also reduced hepatic triglyceride when measured by the gold-standard ^{1}H-MRS from 19 to 7% and improved adipose tissue, hepatic, and muscle insulin sensitivity (all $p < 0.001$). Metabolic and histologic improvements continued after 36 months of treatment. Adverse events were overall no different between groups, but weight gain was greater with pioglitazone (2.5 kg vs. placebo at 18 months and a total of 3.0 kg over 36 months). Patients with NASH but without diabetes also have been reported to improve with pioglitazone therapy [113, 114]. These results suggest that pioglitazone may alter the natural history of the disease in patients with (and without) T2DM and become the standard of care for the management of NASH.

There has been concern about the long-term safety of TZDs regarding weight gain, congestive heart failure (CHF), cardiovascular disease, bladder cancer, and bone loss (reviewed in depth in reference 115). Studies with rosiglitazone reported an improvement in hepatic steatosis, but not of necroinflammation or fibrosis in NASH [116, 117]. However, this TZD is no longer available in most countries and remains restricted in the United States over controversial findings of an increase in coronary events. Of note, no clear association between rosiglitazone and CVD could be firmly established after an in-depth review of all available evidence by the Food and Drug Administration [118]. The most common undesirable side effect of TZDs is weight gain. This is a consequence of an improvement in insulin sensitivity and consequently of fat accumulation in adipose tissue. It ranges from 2.5 [10, 113] to 4.7 kg [114] in RCTs of 12- to 36-month duration. This weight gain is comparable to that observed in RCTs with pioglitazone in studies of similar duration in patients with T2DM (from 2.5 to 3.9 kg) but somewhat higher than with sulfonylurea treatment (ranging from 1.2 to 4.2 kg) in these head-to-head trials [119–123]. A similar or greater increase in weight is typically observed with insulin therapy. Less often fluid retention may account for the gain in total body weight, but this appears to occur in a minority of patients as reported by Balas et al. [124] in an early proof-of-concept RCT of pioglitazone in NASH [74]. Congestive heart failure (CHF) may develop with TZDs if undiagnosed

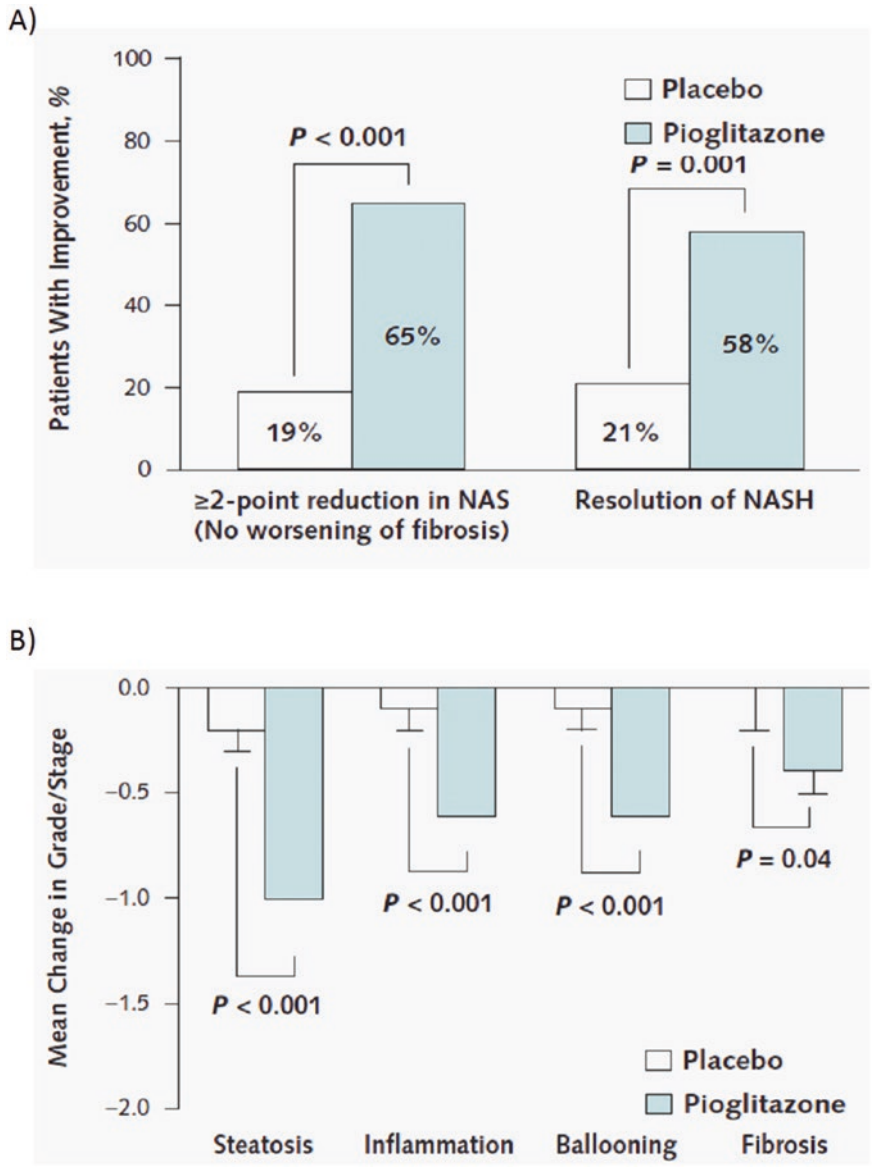

Fig. 4.1 Histologic changes after 18 months of pioglitazone or placebo

diastolic dysfunction is present [1, 115]. In a meta-analysis of 19 trials enrolling a total of 16,390 patients with T2DM, pioglitazone treatment was associated with a significant reduction (18%) in the primary outcome of death, myocardial infarction, or stroke ($P = 0.005$), but there was a higher rate of CHF with the TZD compared to non-TZD-treated patients (2.3% vs. 1.8% in the control group, P = 0.002) [125]. This calls for proper selection of patients, but given the high CV risk of patients with NAFLD and that several large RCTs have suggested a reduction in CV events with pioglitazone in patients with T2DM [122, 123, 125–128], reduction of CVD with pioglitazone would be of additional value. This awaits well-controlled long-term studies in this population. Bone loss may occur in women, a main reason for restricting use to adults only [115]. Recent large epidemiological studies have reported no association between pioglitazone and bladder cancer [129, 130], but the issue remains controversial.

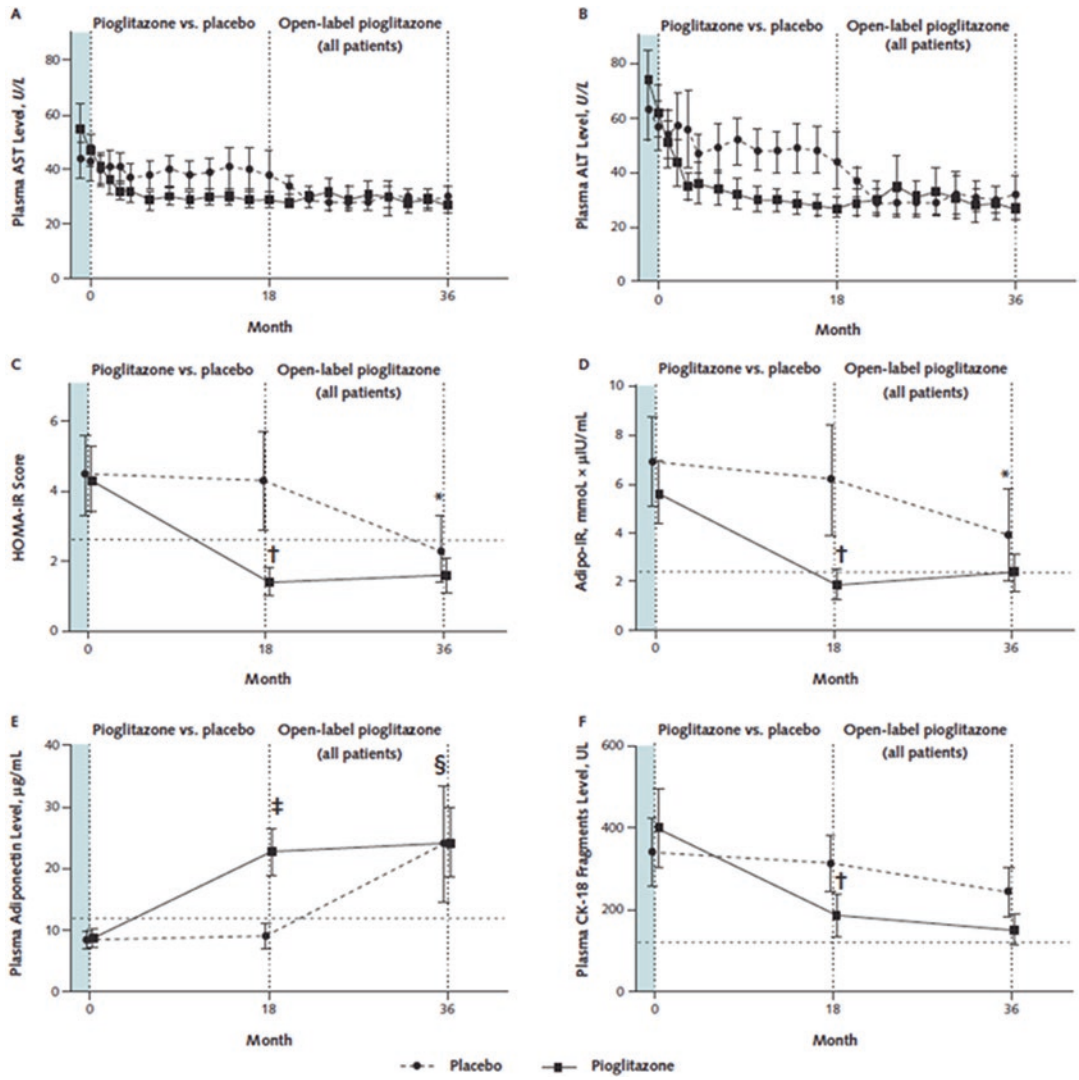

Fig. 4.2 Plasma aminotransferase concentrations and other biomarkers at baseline, after 18 months of pioglitazone or placebo and after 18 or 36 months of pioglitazone treatment. * $P \leq 0.042$ for change in placebo group after starting open-label pioglitazone. † $P \leq 0.026$ for effect of pioglitazone vs. placebo. ‡ $P < 0.001$ for effect of pioglitazone vs. placebo. § $P < 0.001$ for change in placebo group after starting open-label pioglitazone

Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists

GLP-1 receptor agonists (GLP-1RA) are being widely used for the management of patients with T2DM given their broad spectrum of effects on glucose metabolism and potential for weight loss. Having novel GLP-1 chemical structures that are resistant to rapid inactivation in plasma by DPP-4, these compounds have a much longer half-life ranging from hours to days instead of minutes. Agents approved by the Food and Drug Administration (FDA) fall into two classes based on their GLP-1 receptor activation: short-acting exenatide twice daily and lixisenatide once daily and longer-acting liraglutide once daily, exenatide once weekly, albiglutide once weekly, and dulaglutide once weekly. Semaglutide is a newer GLP-1RA in late phases of development with oral and once daily and weekly subcutaneous

formulations. Development of taspoglutide once weekly was discontinued because of unacceptable adverse events in phase 3 trials. Glucose lowering is from a combination of improved insulin secretion, restoration of more normal postprandial glucagon concentration, and inhibition of appetite acting on GLP-1 receptors in the hypothalamus [131]. There has been recent concern over the pancreatic safety of incretin-based agents for the management of diabetes from anecdotal reports of drug-induced pancreatitis, that although a rare event has serious clinical consequences. There are complex interactions between diabetes, pancreatitis, and pancreatic cancer with each serving as both a cause and a consequence of the others. However, careful evaluation of the available literature does not support the existence of additional risk of pancreatitis or pancreatic cancer from the use of incretin-based pharmacological agents for the treatment of T2DM [132].

It has been proposed that there may be direct binding to hepatic GLP-1 receptors that may account for at least part of the beneficial metabolic action in the liver [133, 134], but this has been highly contested as GLP-1 receptors have not been identified by other investigators using state-of-the-art methods [135–137]. A number of animal studies have shown that GLP-1 analogs improve hepatic insulin sensitivity and decrease steatosis [132, 133, 138, 139] and even fibrosis [140]. In humans, exendin-4 significantly reduces hepatic DNL in vitro and in vivo. More recently, exenatide has been reported to improve both hepatic and adipose tissue insulin resistance using a novel dynamic PET technique [141] and to reduce liver and epicardial fat [142] in patients with T2DM. These results were consistent with earlier small proof-of-concept studies [143–145].

A lowering of plasma AST/ALT and hepatic steatosis has been reported in several [146–149] but not all [150, 151] studies with liraglutide. However, the effect appears more linked to a decrease in body mass index (BMI) than a specific effect on the liver. In the most comprehensive study to date, the LEAN (liraglutide efficacy and action in nonalcoholic steatohepatitis) trial treated at 48 weeks 52 NASH patients with maximal doses of liraglutide [152]. Treatment led to resolution of NASH (defined as disappearance of hepatocyte ballooning without worsening of fibrosis) in 39% of patients compared to 9% on placebo. While the mean fibrosis score did not change significantly with liraglutide, fibrosis worsened in more patients in the placebo arm ($p = 0.04$). In a subset of patients who underwent more careful metabolic studies after only 12 weeks of liraglutide treatment, there was a modest improvement in glucose and lipid metabolism at the level of the liver and adipose tissue [153]. These results suggest that GLP-1RA have therapeutic potential for the treatment of NAFLD/NASH in obesity and T2DM.

Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

The mechanism of action of this class of agents is to inhibit the multifunctional protein DPP-4 that degrades glucagon-like peptide-1 (GLP-1), having a major impact on lowering postprandial glucose levels [154]. At the present moment, several agents are approved in the United States: sitagliptin, saxagliptin, linagliptin, and alogliptin. Vildagliptin is approved in Europe and other countries.

The potential of DPP-4 in NAFLD has not been fully tested although they have been reported to ameliorate hepatic steatosis and inflammation in animal models [155]. All studies have been rather small and short term (≤12 months). In a 6-month RCT in 44 patients with T2DM, Macauley et al. [156] found that vildagliptin significantly decreased liver triglycerides. The decrease in plasma aminotransferases correlated closely with the reduction in liver fat as expected from the close correlation between hepatic steatosis and plasma ALT levels [87]. However, there was no improvement in liver, muscle, or adipose tissue insulin sensitivity. In patients with T2DM, plasma aminotransferases have been reported to decrease with sitagliptin in Japanese patients with NAFLD [145, 157]. In contrast, in another study, plasma aminotransferases did not improve in patients with biopsy-proven NAFLD treated with sitagliptin [158], while at 12 weeks in 52 overweight

patients with T2DM treated with metformin and/or sulfonylurea found no significant differences in hepatic steatosis between groups treated with either liraglutide, sitagliptin, or placebo, with reductions in hepatic steatosis of 10%, 12.1%, and 9.5%, respectively (NS) [151]. It is believed that the role of DPP-4 inhibitors in NAFLD will be overall modest.

Sodium-Glucose Co-transporter 2 (SGLT2) Inhibitors

These agents induce a marked reduction of plasma glucose levels by inhibiting ~90% the reabsorption of glucose from the renal proximal tubule. At the present moment, there are three FDA-approved agents: dapagliflozin, canagliflozin, and empagliflozin. Weight loss and lack of risk of hypoglycemia are attractive features [159]. Recently, empagliflozin has been associated with a reduction in cardiovascular mortality [160].

Studies in rodents suggest that SGLT2 inhibitors may decrease hepatic triglyceride accumulation and inflammation [161, 162]. However, their benefit in NAFLD and in NASH is unknown at the present moment. Canagliflozin has been reported to reduce plasma AST/ALT concentration, but in this study, liver biopsies were not performed so their effect on liver histology could not be determined [163]. Use of dapagliflozin has been reported to decrease plasma ALT concentration in a 24-week trial in patients with T2DM [164] but not in another smaller trial [165]. At the present time, there are several ongoing trials with SGLT2 inhibitors in patients with NAFLD and T2DM.

Other Pharmacological Agents Currently Available

Many agents have been tested in clinical trials for the treatment of hepatic steatosis and/or NASH. Some are currently available and others are under investigation (Table 4.3), although most have not been specifically tested only for the treatment of patients with NASH in the setting of T2DM. Lipid-lowering drugs such as statins or ezetimibe have been extensively studied for the treatment of NAFLD/NASH [104, 166]. Statins can be safely given to patients with NAFLD/NASH to reduce their increased cardiovascular risk. Several small studies have suggested some benefit of statins in NAFLD/NASH, although usually they have been short-term, uncontrolled trials using surrogate primary endpoints (such as plasma aminotransferases or imaging) rather than liver histology [167]. There was no histological improvement in patients with NASH when statin therapy was compared to placebo in the only 12-month RCT with liver biopsies before and after treatment [168]. While statins do not improve the inflammation and fibrosis observed in patients with NASH, they are held as safe to use to prevent cardiovascular disease in this high-risk population.

In small uncontrolled studies including 8–15 patients, mixed results have been reported with ezetimibe on plasma ALT, liver fat, and fibrosis [169–171], while in a well-designed RCT in 50 patients with NAFLD treated for 24 weeks, ezetimibe did not significantly reduce liver fat on MRI-PDFF imaging [172], and its efficacy to improve steatohepatitis is unknown. Activation of peroxisome proliferator-activated receptor (PPAR) α receptors with omega-3 polyunsaturated fatty acids (PUFAs) upregulates several genes involved in mitochondrial fatty acid oxidation and may improve the lipid profile in patients with dyslipidemia or T2DM. This observation has led to several trials examining their potential to treat NAFLD/NASH. Most trials have been of limited value due to being small and uncontrolled trials. Some have reported decreases in plasma AST/ALT and in liver steatosis (reviewed in [104, 167]). Of note, the most recent and carefully designed studies with omega-3 fatty acids have been negative [173–176]. In summary, there appears to be no major role for PUFAs for the treatment of NASH.

Vitamin E is an antioxidant that may reduce hepatocyte oxidative stress in the setting of steatohepatitis [1, 8, 9, 24]. In nondiabetic patients with biopsy-proven NASH, vitamin E led to significant histological improvement in the primary endpoint (improvement in ≥2 grades in the NAFLD activity score [NAS], including hepatocellular ballooning and with no worsening of

Table 4.3 Pharmacological agents in phase 2b/3 for the treatment of steatohepatitis (NASH)

Pharmacological agent (manufacturer)	Therapeutic target	Mechanism of action
• BMS986036 (Bristol-Myers Squibb)	• Modulation of FGF21 metabolism	• Improvement of hepatic lipid and glucose metabolism, anti-inflammatory
• Cenicriviroc (Tobira Therapeutics)	• CCR2 and CCR5	• Inhibition of CCR2- and CCR5-mediated monocyte/macrophage infiltration and inflammation
• Elafibranor (Genfit)	• Modulation of hepatic PPARα and PPARδ pathways	• Stimulation of NEFA oxidation, improvement of lipid and glucose metabolism, prevention of inflammation
• Emricasan (Conatus Pharmaceuticals)	• Pan-caspase inhibitor	• Blockade of caspase activation and apoptosis with inhibition of fibrosis
• GR-MD-02 (Galectin Therapeutics)	• Galectin-3 inhibitor	• Prevention of inflammation and fibrosis
• Obeticholic acid (Intercept Pharmaceuticals)	• FXR agonist	• Regulation of glucose and lipid metabolism in the liver
• Px-104 (Phenex Pharmaceuticals/Gilead Sciences)	• FXR agonist	• Regulation of hepatic glucose and lipid metabolism
• GS-4997 (Gilead)	• ASK1 inhibitor	• Inhibition of hepatocyte endoplasmic reticulum stress and oxidative injury
• Aramchol (Galmed Pharmaceuticals)	• Fatty acid, bile acid modifier	• Regulation of hepatic stearoyl coenzyme A desaturase (SCD)-1 metabolism
• MSDC-0602K (Octeta)	• mTOT modulator	• Improvement in adipose/liver insulin sensitivity, anti-inflammatory
• Simtuzumab (Gilead Sciences)	• LOXL2 enzyme activity	• Inhibition of fibrosis by a LOXL2 monoclonal antibody
• Semaglutide (Novo Nordisk)	• GLP-1 receptor agonist	• Weight loss, glucose lowering. Improved insulin sensitivity (?)

fibrosis), compared to placebo ($p = 0.001$) [114]. However, resolution of NASH did not reach statistical significance (36% vs. 21%, $p = 0.05$), an endpoint only reached in the same study by pioglitazone (47%, $p = 0.001$ vs. placebo). Vitamin E also did not significantly improve histology in a large RCT in a pediatric population with NASH, although some histological features did improve (i.e., hepatocellular ballooning) [110]. In summary, vitamin E may be beneficial in patients with NASH without T2DM because it is relatively inexpensive and at the dose used (800 IU per day) it appears to be safe, although questions loom about its long-term use in terms of CVD risk and prostate cancer [177, 178]. However, its long-term efficacy has not been established in NASH. Its safety and efficacy in patients with T2DM, either alone or combined with pioglitazone, is being explored in a RCT that will report results to be reported in 2017 (NCT01002547).

Pentoxifylline is a nonselective phosphodiesterase inhibitor that may decrease inflammatory pathways in NASH, such as TNF-α [104, 167]. Several open-label, small studies reported mixed results on plasma aminotransferases and hepatic steatosis on imaging [179]. Two small 12-month studies in 20–30 patients with NASH reported either no benefit on histology [180] or some improvement [181] compared to placebo. It has not been tested in a population of patients with T2DM and NASH, and currently it is rarely used in the management of patients with NAFLD [182].

Future Treatments

The large of ongoing pharmacological agents under investigation is summarized in Table 4.3. The explosion of research in this field comes from relatively recent awareness about the high prevalence and major health risks linked to NASH, especially in patients with T2DM. Table 4.3 gives a glimpse into these clinical trials, their proposed mechanism of action, and pathways being targeted. Taken together, as reviewed in depth elsewhere [183], they will

offer a broad spectrum of treatment modalities for NASH should they meet regulatory approval. For instance, obeticholic acid, a farnesoid X receptor (FXR) [184] and elafibranor, a PPAR α/δ agonist, believed to combine the benefits on lipid metabolism of a PPARα/δ [185], reported some histological benefit in patients with NASH, which combined with weight loss by lifestyle or pioglitazone may offer a comprehensive and added benefit to such patients.

Rapid changes in the diagnosis and management of NASH are likely to occur in the near future as consensus is developing about the metabolic, cardiovascular, and liver-specific high risks associated with the combination of having diabetes and NASH. Such awareness is reflected in the fact that most ongoing RCTs testing new drugs for the treatment of NASH include a large proportion of patients with T2DM. Future approaches will take advantage of genetic testing for specific polymorphisms linked with worse prognosis in NASH (i.e., PNLPA3) [186], combined with novel plasma biomarkers and more accurate liver fibrosis imaging techniques [9, 24]. Because recent studies suggest that liver fibrosis is common in patients with T2DM, screening for NASH and specifically for fibrosis will become routine as done for microvascular complications of diabetes such as retinopathy, neuropathy, and nephropathy.

We are at an exciting time as we have for the first time a safe and effective long-term treatment in pioglitazone [10]. Combination of this TZD with other agents will soon become routine, and use of pioglitazone in NASH will be what metformin is for the treatment of T2DM – an inexpensive generic pharmacological agent used in the background to treat insulin resistance while other agents may target fibrosis or other/downstream liver-specific pathways. The promise to halt disease progression in patients with T2DM and NASH appears to be at reach. As novel agents become available, combination of several agents to treat NASH will become common practice, as currently for treating of diabetes, dyslipidemia, or hypertension. We are at the dawn of a new era where clinicians will be fully aware of the impact of NASH, and better treatment options will significantly improve the quality of life of many patients with T2DM and NASH, in whom their liver disease is today so often overlooked.

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Part II

Physiological Effects of Exercise in Type 2 Diabetes

Exercise Performance in Youth with Diabetes

5

Susan P. Gross, Amy D. Baumgartner, and Kristen Nadeau

The antecedents of adult cardiovascular disease (CVD) begin in childhood, as risk factors such as inactivity, obesity, dyslipidemia, and diabetes track from childhood to adulthood [1–3]. Accompanying the dramatic increase in childhood obesity and inactivity [4], type 2 diabetes (T2D) in youth increased considerably over the past 20 years [5]. T2D now accounts for up to 45% of new cases of diabetes youth, depending on age and ethnicity [6]. Disadvantaged racial/ethnic groups are at higher risk of T2D at all ages, but the association is especially strong in youth [6]. Although T2D rates in adult men and women are similar, adolescent girls have a 60% higher prevalence than boys [6, 7]. Potential explanations for the sex difference in youth include the earlier onset of puberty in girls vs. boys and the lower level of physical activity reported by adolescent girls [8, 9]. T2D occurring before the age of childbearing also translates to more pregnancies complicated by diabetes. Outcomes of pregnancies in youth/young adults with T2D are quite dismal [10], with high rates of congenital anomalies, and gestational diabetes mellitus greatly increases the risk of offspring themselves developing T2D [11]. Thus, youth-onset T2D increases the risk of CVD not just in an individual but also in future generation.

In addition to early-onset T2D translating to a long disease duration, youth-onset T2D is also now known to have a more aggressive trajectory than in adults [7]. β-cell decline is more rapid in youth and appears to translate to earlier and more aggressive macrovascular and microvascular complications [12–14]. For example, young adults with early-onset T2D have a much higher relative risk of developing CVD and diabetic kidney disease (DKD) compared with age-matched controls than adults with later-onset T2D [12, 15, 16]. This increased relative risk is most striking with myocardial infarction; young adults with T2D had a 14-fold increased risk of myocardial infarction compared with matched controls, which was almost exclusively driven by the increased risk occurring in young women [12]. Among the Pima Indians, T2D raises the risk of death from all causes three times if the age of onset is less than 20 years vs. 1.4 times if the age of onset is after age 20 [13]. Of great concern is that deaths among Pima and Canadian First Nations with early-onset T2D have occurred in middle age, significantly shortening the lifespan [13, 17]. One potential explanation for this more aggressive trajectory is that youth with T2D are often heavier, are less physically active, and are

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more likely to have multiple metabolic syndrome components at diabetes diagnosis than adults, all important contributors to CVD risk [7, 18]. In addition, T2D youth have more evidence of diabetes complications and CVD risk than youth with type 1 diabetes (T1D) of similar age and diabetes duration [14, 19]. Therefore, it is vital to address the contributors to T2D in youth to prevent early morbidity and mortality.

Poor physical fitness is associated with poor health overall, as well as specifically increased cardiovascular morbidity and mortality. For example, low cardiorespiratory fitness predicts mortality in normal weight and obese men and women and predicts cardiovascular events [20] and mortality in adults with diabetes [21]. Poor fitness is also associated with an unfavorable cardiovascular risk profile in children and adolescents [22–24]. Being physically fit increases the overall chance of survival [25, 26], reduces risk of metabolic syndrome [27–30], decreases the incidence of T2D [31, 32], improves cardiovascular function in adults who already have T2D [33, 34], and improves vascular function in youth with T2D [35]. Fitness also correlates with insulin sensitivity in youth [36], even early in life, and increased physical activity and decreased sedentary time correlated with current insulin sensitivity in 8–10-year-old youth and predicted changes in insulin sensitivity and secretion over time [37]. Exercise also helps improve metabolic control in T1D [38, 39]. Thus, exercise is a cornerstone of the prevention and treatment of diabetes [3, 40].

However, despite the extensive data indicating the importance of exercise to T2D, 60–80% of T2D adults do not get the recommended amount of exercise, and adherence to exercise programs is lower than in nondiabetics [41, 42]. Unfortunately, this phenomenon is not limited to adults. Physical activity and fitness in general have progressively declined among children in the USA [43, 44], especially in girls. African-American girls are even less active than white girls, having virtually no physical activity by the end of adolescence, and are also at higher risk for T2D [45]. Although activity has declined among all American youth, T2D youth are particularly inactive [46]. Data from Shaibi et al. report low physical activity levels in T2D youth [47], and baseline data from the large, multicenter TODAY study showed that T2D adolescents were even more sedentary than equally obese adolescents from NHANES [46]. Reason for decreases in physical activity includes a lack of safe outdoor play areas in many cities, as well as car vs. pedestrian travel. Outdoor play is often now replaced by television, video games, computers, and most recently, handheld electronic devices [48, 49]. Budgetary limitations and curriculum changes have also resulted in a de-emphasis on regular physical education programs in many schools.

Recent research has extended to objectively examining cardiorespiratory fitness in youth. In a study of 163 obese Hispanic 8–13-year-olds with a family history of T2D, no significant differences were found in recreational physical activity levels or treadmill VO_2peak; VO_2peak adjusted for sex, age, and body composition; or between obese youth with or without the metabolic syndrome [50] and with or without impaired glucose tolerance [51]. In contrast, Shaibi et al. [47] found lower VO_2peak in T2D adolescents vs. age- and sex-matched controls from NHANES, and self-reported physical activity, bicycle VO_2peak, and heart rate variability were all significantly lower in a study of 27 T2D adolescents in comparison to 105 adolescents with T1D [52]. However, BMI, puberty and habitual level of physical activity, diet, effort, and lean mass are potential confounders in these studies. Therefore, we studied VO_2peak and VO_2kinetics in T2D adolescents, compared to age, BMI, pubertal stage, and activity-matched controls, with additional control for diet and exercise 3 days prior to testing [47, 53]. Despite these highly controlled conditions and similar respiratory exchange ratio (RER) between groups, indicating similar effort, VO_2peak per kg and per kg fat-free mass and VO_2kinetics were abnormal in T2D vs. lean and in T2D vs. obese nondiabetic adolescents. Similarly, Regensteiner et al. found nearly identical findings in T2D adults [54], arguing that T2D confers a specific exercise defect that could make exercise more difficult. The VO_2kinetic data are particularly concerning, as they demonstrate abnormalities at the level of activities of daily life, which would impact day-to-day quality

of life and the likelihood that any exercise can be performed [55]. In addition, in a study of young (34 ± 10 years), healthy, and normal glucose-tolerant adults with either a first-degree relative (FDR) with T2D (n = 183) or no family history of T2D (n = 147), FDRs had significantly lower VO_2max per kg fat-free mass than controls, even after adjusting for sex, age, BMI, habitual physical activity, and insulin sensitivity [56]. Therefore, exercise impairment may precede glucose abnormalities in participants at risk for diabetes, making youth and non-glycemic factors critical to study.

VO_2max is potentially impacted by BMI, insulin sensitivity, autonomic function, cardiac output, vascular function, skeletal muscle performance and O_2 extraction, renal function, effort, glycemia, blood lipids, and respiration, among other factors. Obesity itself negatively impacts fitness, as we and others have documented decreased VO_2peak per kg and per kg fat-free mass in nondiabetic obese vs. lean youth who were controlled for age, pubertal stage, level of habitual physical activity, and acute diet and activity. Similarly, we found lower VO_2peak in T2D vs. nonobese T1D adolescents [53, 57].

Insulin resistance itself is likely a strong culprit in the link between T2D and exercise dysfunction. We and others found a clear relationship between insulin resistance and VO_2peak in adults [58, 59]. We also found VO_2peak per kg and per kg fat-free mass to be strongly inversely and independently correlated with whole-body insulin sensitivity as measured by a hyperinsulinemic-euglycemic clamp ($r = -0.83$, $p < 0.0001$) in T2D youth, suggesting that muscle insulin sensitivity is an important component of exercise function in T2D adolescents [53]. Moreover, we also found that adipose insulin resistance, as assessed by elevated free fatty acids, correlated independently with VO_2peak [53], further evidence of a link between insulin resistance and exercise dysfunction. Moreover, after an exercise intervention [60] in obese youth, improvement in predicted VO_2max correlated with reductions in fasting insulin levels [61], and in another trial in obese youth, change in fitness was related to change in insulin sensitivity in response to lifestyle modification and exercise [62]. Also supportive of the concept of insulin resistance impairing exercise function, Regensteiner et al. found that the insulin sensitizer rosiglitazone alone improved VO_2peak in T2D adults, even without an exercise intervention [58]. Rosiglitazone's effect may act directly through improvements in insulin sensitivity or via its ability to improve endothelial function or other factors [63].

Studies in severely obese adolescents show higher resting heart rates but lower maximal heart rates during exercise than lean controls [64], indicating autonomic dysfunction during exercise. In addition, there was evidence of decreased VO_2peak and heart rate variability, another sign of autonomic dysfunction, in T2D vs. T1D youth [52]. This autonomic dysfunction could contribute to decreased exercise ability, but further research regarding the role of autonomic defects in exercise function in youth is needed.

Data in T2D adults and youth suggest abnormalities in the cardiovascular system, which may limit nutrient delivery to the skeletal muscle [65, 66]. Cardiac findings in adults are more severe, including abnormalities in cardiac output [67], diastolic dysfunction [68], left ventricular hypertrophy, and atrial enlargement and eventually reduced ejection fraction, myocardial infarction, and heart failure [69]. Even subclinical changes in left ventricular (LV) function are common and reduce cardiac reserve and exercise capacity in T2D adults [70]. Early cardiac damage can be detected in youth with obesity and T2D, often correlated with BMI, but unlike adults, heart failure and significant ventricular dysfunction with reduced ejection fraction typically don't occur. In youth, LV mass is higher with increased lean mass and with increased fat mass [71], correlating with hyperinsulinemia and hyperleptinemia [72]. In TODAY, echocardiograms obtained at a mean age of 18 years with an average T2D duration of 4.5 years found lean LV mass to be at ~90th percentile [73], and predictors of higher LV mass and thickness were male sex, African-American race, BMI, blood pressure (BP), and HbA1c. Among girls, those with T2D were also found to have increased LV mass vs. T1D and lean controls but not different vs. obese nondiabetic girls [74]. Reports regarding diastolic dysfunction using

echocardiogram are conflicting, with one study showing normal diastolic function [53] and two showing worse diastolic function, although the T2D participants in the latter two studies had higher BMI which correlated with diastolic function, a potential confounder [74, 75]. More recently, using MRI in a BMI-matched group, Pinto et al. reported 10–13% smaller LV end-diastolic volume in T2D adolescents, consistent with LV stiffness and diastolic dysfunction, as well as decreased LV reserve with exercise [76]. Finally, regarding systolic function, in TODAY, mean LV shortening fraction was in the high normal range, correlated with BMI and systolic BP [73], and Shah et al. reported increased systolic function and lower wall stress that did not differ from obese controls [75]. Using speckle-tracking echocardiography, we reported reductions in LV strain in T2D adolescents vs. obese controls, which importantly correlated with VO_2peak as evidence of cardiac dysfunction contributing to decreased exercise capacity [66].

Multiple studies also implicate vascular disease in T2D, including reduced blood flow, endothelial dysfunction, arterial stiffness, and increased carotid intimal medial thickness (cIMT) [77, 78]. We found that T2D adolescents had significantly less limb blood flow as assessed by venous plethysmography than lean youth, which correlated negatively with VO_2peak/kg ($r = -0.59$ $p < 0.0001$), suggesting that endothelial dysfunction contributes to exercise dysfunction. Studies also demonstrate elevated pulse wave velocity (PWV) in T2D youth vs. normal weight controls, indicating arterial stiffness [79]. T2D youth also had higher cIMT vs. lean and obese controls [80]. Moreover, Bacha et al. demonstrated a significant association between cIMT and HbA1c, whereas PWV was more related to insulin resistance and inflammation [81]. Therefore, more research is needed on the vascular contribution to exercise dysfunction in T2D youth.

In addition to the heart and vasculature, intrinsic skeletal muscle properties also contribute importantly to fitness. Adults with T2D have evidence of abnormalities in skeletal muscle blood flow and glucose transport [82] as well as in oxidative enzyme activity [83]. Moreover, capillary density is decreased in T2D adults, which would limit skeletal muscle perfusion [84]. T2D adults also have an increased ratio of type IIb-to-type I muscle fibers [84], which could cause dysfunction in muscle metabolism. Finally, muscle mitochondrial abnormalities are reported in some adult T2D studies [85]; however, the relationship is extremely complex and may differ by cell type [86–89]. Less is known about the skeletal muscle in youth, since biopsies are difficult to perform in children. However, using magnetic resonance spectroscopy (MRS), we demonstrated that T2D youth with reduced VO_2peak had elevated intramyocellular lipid (IMCL) [53]. However, IMCL was not independently correlated with VO_2peak. Moreover, an exercise training study in obese youth showed an increase in IMCL with exercise training that correlated with improved resting energy expenditure and respiratory quotient, which may reflect greater muscle lipid oxidative capacity [62]. Therefore, IMCL does not seem likely to impair exercise function. In a more recent cohort, we demonstrated that muscle mitochondrial function assessed with MRS was abnormal in T2D adolescents [90]. Specifically, ADP time constant, a blood flow-dependent mitochondrial function measure, was slowed, and oxidative phosphorylation rates were also lower. These findings further support mitochondrial and blow flow abnormalities as potential contributors to muscle dysfunction and argue for further research on vascular and mitochondrial function in T2D youth.

Diabetic kidney disease (DKD) is closely related to vascular disease and may also contribute to exercise dysfunction. In support, in T2D adults, microvascular disease in the form of DKD and neuropathy correlates with reduced exercise capacity [91]. We also recently found that renal function as measured by estimated glomerular filtration rate was inversely associated with VO_2peak per kg and VO_2peak per kg lean mass in adolescents with T1D, even after adjusting for sex, pubertal stage, insulin sensitivity, HbA1c, systolic blood pressure, and LDL cholesterol [92], arguing that impaired renal function may impact exercise function in youth with diabetes. More research is now required in youth with T2D, who present with signs of DKD even earlier than youth with T1D [15].

Another factor impacting exercise capacity is the perceived level of exertion at any given workload. For example, a small study of adult women with T2D found a higher level of perceived exertion when compared to obese, nondiabetic, or lean controls at 20 watts of bicycle exercise, even when corrected for relative work intensity [93]. A larger study failed to find a difference in perceived exertion in T2D women, but those with T2D had higher lactate, and rate of perceived exertion correlated with higher lactate, higher heart rate, and hypertension [94]. We found no differences in perceived exertion in a small study of T2D vs. obese nondiabetic vs. lean nondiabetic controls who were matched for habitual level of physical activity [53]. However, a larger study reported a higher level of perceived exertion in obese nondiabetic youth at equal levels of work, leading to exercise for shorter duration [95] and a poorer performance during sustained exercise than lean controls [64]. Therefore, perceived exertion may need to be taken into account when designing exercise training studies in obese/T2D youth.

The literature on exercise training response in T2D is mixed. A meta-analysis determined that home exercise interventions in T2D adults can improve VO_2peak [96], and one study found that an exercise training intervention improved VO_2peak in T2D adults more than in nondiabetic adults [97]. However, another study found no change in VO_2peak but an improvement in ventilatory threshold and time to exhaustion in T2D adults given exercise training vs. T2D adults in usual care [60]. Regular exercise in T2D adults does clearly improve insulin sensitivity [98], HbA1c, and diastolic blood pressure [99], and self-directed exercise has been found to be beneficial for T2D adults regarding glycemic control, physical characteristics, functional measures, and other metabolic outcomes [96]. However, established CVD, which disproportionately affects people with T2D, is not reduced by regular exercise, and heart disease remains the leading cause of death for people with T2D, arguing that more vigorous exercise may be needed to improve LV dysfunction and CVD [70]. In adults with prediabetes, a lifestyle intervention including a goal of least 150 min of physical activity per week (approximately 30 min 5 days per week) reduced the progression to T2D vs. placebo by 58% and did so more strongly than the 31% reduction in the metformin arm [32]. However, due to the low incidence of T2D in youth overall, no RCTs have been completed in youth to date to assess whether physical activity or exercise prevents T2D or the dose of physical activity required to optimally manage T2D. Moreover, adolescents are still experiencing growth and the hormonal milieu and insulin resistance of puberty [100] and have not yet reached peak muscle mass, bone strength, or cognitive maturation. In addition, teenagers live in families, attend school, and exist among the social and psychological issues of adolescence, all affecting their response to potential interventions and limiting the ability to extrapolate from adult studies [101].

Various controlled, traditional, school-based, and residential exercise intervention studies done in obese nondiabetic youth report improvement factors such as fitness (VO_2peak, muscle strength, and endurance) and cardiometabolic factors including body composition (BMI, visceral and total-body adiposity, waist circumference, waist-to-hip ratio), insulin sensitivity (fasting insulin, homeostasis model assessment for insulin resistance, postprandial glucose), lipids (HDL, triglycerides, LDL, and LDL particle size), vascular function (blood pressure, endothelial function, microvascular endothelial function, endothelial progenitor cells, endothelial microparticles, endothelin-1), inflammation (fibrinogen, high-sensitivity C-reactive protein, IL-6), and adiponectin [51, 62, 102–105]. Therefore, exercise can improve fitness and multiple markers of cardiometabolic health in obese nondiabetic pediatric participants, often despite the absence of weight loss, but specific data is needed in T2D youth. In a very small study of T2D youth [35], eight youth were randomized to a 12-week exercise program consisting of three, 1 h supervised sessions/week of combined aerobic (65–85% of maximum heart rate) and resistance (55–70% of maximal volitional contraction) training vs. five youth to standard care. Youth in the exercise training group

had improved endothelial function, microvascular function, lean mass, and muscle strength, but there were no changes in VO_2peak, body weight, BMI, or insulin sensitivity as assessed by hyperinsulinemic-euglycemic clamp. Further, 12-week post-study cessation, improvements in vascular function were reversed. In the TODAY study of T2D youth, metformin plus an intensive lifestyle intervention (goal of a minimum of 200 min/week of moderate to vigorous intensity activity; up to 300 min per week for participants who entered the study already engaging in some regular, physical activity) did not add benefit vs. metformin alone in terms of the primary outcome of glycemic control or secondary outcomes of CVD risk factors (hypertension, low HDL, hypertriglyceridemia, and microalbuminuria). However, the exercise intervention did have a favorable effect on BMI and fat mass vs. metformin plus rosiglitazone [7]. These results could argue that introducing a lifestyle intervention after the diagnosis of T2D may be too late to impact glycemic control or standard CVD markers or alternatively that increased levels of physical activity are more difficult to achieve in youth with T2D than in nondiabetic youth or in adults.

In summary, evidence to date suggests that adolescents with T2D have decreased maximal and submaximal exercise performance, not entirely explained by their obesity or low levels of physical activity. In addition to the negative impacts of obesity and inactivity, there are numerous other potentially modifiable contributors to exercise dysfunction in T2D youth. In particular, there are inadequate data on T2D prevention or therapy in youth and on how standard T2D medications affect exercise capacity or its correlates in youth. Based on studies in adults and in adolescents with obesity and insulin resistance, exercise interventions appear helpful, yet current data do not support typical approaches to exercise intervention in T2D youth. Therefore, since exercise capacity predicts cardiovascular and all-cause mortality, it is critical to further assess the impact of standard T2D treatments as well as more novel interventions focused on the contributors to exercise dysfunction in T2D adolescents summarized in this chapter. In conclusion, due to the current epidemic of obesity and T2D in pediatrics, and its potential to prematurely end lives, we require additional data on why adolescents with T2D are unable to exercise and how to best intervene.

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Exercise Performance Impairments and Benefits of Exercise Training in Diabetes

6

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Introduction

Low cardiorespiratory fitness and physical inactivity consistently predict increased mortality for men and women, for obese and normal weight individuals, and for people with type 2 diabetes mellitus (T2DM) [1–11]. Sedentary behavior clearly leads to both the development of diabetes and also worse cardiovascular (CV) outcomes for people with diabetes [12–15]. Physical inactivity has become so common that one group coined the term—"sedentary death syndrome"—to call attention to its dangers [16]. This model proposes that humans evolved in agrarian societies to require physical activity for long-term health and that sedentary behavior is maladaptive.

Exercise is a cornerstone of treatment for people with T2DM [17]. Over 80 years ago, Allen and colleagues reported that a single bout of exercise lowered the blood glucose concentration of patients with diabetes and improved glucose tolerance temporarily [18]. Since that observation, numerous studies have confirmed that regular exercise improves glycemic control for the person with T2DM and have identified several additional benefits [19–28]. For example, meeting or exceeding the physical activity guidelines of 150 min per week of moderate intensity physical activity is linked to improvements in all-cause mortality, blood pressure, incidence of breast/colon cancer, mood, sleep, and physical function [29]. Paradoxically, despite extensive data indicating the importance of meeting physical activity guidelines, 60–80% of adults with T2DM do not meet these guidelines, and adherence to exercise programs is low in these patients [30, 31]. This avoidance of exercise is likely due to both behavioral and

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functional factors. Behavioral factors leading to avoidance of exercise may include fear of injury as well as other diabetes-related concerns—a fuller description of these behavioral barriers to exercise may be referenced elsewhere as it is outside the scope of this chapter [32–35]. An important functional reason for avoidance of exercise may relate to the linkage between type 2 diabetes mellitus (T2DM) and impairments in exercise performance, even in early, uncomplicated T2DM [36–39].

T2DM Impairs Exercise Performance

Introduction

Persons with T2DM are at higher risk than persons without diabetes for CV disease (CVD), including coronary heart disease, stroke, and peripheral artery disease due to accelerated atherosclerosis [15, 40]. Thus, we would expect that the CV benefits of exercise training to be especially beneficial in people with T2DM. Specifically, exercise training improves blood pressure, dyslipidemia, cardiorespiratory fitness, and insulin resistance/glycemic control, and these factors are important because they are linked to CV morbidity and mortality [15, 41, 42]. Because these benefits do not require formal exercise training, but also accrue with ≥150 min per week of brisk walking or other moderate-intensity physical activities, people with T2DM have flexibility to select from a variety of moderate-intensity physical activities to improve their DM management [29]. However, despite the dramatic CV and metabolic benefits of regular physical activity, people with T2DM are generally less active than nondiabetic people [30, 31]. While some aspects of this behavior may be accounted for by sedentary lifestyle choices that contributed to the initial development of diabetes, recent evidence suggests that pathophysiological factors may also contribute to avoidance of physical activity [43]. This chapter will address the consistent evidence of impairments in cardiopulmonary exercise performance in people with T2DM, even in the absence of clinically apparent CV disease. In terms of cardiopulmonary exercise performance, impairments have been observed in the gold standard cardiorespiratory fitness measure of maximal oxygen consumption (VO_2max) and also in terms of the kinetics of oxygen consumption during submaximal exercise (VO_2 kinetics). These data suggest that the cause and effect relationship of the correlation between low physical activity and diabetes may be bidirectional.

Maximal Exercise Performance

As compared with sedentary non-DM people matched for age and activity level, sedentary people with T2DM clearly have a reduced CV exercise performance demonstrated by a lower VO_2max (Table 6.1) [22, 23, 38, 43–54]. The overall reduction in VO_2max between healthy persons and persons with T2DM is approximately 20%. Of note, differences in effort across study groups do not explain the VO_2max differences observed, as those with T2DM and the nondiabetic groups each performed testing at similar levels of maximal effort, based on the respiratory exchange ratio of carbon dioxide to oxygen (Table 6.1) [49, 55, 56]. VO_2max reductions have been observed across the lifespan in T2DM: adolescents, middle-aged adults, and older adults with T2DM had lower VO_2max than their age-similar counterparts without T2DM [22, 23, 38, 43–54]. Interestingly, limited data suggest that although both men and women with T2DM demonstrate the exercise abnormality, women with T2DM often have a greater degree of exercise impairment than men with T2DM [48, 52, 57]. The mechanisms for lower VO_2max in people with T2DM have not been completely elucidated. However, based upon available data, central cardiac and peripheral vascular factors appear to limit systemic oxygen delivery to exercising muscles; in addition, defects at the level of the exercising skeletal muscle tissue may also play a role. These potential mechanisms will be summarized later in this chapter and will be addressed in further detail elsewhere in this book in Chap. 11.

Table 6.1 Maximal exercise performance is impaired in type 2 diabetes mellitus

	Lean control	Obese control	T2DM
Age (years)	36 ± 6	37 ± 6	42 ± 7
Fat-free mass (kg)	42 ± 7	48 ± 5	47 ± 5
HgbA1c	6.0 ± 0.6	5.3 ± 0.5	9.0 ± 0.4*
Maximal exercise response			
VO_2max (pre)	25.1 ± 4.7	21.8 ± 2.9	17.7 ± 4.0*
VO_2max (post)	26.0 ± 6.0	23.0 ± 1.8**	22.4 ± 5.5**
Maximal RER	1.13 ± 0.08	1.12 ± 0.06	1.16 ± 0.13

Data are mean ± SD (Printed with permission from *J. Applied Physiol* and *Diabetes Care* [38, 47])
T2DM; type 2 diabetes mellitus; *RER*; respiratory exchange ratio
*$P < 0.05$ for difference between T2DM and controls. **$P < 0.05$ for difference between pre and post training

Submaximal Exercise Performance and Oxygen Uptake Kinetics (VO_2 Kinetics)

Exercise abnormalities in T2DM have also been observed during less vigorous physical activity (i.e., submaximal exercise) in some, but not all, studies. One key measure of submaximal exercise performance is VO_2 kinetics—a measure of the rate of adaptive increase of VO_2 following the onset of constant work rate exercise. Slower VO_2 kinetics signify impairments in the integrated systems of cardiorespiratory gas exchange, muscle oxidative metabolism, oxygen delivery, or some combination of these problems [58].

To understand how VO_2 kinetic measurements are calculated, it is important to understand the three phases of the VO_2 kinetic response to the onset of exercise [58, 59]. In the first phase, pulmonary gas exchange in the lungs increases abruptly for the first 15–20 s as cardiac output and pulmonary blood flow initially increase (cardiodynamic phase or phase 1). Following the circulatory transit delay of phase 1 (usually about 20–40 s), VO_2 then increases exponentially (phase 2), reflecting the increase of muscle VO_2 as tissue oxygen extraction and blood flow increase to meet the exercise demand [60, 61]. Phase 2 is the primary component of VO_2 kinetics and is described by a time constant (tau_2) reflecting the time to reach ~63% of the increase in VO_2. Phase 2 ends as muscle VO_2 and pulmonary gas exchange reach a steady state. Phase 3 is the steady-state VO_2 during exercise below the lactate threshold.

In the healthy individual, VO_2 kinetics may be limited by either a maldistribution of blood flow to the working tissues limiting O_2 transfer or by the inertia of oxidative metabolism [60, 62]. In disease states where oxygen delivery is compromised, as with CVD, VO_2 kinetics are also limited by the body's ability to deliver oxygen to working muscle and therefore may directly reflect impaired oxygen delivery [63, 64]. Since impaired cardiac output and/or impaired local distribution of blood flow to exercising muscles are components of the O_2 delivery process, VO_2 kinetics may thus provide a measure of the effectiveness of the CV system in delivering sufficient oxygen to satisfy the requirements of muscle during exercise [65]. In this regard, the time constant of phase 2 VO_2 kinetics is prolonged in patient groups with abnormal CV responses to exercise and is sensitive to alterations in oxygen exchange at the lungs, cardiac output, blood flow distribution, oxygen diffusion, and rates of tissue oxygen consumption.

A slowed VO_2 kinetic response has been reported in some [38, 51, 53, 56], but not all, prior studies of people with T2DM [48–50]. The reason for the inconsistent association between T2DM and slowed VO_2 kinetics is not fully clear. One possibility is age differences in the populations studied [38, 48–50, 56]. For example, across these prior studies, the tau_2 measure of VO_2 kinetics appears to be slower in older nondiabetic control participants as compared to the younger nondiabetic control adolescents and premenopausal women [38, 48–50, 56], consistent with the notion that aging in older control participants may eradicate differences that are more notable in younger populations. One might conclude that the VO_2 kinetic differences observed in younger populations with T2DM may represent a phenotype of premature CV aging [43]. Other demographic differences may also be relevant predictors of VO_2 kinetic differences by T2DM status, such as duration of T2DM.

To further evaluate the potential causes of theT2DM VO_2 kinetic impairment, we have conducted VO_2 kinetic testing in conjunction with measures of skeletal muscle oxygenation using near infrared spectroscopy in 11 T2DM and 11 healthy, sedentary subjects [66]. This combination of measurements allowed the investigation of changes in oxygen delivery relative to VO_2 at the level of the exercising muscle. We found slowed VO_2 kinetics and an altered profile of muscle deoxygenation following exercise onset in the T2DM subjects (Fig. 6.1). As compared with healthy participants, these data indicate that a transient imbalance of muscle oxygen delivery relative to muscle VO_2 may occur with the onset of exercise in people with T2DM, consistent with a subnormal increase in microvascular blood flow in the skeletal muscle during exercise. Interestingly, in this mixed set of men and women with T2DM, there were no differences in heart rate kinetics compared with sedentary control subjects, suggesting that the exercise abnormality during moderate exercise may be mediated more so by peripheral factors limiting oxygen delivery rather than central CV defects. Further studies are under way to investigate the roles of abnormal control of peripheral blood flow and muscle metabolism during exercise on the observed exercise impairment in T2DM.

Potential Mechanisms Leading to Impaired Exercise Performance in T2DM

There are several potential pathogenic mechanisms that may contribute to the decreased capacity for exercise in T2DM. These include metabolic and non-metabolic sequelae of diabetes in the vasculature and in cardiac and skeletal muscle. These are discussed in the following sections.

Hyperglycemia

The relationship between markers of glucoregulation and exercise has been investigated to determine whether these factors are likely determinants of exercise performance. To date, associations have not been found between hemoglobin A_1c or

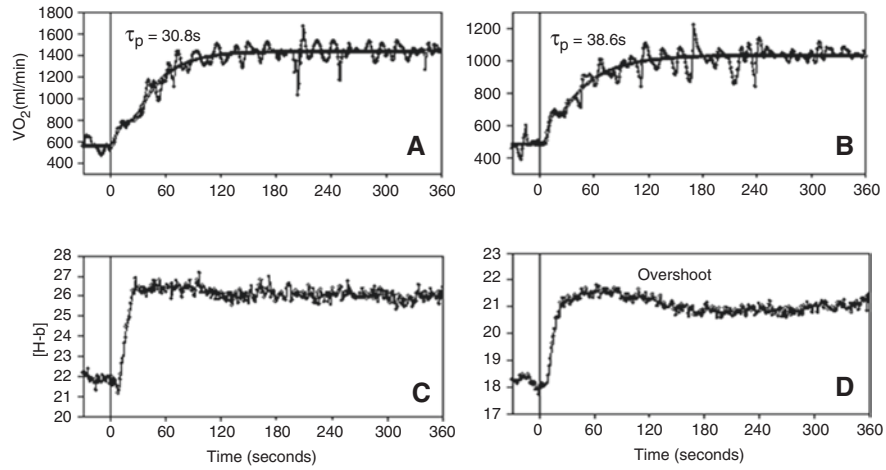

Fig. 6.1 Pulmonary VO_2 kinetic and skeletal muscle deoxygenation ([HHb]) responses during the transition from unloaded cycling to moderate constant work rate exercise in a healthy control (**A**, C) and T2DM subject (**B**, **D**) [66]. Loaded cycling beings at time = 0. τ_p, time constant of phase 2 pulmonary VO_2 kinetics. *Solid dark lines* represent curve fit of VO_2 kinetic response. Note slower VO_2 kinetics (**B**) and overshoot of [HHb] response (**D**) following onset of loaded exercise in the T2DM subject (Reprinted with permission from Diabetes Care)

fasting serum glucose concentration and exercise performance [39, 45, 46, 56, 67–69]. One trial did find a significantly blunted heart rate response to exercise in people with T2DM and worse glycemic control compared to people with T2DM and better glycemic control (hemoglobin A_1c), but this did not translate to impairments in VO_2max between study groups [69]. In sum, although a single bout of exercise improves glycemic control (albeit temporarily), the relationship between markers of glycemic control and exercise performance does not appear to be directly related.

Insulin Resistance

In contrast to hyperglycemia, several reports have suggested that insulin resistance is associated with reduced VO_2max in T2DM [56, 70–72]. Insulin resistance has also been reported to be inversely correlated with VO_2max in several other disease states, including heart failure and chronic renal failure [73, 74]. This supports an interesting theory that the decrement in exercise capacity is related in some way to abnormalities of insulin signaling and function—one consideration for this theory is that the decrement in exercise capacity may relate to the dysmetabolic milieu that typically accompanies insulin resistance, rather than being strictly related to abnormal insulin signaling and function, per se [75, 76]. Consistent with this working theory, studies have observed exercise defects in nondiabetic people with insulin-resistant conditions of metabolic syndrome [77–82] and polycystic ovarian syndrome (PCOS) [83]. Among subjects with PCOS compared to age- and weight-matched controls, the significant decrement in VO_2max correlated with all measures of insulin resistance studied [83].

The causal relationship between insulin resistance and impaired exercise performance is not well understood. More recent trials have investigated the use of a pharmacological intervention to improve insulin sensitivity. Favoring the theory that insulin resistance leads to worse exercise performance, insulin-sensitizing medications have demonstrated improvements in exercise performance. In two separate clinical trials of adults with uncomplicated T2DM randomized to rosiglitazone or placebo, those in the rosiglitazone treatment arm experienced a significant 7% improvement in VO_2max [70, 84]. In both studies, improvement in VO_2max also correlated with insulin sensitivity [70, 84].

While exercise clearly improves insulin resistance, the above results support the hypothesis that insulin resistance also negatively effects exercise capacity. Other literature lends support to multiple possible mechanisms for such a relationship, including insulin resistance at the level of the vasculature leading to endothelial dysfunction (in both peripheral and cardiac circulation), insulin resistance at the level of the muscle (cardiac and skeletal) leading to a decline in mitochondrial content and/or function, and insulin resistance at the level of the heart and/or skeletal muscle leading to inefficient substrate utilization [70, 84]. Recent attention has been focused on changes in substrate utilization and metabolic inflexibility in insulin resistance. Simply stated, insulin promotes carbohydrate utilization. In insulin resistance, the absence of sufficient insulin signaling causes metabolism to rely more heavily on fatty acids, a less oxygen-efficient fuel source. These mechanisms and their potential relationship to exercise capacity are discussed further in the following sections.

Endothelial Dysfunction

One possible mechanism for the exercise abnormalities observed in persons with T2DM invokes endothelial dysfunction as a contributing factor. In healthy individuals with normal endothelial function, the increased vascular shear stress induced by exercise leads to an acute vasodilator response mediated by nitric oxide [85–87]. In contrast, endothelial dysfunction in T2DM leads to a deficient endothelial vasodilator response to the metabolic demands of exercise in the cardiac and skeletal muscle. In this scenario, exercise capacity may be partly limited by peripheral blood flow and/or coronary blood flow. The measurements of endothelial function that are abnormal in adults with T2DM, as compared to nondiabetic controls, include the vascular response to the stress of exercise [88, 89] and also the vascular response at rest to pharmacological stresses of vasodilators and cuff ischemia [90, 91].

Every insulin-resistant state studied to date has been found to have associated endothelial dysfunction [92]. It has been proposed that insulin resistance at the level of the endothelial cell is invariably associated with endothelial dysfunction [92]. This is supported by the observation that obese subjects with and without T2DM have endothelium-dependent vasodilation that is reduced by ~50% compared with lean control subjects [43, 93].

Support for the ability of endothelial dysfunction alone to cause exercise defects comes from the studies of Jones et al. using N-nitro-L-arginine methyl ester (L-NAME) to reduce nitric oxide (NO) levels prior to performing exercise. They found a decrease in maximal oxygen uptake (VO_2max) with L-NAME use that correlated with the expected reduction in vasodilation and decreased perfusion of large muscle groups [94]. However, in contrast to our studies with T2DM subjects, L-NAME induced faster VO_2 kinetics than were observed without L-NAME use [94, 95]. This could be explained by recent studies in animals and man demonstrating a role for NO in the regulation of mitochondrial oxygen and substrate utilization. Inhibition of NO synthase with L-NAME in dogs results in a marked increase in glucose oxidation and a decrease in free fatty acid metabolism [96]. It has been proposed that NO interferes with oxidative metabolism by competing for O_2 binding at cytochrome c oxidase in the mitochondrial electron transport chain [97–99]. Overall, inhibition of NO synthesis by L-NAME decreases VO_2max and improves submaximal exercise performance (faster VO_2 kinetics). The fact that both VO_2max and VO_2 kinetics are affected negatively in diabetes implies that changes in exercise parameters in diabetes cannot be fully explained by changes in NO synthesis or, presumably, endothelial dysfunction alone.

In summary, people with T2DM have endothelial dysfunction that impairs the exercise demand-dependent increases in blood flow to skeletal muscle. A range of effective treatments for endothelial dysfunction in T2DM have been identified, including supervised exercise training [100] and medications that improve insulin resistance (thiazolidinedione) [101] or that improve lipids/inflammation ("statins") [102, 103]. Although effective treatments for endothelial dysfunction have been identified in T2DM, the mechanisms by which endothelial dysfunction develops and its exact relationship to the exercise abnormalities of T2DM remain areas of active investigation.

Myocardial Dysfunction

There are likely to be cardiac factors contributing to the exercise abnormalities of T2DM, as well. Evidence has accumulated for the existence of myocardial dysfunction that is unrelated to coronary artery disease in many individuals with diabetes, even in early uncomplicated diabetes in youth and adults [104–114]. This condition has been termed "diabetic cardiomyopathy," and in people with T2DM, this phenotype is defined as impaired left ventricular (LV) diastolic function in the absence of major coronary disease, valvular disease, congenital heart disease, or hypertension [115]. In people with T2DM, diastolic dysfunction is the key myocardial abnormality—LV ejection fraction is usually preserved [104–111, 115]. Recent studies in youth have identified that some of the earliest CV abnormalities to develop in adolescents with T2DM include measures of diastolic dysfunction, increases in LV mass, and measures of LV strain that suggest subclinical myocardial fibrosis [112–114, 116].

A broad spectrum of diastolic functional abnormalities exists in people with T2DM, ranging from the earliest and mildest form of diastolic dysfunction that is unmasked only during exercise [106, 108] extending to a moderately advanced presentation where asymptomatic diastolic dysfunction is also identifiable at rest [104, 107, 109, 110, 117] and including the most severe form that presents as symptomatic diastolic heart failure, also termed heart failure with preserved ejection fraction [118]. Diastolic function tends to worsen over time with typical aging, but the influence of T2DM on diastolic dysfunction has been likened to a form of "premature aging" [43]. In support of this premature aging theory, changes in diastolic function over time

were fivefold worse in a study of people with T2DM as compared to a separate cohort of people without T2DM [119, 120].

Some studies have demonstrated that cardiac diastolic dysfunction correlates with impairments in CV exercise capacity in heart failure [121], in diabetes [108], as well as in normal subjects [122]. In contrast, some studies have not observed an association between diastolic dysfunction and cardiorespiratory fitness [123, 124]. One reason for this discrepancy may be the lack of sensitivity of measures of diastolic dysfunction at rest to identify participants who will exhibit diastolic dysfunction with exercise. For example, in our studies of exercise dysfunction in T2DM, we observed that pulmonary capillary wedge pressure rose more steeply and to a greater level with exercise in T2DM than in controls, consistent with diastolic dysfunction unmasked by exercise [125]. Using noninvasive echocardiographic techniques, a separate study has also reported abnormalities in diastolic dysfunction that were observed only during exercise and were not present at rest [126]. Thus, while the prevalence and clinical significance remain unclear, it is possible that preclinical manifestations of diabetic cardiomyopathy play a significant role in the exercise defects seen in people with early and uncomplicated T2DM—adolescents with T2DM may be even be affected more so than adults with T2DM [112, 114, 127].

The mechanisms responsible for the diastolic dysfunction of T2DM have been comprehensively reviewed elsewhere [115, 128]. In brief, the mechanistic underpinnings of diastolic dysfunction appear to include coronary microvascular endothelial dysfunction, myocardial hypertrophy, and cardiac interstitial fibrosis (Fig. 6.2) [115]. Support for the important role of coronary artery endothelial dysfunction comes from several studies, including biomarkers of endothelial dysfunction on myocardial biopsies [129] and by clinical findings that diastolic dysfunction during exercise correlates with reduced myocardial perfusion during exercise [125]. The multi-faceted origins of coronary endothelial dysfunction relate to a milieu of oxidative stress, hyperglycemia, insulin resistance, lipotoxicity, exposure to advanced glycation end products deposited in the endothelium and myocardium, and reduced capillary density (i.e., microvascular rarefaction) [115, 130, 131]. In T2DM, coronary endothelial dysfunction leads to abnormal left ventricular remodeling by lowering the bioavailability of nitric oxide to the myocardium and by lowering the protein kinase G activity in the adjacent cardiomyocytes [115]. Finally, high insulin levels and lower protein kinase G activity lead to myocardial hypertrophy, reactive interstitial fibrosis, and stiffer cardiomyocytes (i.e., high measurements of passive force). Providing proof of concept for the central role of protein kinase G in this pathway, the administration of protein kinase G in vitro to cardiomyocytes from patients with diastolic dysfunction significantly improved the outcome of passive force [132].

Skeletal Muscle Changes in Diabetes

The distinct role of skeletal muscle in the impaired exercise responses of persons with T2DM has not been completely elucidated. Current data suggest that people with T2DM experience insufficient oxygen supply for the oxidative demands of the skeletal muscle during exercise. It is not well understood to what extent the insufficient oxygen supply to skeletal muscle is due to cardiac or vascular defects in oxygen delivery as compared to defects in oxidative metabolism, but each pathway is likely to contribute to the exercise defects seen in people with T2DM.

In addition to the cardiac abnormalities that may impair oxygen delivery during exercise, prior studies have demonstrated vascular oxygen supply defects to exercising skeletal muscle in people with T2DM as compared to control participants without T2DM, based on impaired limb blood flow in large conduit arteries [88, 91, 133–136]. Such defects in impaired limb blood flow in people with T2DM are often present at rest [88, 133–136], are exacerbated by exercise, and occur in the absence of peripheral artery disease [88]. Potential mediators of impaired limb blood flow during exercise include insulin resistance, endothelial function, and arterial stiffness [75, 91, 137, 138].

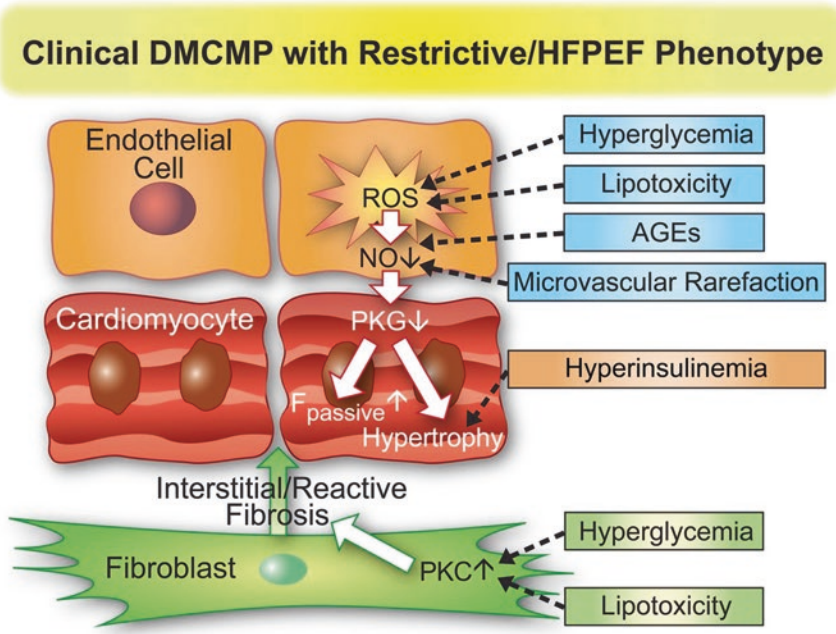

Fig. 6.2 Pathophysiological mechanisms in diabetes mellitus-related cardiomyopathy (DMCMP) with heart failure with preserved ejection fraction (HFPEF) phenotype [115]. *Abbreviations*: *DM* diabetes mellitus, *DMCMP* diabetic cardiomyopathy, *HFPEF* heart failure with preserved ejection fraction, *ROS* reactive oxygen species, *NO* nitric oxide, *PKG* protein kinase G, *Fpassive* cardiomyocyte resting tension, *AGEs* advanced glycation end products, *PKC* protein kinase C (Reprinted with permission from Oxford University Press on behalf of the European Society of Cardiology)

Another defect in oxygen supply during exercise in T2DM may relate to abnormalities in the capillary microcirculation of skeletal muscles. For example, capillary density is reduced in T2DM skeletal muscle [139, 140], and basement membrane structures are altered [141]. These structural changes could directly contribute to alterations in microvascular hemodynamics that impair O_2 exchange from capillary to myocyte, as suggested by the work in diabetic rodent models [140, 142, 143]. Indeed, the relationship between oxygen diffusion (potentially decreased in T2DM) and exercise performance in T2DM has not been extensively explored [144, 145]. However, microvascular complications of T2DM have been associated with abnormal vascular function and lowered exercise capacity [146] further suggesting this mechanism as a possible component to the exercise dysfunction in T2DM.

Other noncardiac components of oxygen delivery could also cause impairment in exercise performance in T2DM. Increased blood viscosity has been reported in persons with T2DM compared to nondiabetic individuals [144, 145]. However, we found that while average whole blood viscosity was higher in persons with T2DM than nondiabetic controls, there was not a statistical relationship between viscosity and exercise performance [39].

A final potential defect in the oxygen supply for exercising skeletal muscles in T2DM includes abnormalities of oxygen utilization related to impaired oxidative metabolism, due to either abnormal mitochondrial function or reduced mitochondrial content. Current evidence of abnormal oxygen utilization during exercise comes from studies in adults with T2DM that demonstrated reduced skeletal muscle oxidative enzyme activity [147], lower

mitochondrial content [148, 149], and an increased type IIb-to-type 1 muscle fiber ratio [150], as compared with healthy subjects. Any of the above factors may lead to impaired fractional oxygen extraction during exercise. There is currently debate regarding whether the observed abnormalities in mitochondrial function [37, 147, 149, 151] truly reflect functional abnormalities or simply reflect reduced mitochondrial content secondary to de-training [152]. Overall it appears that the ability of the limb vessels and capillary microcirculation to deliver oxygen to the skeletal muscle and the ability of the skeletal muscle to utilize oxygen during exercise are compromised in T2DM—these abnormalities likely relate to the exercise defects seen in T2DM.

Sex Differences in the Effects of T2DM on Exercise Performance

An under-studied area is the assessment of whether the effects of T2DM on exercise performance are different between men and women. Of the three prior studies that have assessed for sex differences in the association between T2DM and exercise performance, two studies observed that women with T2DM had a more impaired exercise performance relative to their nondiabetic female counterparts than did men with T2DM compared to their nondiabetic male counterparts [48, 55]. One study reported that the decrement in VO_2peak levels between subjects with and without diabetes was worse in women (31%) than in men (20%) [55]. Another study found that VO_2peak was 24% lower in women with T2DM than nondiabetic women compared to 16% lower in men with T2DM compared to the nondiabetic men ($P < 0.05$) [48]. In the study that did not find sex differences in the effects of T2DM on exercise performance [53], O'Connor et al. studied participants who were on average one decade older than in the studies where sex differences were observed [48, 55]. Although the small sample size of these studies makes these findings preliminary, the results are suggestive of possible sex differences in exercise performance between men and women with T2DM.

Effects of Exercise Training on Exercise Performance in T2DM

Exercise training can substantially improve exercise performance of individuals with T2DM [22, 68, 153–156]. Improvements in VO_2max in men and women with diabetes ranging from 8 to 30% have been documented with exercise training [47, 153, 157]. In addition, a behavioral intervention targeting weight loss through dietary restriction and regular physical activity goals of 175 min per week led to a 20% improvement in VO_2max in the large Action for Health in Diabetes (Look AHEAD) trial [25]. In terms of other benefits, a decreased heart rate per submaximal workload has been reported after exercise training [68], suggesting an improved exercise efficiency that is also found after training in nondiabetic persons. VO_2 kinetics and heart rate kinetics also became faster after 3 months of thrice-weekly exercise training in persons with T2DM, as compared to their pre-intervention VO_2 kinetic responses [47]. Thus, both exercise training and regular physical activity can successfully attenuate, but not completely resolve, the defects in exercise performance observed for people with T2DM [43, 47].

Exercise Training: Mechanisms of Improvement

The mechanisms by which exercise training improves exercise performance are incompletely understood. Exercise training induces a series of metabolic and CV adaptations that result in significant benefit to people with T2DM. Metabolic benefits are likely related to increased tissue sensitivity to insulin due to regular exercise conditioning [158, 159]. Studies have shown that insulin binding to monocytes

[160, 161] and erythrocytes [162] is increased by exercise conditioning and decreased with inactivity. It is possible that exercise conditioning causes a diminished secretion of insulin in response to a particular glucose concentration [163]. Studies have suggested that exercise conditioning magnifies insulin-induced increases in the intrinsic activity of plasma membrane glucose transporters [164].

CV benefits of exercise training include improvements in endothelial vasodilator function [165–168] and the possibility of exercise to improve diastolic function as well [169–172]. Improvement in diastolic function with exercise training has occurred in some, but not all, RCTs. Some factors that may relate to the success of exercise interventions in improving diastolic dysfunction include: exercise intensity [171] and targeting earlier stages of diastolic dysfunction as a "window of opportunity" to remediate diastolic dysfunction that may be lost as cardiac dysfunction progresses [43]. Regarding endothelial function, exercise training interventions have led to significant improvements in reactive hyperemic brachial artery vasodilation and forearm blood flow [165, 168]. In adults with T2DM randomized to 6 months of exercise training as compared to a control group, coronary artery endothelial function and coronary artery flow significantly improved in response to aerobic bicycle ergometer exercise. It is thought that the improvements represent a systemic rather than a local benefit of exercise, based on improvements in endothelial function in the heart and brachial arteries, respectively, while the exercise program utilized the lower extremity muscles. Further research in this exciting area is under way.

Although research is necessary to determine the mechanisms responsible for impaired maximal and submaximal exercise performance in T2DM, there is already indisputable evidence that regular physical activity provides clear clinical benefits to people with T2DM. The next section of this chapter will describe several clinical benefits of exercise training and/or regular physical activity for the population at large, with an emphasis on the scope of benefits for people with T2DM.

Clinical Benefits of Regular Physical Activity

CV Disease and All-Cause Mortality

In the general population, several meta-analyses and large cohort studies provide indisputable support for the benefits of regular physical activity to reduce CVD [173–178]. There is a clear dose-response relationship between physical activity and CVD, suggesting that physical activity is associated with lower rates of CVD [7, 175]. For example, a large meta-analysis that represented more than 1.3 million person-years of follow-up demonstrated a linear decrease in CVD risk with physical activity [7]. A more recent meta-analysis that assessed studies of people without T2DM published since 1995 observed a curvilinear dose-response relationship between physical activity and risk of CVD event. Specifically, CVD risk was reduced by 14% and 20%, respectively, with the attainment of 150 min and 300 min of weekly moderate intensity physical activity [175]. Analysis of the relationship of CVD risk to fitness has also demonstrated a curvilinear relationship, with a precipitous decline in CVD risk occurring before the 25th percentile of fitness level [7]. Two meta-analyses have demonstrated that the strength of association of regular physical activity with lower CVD risk is comparable in people with DM as has been shown in studies of nondiabetic individuals [179, 180].

In addition to improving CVD risk, regular physical activity typically increases cardiorespiratory fitness levels. Demonstrating the importance of consistent physical activity habits over a lifetime, large observational trials have consistently observed that improvements in fitness over time predict lower mortality; conversely, worsening fitness over time predicts higher all-cause mortality [181–183]. Importantly for people with T2DM, better fitness levels are consistently linked to lower overall mortality for both healthy and diseased individuals [6, 10, 182–188]. For example, in a large cohort of 25,714 healthy men, high CV fitness predicted lower CV and all-cause mortality [3]. The same observation held true for

a cohort of 1263 men with DM, and the mortality benefit of CV fitness was significant even in obese participants (Fig. 6.3a) [2]. The relationship between fitness, obesity, and mortality has also been evaluated directly in men with and without DM. In men without DM, Blair and colleagues stratified participants by three BMI categories (<25, 25–30, >30) and found that higher fitness levels were associated with lower mortality in each BMI category [184]. In men with DM, a similar dose-response relationship between higher fitness levels and lower mortality was observed across BMI categories (Fig. 6.3b) [6]. In study populations of women and/or men with DM or impaired glucose tolerance, higher fitness levels were also linked to lower mortality rates [6, 10, 188]. In addition, performing regular walking or other moderate intensity physical activity has also been associated with lower mortality rates in people with DM [8, 179].

Despite the consistent epidemiologic linkage between physical activity and CV outcomes/mortality, the data from randomized controlled trials have been mixed. Lower stroke event rates (HR = 0.62 (0.35–0.98)) were observed in the intervention vs. placebo group of the Japan Diabetes Complications trial of a behavioral intervention that increased physical activity and promoted weight loss [189]. In contrast, the landmark Action for Health in Diabetes (Look

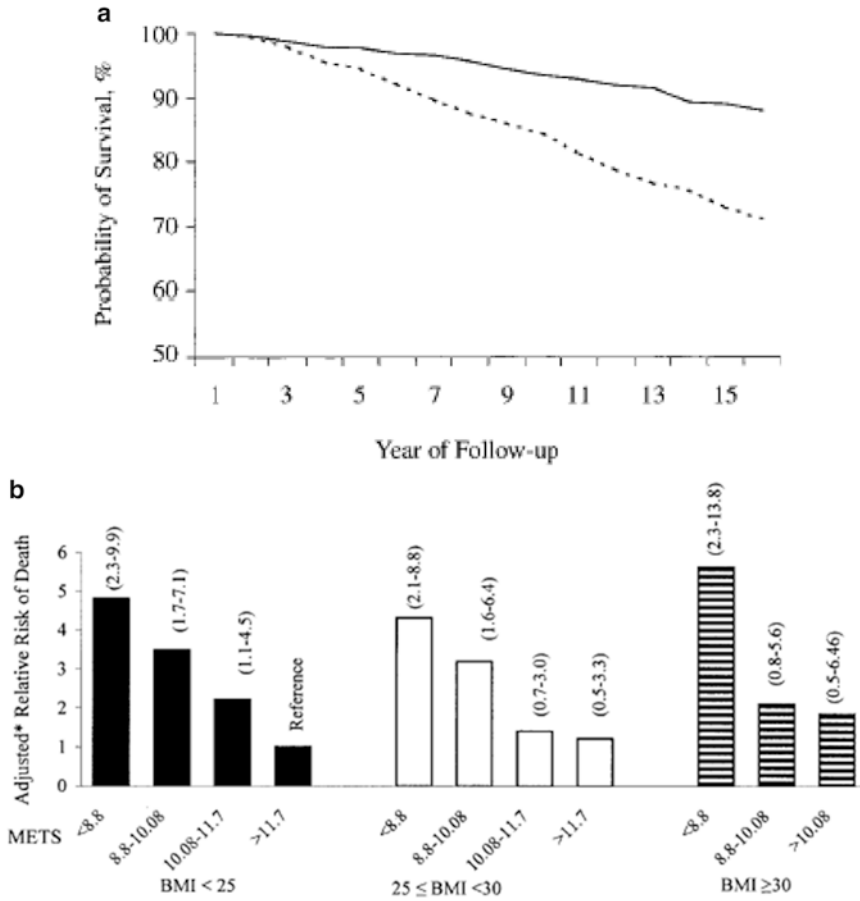

Fig. 6.3 (**a**) Improved survival in cardiovascularly fit (*solid line*) vs. unfit (*dotted line*) men with type 2 diabetes mellitus (T2DM) over 12 years of follow-up in a cohort of 14,777 men [2]; (**b**) lower age-adjusted relative risk of all-cause mortality with higher CV fitness in all weight categories in 2196 diabetic men over 32,162 person-years of observation [6] (Reprinted with permission from *Diabetes Care* and *Ann Int Med*)

AHEAD) trial did not demonstrate differences in CV outcomes despite significant weight loss and fitness improvement in the intervention group as compared to the control group [190]. Lower than expected CV outcomes in the entire Look AHEAD patient population may have underpowered this study to detect an intervention effect, for reasons that have been hypothesized elsewhere [191, 192], including the potential that benefits of lifestyle interventions may accrue over decades rather than months to years. To this point, a weight loss and exercise lifestyle intervention in the Da Qing Diabetes Prevention Study of patients at risk for diabetes required two decades of follow-up before identifying significant improvements in CV outcomes [193]. Overall, a cause and effect relationship between regular physical activity and CVD events/mortality in people with T2DM is supported by two key factors: (1) the consistency of the epidemiologic observations of a dose-response effect between physical activity/fitness and CV outcomes/mortality and (2) proof of concept that lifestyle interventions can improve CV outcomes [189, 193] and mortality [193] in people with T2DM. This cause and effect relationship is likely mediated by the beneficial effects of physical activity on lipids, blood pressure, endothelial function, glucose regulation, and insulin sensitivity, with a potential role based on the effects on inflammation and fibrinolysis. The next sections will review the clinical benefits of physical activity on these predictors of CVD.

Glucose Regulation and Insulin Sensitivity

Glucose metabolism in response to exercise has been extensively studied because optimal glycemic management in DM poses an important clinical challenge. Exercise has two different impacts on carbohydrate metabolism: the bout effect and the training effect [27, 194, 195]. The bout effect refers to the direct impact of an episode of exercise on glucose metabolism that lasts for 12–48 h after the exercise is complete [196–199]. In the glucose regulation literature, the exercise training effect refers to the physiological adaptation to regular bouts of aerobic physical activity that increase functional exercise capacity and cardiorespiratory fitness [200]. Resistance exercise has also been demonstrated to improve glucose metabolism [201, 202].

The benefits of aerobic and resistance exercise training for glycemic regulation likely result from a combination of the bout and training effects, but the influence of the most recent bout of training is substantial [41, 196]. In support of this concept, Devlin et al. reported that a single bout of glycogen-depleting exercise in patients with T2DM significantly increased glucose disposal for up to 12–16 h post-exercise, due to an enhanced rate of nonoxidative glucose disposal by the liver and muscle tissues [196, 203]. Others have found that exercise conditioning for 1 week increases whole body insulin-mediated glucose disposal [204] and glucose tolerance [19] in patients with T2DM. It is not completely clear how much metabolic benefit is derived from a single bout vs. the effect of cumulative bouts of exercise, but it is clear that the benefit of a single bout of exercise attenuates rather quickly so that it is optimal to exercise every 1–2 days to maintain the bout-specific benefits on glucose metabolism. In addition, very brief periods of exercise such as a single bout or even a week of regular exercise is clearly insufficient to cause increases in $V0_2max$. Longer periods of exercise training are required to increase $V0_2max$, to change body composition, and to improve other risk factors for CV disease, such as blood pressure and lipids [25, 205, 206].

The effects of exercise training or routine physical activity on insulin sensitivity are complex and multifactorial, and the relative roles of decreased visceral fat, increased fitness, and cumulative bout effects of exercise have yet to be fully defined [194, 195, 207, 208]. Prior studies clearly demonstrate that exercise training leading to increased VO_2max also results in improved insulin sensitivity, as measured by the gold standard hyperinsulinemic-euglycemic clamp [209, 210]. These studies also compared exercise regimens consisting of moderate- vs. high-intensity aerobic activity with equal exercise energy expenditure and found greater effects on insulin

sensitivity with higher intensity physical activity despite similar effects on VO_2max [209, 210]. These results suggest that the degree of fitness may not correlate directly with insulin sensitivity. Others have asked whether changes in visceral adiposity may account for the benefits of long-term exercise training on insulin sensitivity, as opposed to the bout effect. The exact mechanism by which insulin sensitivity improves with exercise training remains unclear, as reviewed comprehensively elsewhere [194].

The clinical implications of exercise training were assessed in a meta-analysis that concluded that exercise training ≥12 weeks led to an absolute reduction in hemoglobin A_1c of 0.8% in people with T2DM, an effect that is comparable to the improvement typically achieved by dietary or single agent drug therapies [200]. In this meta-analysis, the intensity of training was fairly comparable across the different forms of training: aerobic training alone (typically three bouts weekly for 30–50 min per bout), resistance training alone (typically three bouts weekly for 45–60 min per bout), and combined aerobic/resistance training (typically three bouts weekly for 60 min per bout) [200]. Hemoglobin A_1c improvements were similar for aerobic training alone, resistance training alone, or for combined aerobic resistance training in this meta-analysis [200], but a subsequent RCT demonstrated a synergistic benefit on Hemoglobin A_1c for combined aerobic and resistance training [155]. Regular physical activity like brisk walking also leads to clinically and statistically significant improvements in Hemoglobin A_1c, as observed by other meta-analyses [27, 28].

Lipids

The lipoprotein benefits that have often been observed with regular physical activity include increases in high-density lipoprotein (HDL) levels, decreases in triglyceride (TG) levels, and changes in the sizes of lipoproteins to a less atherogenic profile [211, 212]. However, such improvements have not been observed consistently in studies examining the effect of exercise interventions on lipid levels, as reviewed comprehensively elsewhere [211, 212]. Clouding the issue further, the effects of diet have not been distinguished from those of exercise in many available studies [211, 213]. Two recent meta-analyses of the effects of exercise on lipids also found conflicting results. A meta-analysis of studies of 2–12 months of exercise in subjects with T2DM found a significant decrease in TG levels, but no significant change in HDL or LDL [214]. In contrast, a recent meta-analysis of 25 randomized controlled trials with exercise interventions and lipid endpoints measured in study populations with BMI ranging from normal to obese found a clinically modest but statistically significant increase in HDL (2.53 mg/dL, $p < 0.001$) with aerobic exercise [215].

There are several modifiers of lipoprotein response to exercise that may explain the heterogeneity of findings in prior trials, but the dose of exercise may be the most important factor. For example, the dose of exercise that predicted HDL response in a meta-analysis of adults included bout duration >30 min and weekly physical activity levels >120 min or >900 kcal of energy expenditure [211]. In addition to dose of exercise, other factors that influence a favorable HDL and triglyceride response to exercise training appear to include: lower levels of adiposity at baseline, higher baseline lipids, certain genotype variants, and possibly gender [211, 213]. Recently, two randomized-controlled trials have reported on the genetic determinants of lipid responses to exercise. Hautala et al. demonstrated that a polymorphism in the PPAR delta receptor (more common in Caucasians) was associated with a significantly greater improvement in HDL with exercise training among healthy adults [216]. Huggins et al. demonstrated that several genetic variants significantly influenced the HDL and triglyceride response to a combined weight loss and physical activity intervention among people with T2DM [213]. The strongest influences observed among people with T2DM were the effects of genetic variants of phosphatidylglycerophosphate synthase-1 on decreases in triglycerides ($p = 0.0009$) and variants of the cholesterol ester transfer protein on increases in HDL ($p = 0.004$) [213].

Low-density lipoprotein (LDL) is a major CV risk factor, but its relevance as a risk factor is related both to the absolute LDL levels and particle size characteristics. Of these two factors, exercise training leads to shifts in LDL particle size to a more favorable large particle size more consistently than a decrease in measured LDL levels. In a meta-analysis of healthy adults, there were significant improvements in LDL particle size ($P = 0.004$), including a significant decrease in small particle size LDL ($P = 0.02$) and a significant increase in the large particle size LDL levels ($P = 0.0004$) [212]. In the same meta-analysis, no significant change was observed in overall LDL levels ($P = 0.21$). Demonstrating the potential for exercise to lower LDL, however, Kraus et al. found significant reduction in low-density lipoprotein (LDL) and TG levels and improvement in HDL level with their highest intensity intervention in 111 sedentary, overweight people with mild to moderate dyslipidemia [217]. This trial also found increases in LDL particle size in all exercise groups after a 6-month intervention [217]. In contrast, a combined physical activity and weight loss intervention in adults with T2DM led to improved HDL and triglyceride levels but failed to improve LDL levels [218].

Overall, it is reasonable to conclude that exercise training may have a positive effect on lipids, but this response is by no means certain, and exercise training should not be employed in lieu of indicated lipid-lowering pharmacotherapy, such as "statins" for individuals with elevated CV risk [219]. At present, physical activity does represent one of the very few effective and safe interventions to raise HDL. There also appears to be a consistent benefit to regular physical activity to improve lipoprotein particle sizes to be less atherogenic. In addition, regular physical activity may also improve absolute levels of HDL and triglycerides, especially when performed for a minimum of 2 h per week and when performing bouts of moderate intensity exercise that last at least 30 min.

Blood Pressure

High blood pressure is a leading contributor to CV mortality, and there is a consistent inverse relationship between physical activity and blood pressure in cross-sectional studies. The first study to examine the impact of training upon blood pressure was conducted by Jennings with a very rigorous exercise program in sedentary men [220]. Over the last few decades, a dose-response effect of exercise on blood pressure has been observed in both men and women, including those with CV and metabolic comorbidities. A recent meta-analysis assessed 72 longitudinal intervention studies to determine the impact of exercise training on blood pressure [221]. Studies included both hypertensive and normotensive subjects and people with and without T2DM. Overall, the analysis by Fagard et al. demonstrated a small (3 mmHg) but clinically and statistically significant decline in both systolic and diastolic average blood pressure [221]. The magnitude of improvement in blood pressure was greater in hypertensive subjects [221]. No subgroup analyses for participants with T2DM were reported by Fagard et al. However, a separate meta-analysis by Figueira et al. of the effects of either supervised exercise training or physical activity counseling for 9540 people with T2DM [222] demonstrated significant improvements in systolic blood pressure (~3–4 mmHg) and diastolic blood pressure (2 mmHg) that were fairly comparable to the effects of exercise on blood pressure in the meta-analysis by Fagard et al. As compared to shorter training regimens, training regimens that exceeded 150 min of weekly exercise demonstrated greater blood pressure benefits in the meta-analysis of people with T2DM [222]. Experts have postulated that the mechanism for endurance training to decrease blood pressure includes a reduction in systemic vascular resistance secondary to decreased sympathetic nervous system and decreased renin–angiotensin system activity [221]. Overall, lowering the disproportionately high risk of CVD in people with T2DM by improving blood pressure with exercise training is a very important benefit of physical activity for people with T2DM.

Endothelial Function

Coronary and peripheral artery endothelial dysfunction, most often measured as an impaired ability of the artery to dilate in response to mechanical or pharmacologic stimuli, is closely linked to CVD risk, cardiac events in known CVD, and poor prognosis in CVD [223–228]. Diabetes is tightly linked with endothelial dysfunction; their relationship and the benefits of exercise to improve endothelial dysfunction may be found elsewhere in this book in chapter "Endothelial Dysfunction, Inflammation, and Exercise." Because endothelial function may be a potential cause of abnormal exercise performance in people with T2DM, and because exercise training often improves endothelial function in the context of metabolic disease and CVD [43, 100], it is important to note that the weight of evidence suggests that exercise training does significantly improve impaired endothelial function but that exercise has no significant impact on endothelial function in normal arteries [43, 100, 229, 230].

Inflammation and Immunity

The relationship between exercise and immune function is reported to be a "J"-shaped curve wherein increasing from sedentary to moderate activity improves immune function but exercise training in elite athletes may diminish immune function, especially in the first 24 h after a bout of exhaustive exercise [231]. Regular performance of about 2 h of moderate exercise per day is associated with a reduction of risk for common viral infection of 29%, as compared to sedentary subjects [232]. In contrast, exhaustive exercise such as a marathon is associated with a 100–500% increase in the risk of viral infection [233]. It is worth noting that it is the rare individual who will exercise rigorously greater than 2 h per day, so the potential deleterious effects of exhaustive exercise are not likely to be observed in the general population.

Inflammation, the other face of the immune spectrum, is one of the universal mechanisms contributing to the initiation and progression of atherosclerosis [234] and the development of T2DM [235, 236]. In general, short-term moderate-intensity exercise interventions have a modest positive impact on some subset of circulating cytokines such as interleukin-1 (IL-1), IL-6, IL-18, C-reactive protein (CRP), and tumor necrosis factor-α (TNF-α), presumed anti-inflammatory markers such as adiponectin and possibly IL-6, and inflammation-related cell adhesion molecules such as vascular cell adhesion molecule (VCAM), intercellular adhesion molecule (ICAM), and the selectins [229, 237–241], but these findings have not been observed consistently. For instance, Zoppini et al. found stable CRP and decreased ICAM and P-selectin following 6 months of aerobic exercise in older, sedentary, overweight people with diabetes [238]. In contrast, Olson et al. found reduced CRP and increased adiponectin but stable cell adhesion markers after 1 year of resistance training in overweight women [237]. In addition, there are studies that do not demonstrate any exercise-induced change in circulating inflammatory markers [242]. Thus, evidence regarding the effect of exercise on inflammation is mixed and appears to be modified by the baseline status of the population and the dose of the exercise intervention [229, 237–242]. Overall, each bout of exercise leads to a transient inflammatory burst that stimulates metabolic adaptation of the muscle [243]. Repeated exposure to these acute inflammatory bursts appears necessary to reap the full benefits of exercise training on skeletal muscle [243]. In addition, an inflammatory burst during exercise may induce anti-inflammation pathways, thus potentially reducing chronic inflammation that is linked to CVD risk [208]. Further studies will extend our understanding of the mechanistic effects of exercise on systemic inflammation. The relationship between inflammation and exercise is also addressed further in a separate chapter in this book, "Endothelial Dysfunction, Inflammation, and Exercise."

Obesity

Obesity is a common problem for persons with T2DM. Exercise training may serve as an adjunct therapy to weight loss when added to dietary

caloric restriction. Beneficial changes in body composition with exercise training include decreased visceral adiposity and increased fat-free mass [244]. However, in the absence of dietary restriction, exercise does not generally lead to weight loss [245], even when daily exercise duration exceeds 60–90 min [246]. In contrast to the limited impact of isolated exercise for weight loss, exercise is very effective for the prevention of weight gain, acceleration of weight loss in combination with diet, and perhaps most importantly—maintenance of weight loss. In a community-based study, introduction of walking and healthy snacks prevented weight gain [247]. Similarly, in the National Weight Control Registry, physical activity of greater than 2000 calories per week appears to be a crucial predictor of maintaining one's weight loss >12 months [248]. When exercise mediation of weight loss has been examined prospectively, similar results are reported. For example, an intervention with diet with or without exercise for 12 weeks resulted in a weight loss of 10 kg with diet alone and 14 kg with diet plus exercise. After 12 weeks, the dietary intervention was discontinued but the exercise intervention continued. At 36 weeks, the diet group had regained all but 4 kg, whereas the exercise group maintained 12 kg of weight loss [249]. It is critical to understand that exercise alone does not lead to weight loss and to counsel patients to appreciate the appropriate role of exercise, so they will not be discouraged by an apparent lack of weight loss results from taking up a new exercise regimen.

Prevention of Diabetes

The role of exercise in the prevention of diabetes is unequivocal, but it has been most often studied in the context of a combined diet and exercise intervention. Early epidemiological and sociological evidence demonstrated a strong inverse correlation between habitual physical activity and incidence of diabetes. This evidence included the change in incidence of diabetes with a move from a rural lifestyle, observed in American vs. Mexican Pima Indians. This effect has been observed across diverse populations including male college alumni, female college alumni, registered nurses, and British men [250]. These observations were followed by a set of prospective studies, the Finnish Diabetes Prevention Study [251], Da Qing Diabetes Prevention Study [252], and the Diabetes Prevention Program [253]. In all of these studies, a diet and exercise intervention prevented transition from impaired glucose tolerance to diabetes in 50–60% of individuals. Only the Da Qing Diabetes Prevention Study included an exercise-alone arm. The preventative effect of exercise in this arm was similar to that observed with diet alone and was independent of weight loss, though body composition was not addressed. The success of exercise in diabetes prevention is likely to result from one or more of the effects described above: improved insulin sensitivity, decreased visceral adiposity, and/or modulation or inflammation and oxidative stress.

Summary

The relationship between CV exercise capacity and diabetes is complex and involves multiple physiological systems. Furthermore, the relationship is likely to represent bidirectional causality. The benefits of exercise on CV risk factors, endothelial function, insulin sensitivity, diabetes prevention, and CV and all-cause mortality are clear. Other benefits including maintenance of mitochondrial health and number and effects on hemostasis and systemic inflammation are likely but less well defined. On the other hand, individuals with T2DM who would be expected to benefit the most from exercise have been shown to be relatively inactive and unfit. While the increased risk of diabetes in sedentary individuals is undoubtedly one contributor to this relationship, this chapter summarized compelling evidence that T2DM and insulin resistance appear to cause a reduction in both maximal and submaximal exercise performance. In turn, exercise performance limitations may make exercise more difficult and uncomfortable and thus encourage sedentary behavior in the

very population that would most benefit from exercise. The mechanism of decreased exercise capacity in T2DM is incompletely understood but appears to involve impaired oxygen delivery through cardiac and vascular mechanisms, as well as impaired oxygen utilization at the tissue level. A better understanding of these mechanisms and of the benefits of exercise in this population is essential and awaits further research.

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7 Sex Differences in Exercise Performance and Exercise Training Among Persons with Type 2 Diabetes

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Introduction

The effects of exercise and physical activity on patients with type 2 diabetes (T2D) are well established and include benefits on quality of life, glycemic control, lipid profile, blood pressure, cardiovascular events, and mortality [1]. Despite this, many with T2D fail to achieve an active lifestyle. Research suggests that patients with diabetes have impaired exercise performance, which might explain the difficulty many patients have in achieving regular physical activity [2]. Regardless, consensus clinical guidelines recommend regular physical activity for patients with diabetes. While the specifics of recommendations vary, most organizations recommend at least 150 min per week of aerobic exercise (or 30 min for 5 days a week) along with resistance training, typically 2–3 days per week and with at least two to four sets of eight repetitions per muscle group [3]. While helpful, these guidelines do not currently stratify recommendations based on sex or offer advice on specific exercise plans. Growing research suggests that sex differences in the effects of exercise training on people with T2D do exist, which may impact the way providers counsel patients with T2D in the future. Some but not all evidence suggests that women with T2D have worse exercise capacity compared to nondiabetic age-matched counterparts than men with T2D compared to their

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nondiabetic counterparts, as well as worse cardiovascular consequences of T2D. However, these differences are not well understood and in addition, differences in the responses to exercise training are not well delineated. The first section of this chapter will focus on the sex differences in exercise performance in those with T2D. The second section of the chapter will summarize the differences in effects of exercise training between men and women with T2D.

Sex Differences in Self-Reported Exercise and Physical Activity in T2D

Physical activity behaviors and attitude toward exercise are often considered when formulating a patient-specific exercise plan. Certain subgroups of patients with T2D might require additional counseling and different motivation techniques depending on their usual habits and demographics, and this may differ by sex. However, this type of prescription has not been developed to date.

For example, the Look AHEAD trial of overweight patients with T2D (mean age 59) measured baseline physical activity via accelerometry. In this study, men had about twice as many bouts of moderately vigorous activity (≥3 METs of greater than 10 min duration) and for about twice as long (10 min versus 20 min) than women, consistent with other studies in the general population [4–6]. Interestingly, when stratified by income, low-income women had the lowest rates of physical activity, about 50% lower than low-income men [7]. Racial differences in physical activity may also differ by sex [8]. In another study specifically among an African American population with T2D, a lower percentage of women (29%) compared to men (40%) reported engaging in regular physical activity for the purpose of exercise [9].

To address the effect of counseling, a Finnish cross-sectional study (mean age 62) performed oral glucose tolerance testing (OGTT) to uncover undiagnosed (screen-detected) T2D and then compared their physical activity level to those with previously diagnosed T2D. Among women, 25% more of the diagnosed women reported average activity sessions of greater than 30 min compared to the screen-detected group. The women with T2D also reported 50% more moderate-high physical activity sessions per week. No differences in activity levels were noted between men with screen-detected versus known T2D, potentially indicated that counseling patterns at diagnosis are more efficacious in women [10]. An analysis of a Kaiser Permanente database (mean age 60) studied patients with T2D and inactivity reported at their first visit, without any standardized intervention provided. Women were 23% less likely to report increased physical activity than men at the next visit [11]. Predictors of which individuals are likely to increase activity also appear to vary within each sex. A nested study within the Detection of Ischemia in Asymptomatic Diabetics (DIAD) study (mean age 61) found that among men, higher body mass index (BMI), higher hemoglobin A1c (HbA1c) level, lower level of education, no exercise at baseline, lower baseline HDL, and presence of peripheral neuropathy were all independent predictors of physical inactivity at 5 years. However, in women, no exercise at baseline, level of education, black ethnicity, and waist circumference were the only independent predictors [12].

Perception of the benefits of exercise and attitude toward physical activity can also influence a change in exercise habits. In one study, women with T2D were more likely to be concerned that exercise "would take too much time," while men were not [7]. The SHIELD US study showed that there were only small sex differences regarding the percentage of participants with T2D believing that physical activity would keep them healthy and the percentage that intended to follow their provider's advice on physical activity [8]. Reasons for avoiding physical activity are numerous, but some appear to be sex specific among persons with T2D. Men with moderate to severe overall anxiety are 2.5 times more likely to be physically inactive than men without anxiety. In women, those with moderate to severe anxiety did not have higher levels of inactivity than those without anxiety, though women with mild anxiety were found to be 1.5 times more likely to be inactive [13]. Another study examined the relationship of physical inactivity to "diabetes distress," a construct of negative emotions specifically surrounding their T2D diagnosis and

Table 7.1 Usual exercise reported and/or preferred in patients with T2D

Component	Women	Men
Workout with others versus alone [15]	++	+
Moderate/vigorous > mild intensity exercise [15]	+	++
Supervised exercise [15]	+	–
Scheduled exercise [15]	+	–
Non-leisure/lifestyle activity (take stairs, etc.) [7, 115]	++	+
Leisure time physical activity [7, 115]	+	++

++ vs. + indicates relative preference
"–" Prefers opposite

care. In women, both moderate and severe diabetes distress were associated with a greater likelihood of inactivity. In men, only severe distress was associated with inactivity [14].

Lastly, exercise preference may also differ by sex and impact exercise adherence (see Table 7.1). In a Canadian study, men with T2D were twice as likely to prefer exercising alone and preferred moderate to vigorous intensity exercise when compared to women. Women were more likely to prefer structured and supervised physical activity that was scheduled [15].

Overall, usual exercise and physical activity levels are higher in men with T2D than in women with T2D, particularly moderate to vigorous activity. Predictors of barriers to increased physical activity differ between the sexes and may impact counseling strategies, but perception of exercise should be addressed with patients. Men with T2D appear to favor flexible exercise schedules with moderate to vigorous types of activity whereas women preferred structure activity. With more research in this area, individualized programs may be developed to facilitate success in increasing exercise performance in both sexes.

Sex Differences in Exercise Performance and Cardiovascular Parameters

Most studies of exercise performance, using peak oxygen uptake (peak VO_2) or the surrogate of metabolic equivalents (METs) show that persons with T2D have poorer exercise performance compared to those without T2D [2, 16–20]. Additionally, in those without diabetes, women generally have poorer exercise capacity than men [21]. However, sex differences in exercise performance among persons with T2D are less clear. In one study, the VO_2 decrement observed between patients with T2D compared to nondiabetic counterparts did not differ by sex [16]. However, in another study of younger persons, women with T2D had a 22% decrease in peak VO_2 versus control women, while men had only an 8% decrease [19]. Further, women with T2D had lower peak VO_2 but also slower VO_2 kinetics and heart rate versus overweight controls [22].

In studies focused on metabolic equivalents (METs) achieved during stress testing in those with T2D, a higher percentage of women were found in the lowest-MET-achieving group and a much smaller percentage in the highest-MET-achieving group when compared to men [23], consistent with other studies [17]. Pre-intervention data from Look AHEAD showed that twice as many women (15%) versus men had an exercise capacity less than five METs [24]. A Nigerian study found that at baseline men with T2D achieved higher METs (7.5) compared to women with T2D (6.4) and were able to exercise about 20% longer, on average. That study also showed a significant difference in the percentage of participants achieving age-specific normal exercise goals: 73% of men compared to 60% of women [25]. Women with T2D have higher lactate levels both at baseline and during exercise, possibly indicating a lower level of fitness and exercise performance [18]. The predictors of lower exercise performance may also differ within sex [17, 26]. Taken together these studies suggest that women with T2D have a lower exercise capacity prior to a structured intervention.

While men without T2D have higher risk of cardiovascular disease when compared to premenopausal women, this effect appears equalized by sex in those with T2D [27], suggesting that women with T2D may inherit a disproportionately higher cardiovascular risk than men [28, 29]. Ideally, a major benefit of exercise is to lower the risk of cardiovascular disease. Higher physical activity level at baseline appears related to a reduced risk of cardiovascular events among patients with T2D. Iijima et al. studied older

Japanese men and women with T2D and followed participants for an average of over 5 years. Participants were divided into quartiles based on baseline physical activity level. Overall, the highest versus lowest quartile was associated with a 45% risk reduction of CV events. When studying this in sex-specific groups, the risk reduction was only significant for women in the highest versus lowest quartile, with a 53% risk reduction in CV events whereas there was only a trend for significance in men [30].

Cardiovascular responses to exertion might help explain sex differences in exercise performance and might predict future cardiovascular disease. Diabetes has been associated with an increased pulse pressure and exaggerated rise in systolic blood pressure during exercise, which could be a sign of arterial stiffening and risk of future essential hypertension, stroke, and mortality [31]. Male sex is an independent predictor of hypertensive response to exercise [32]. A Nigerian study of middle-aged participants with T2D found that while resting systolic blood pressure was similar in males and females, men had significantly higher peak systolic blood pressure (216 mmHg) versus females (203 mmHg) during treadmill exercise [25].

Heart rate recovery (HRR) after exertion has been recognized as a tool to assess the autonomic regulation of the heart and has been associated with all-cause mortality [33]. Studies have reported mixed findings regarding sex-specific differences in HRR among persons with T2D [17, 25, 34]. Pre-intervention data from the Look AHEAD study of participants with T2D showed that men were 35% more likely to have heart rate recovery abnormalities (6% overall) after exercise when compared to women [24].

Patients with T2D have an increased risk of heart failure. While small studies have shown that left ventricular mass is higher in patients with T2D, this does not appear to differ by sex [32]. However, risk factors for left ventricular hypertrophy in persons with T2D may be sex specific [35]. Though ventricular mass may not differ by sex, ventricular stiffness and other predictors or future heart failure may differ. In one study, pre-exercise elastance did not differ between men and women. However, after graded aerobic exercise, ventricles were stiffer in the T2D patients and significantly more so in women with T2D than in men with T2D [36]. Additional studies on sex differences of exercise in heart failure and diabetes are lacking.

Blood supply to the large muscle groups of the arms and legs is essential for effective aerobic activity and reduced blood flow could be a major contributor to the poorer exercise performance seen in persons with T2D [37]. Both women and men with T2D have been found to have less flow-mediated dilation of peripheral vessels than controls without T2D during exercise. However, women with T2D had less peripheral blood flow than women without T2D, while no flow difference existed in men by diabetes status [19]. However, another study found that those with T2D versus controls without T2D achieved a lower peak force and lower maximal blood flow responses which was not sex specific [38]. Thus, persons with T2D may have sex differences in blood flow during exercise, though findings are mixed.

Sex-specific exercise performance and cardiovascular parameter responses to exertion are summarized in Table 7.2. At baseline, men with T2D appear to have better exercise performance than women, but may have more concerning

Table 7.2 Differences in cardiovascular parameters among men and women with T2D relative to men and women without T2D

Parameter	Women	Men
VO_2 peak [16, 19, 22]	↓↓ or ↓	↓
METs [17, 23–25]	↓↓	↓
Exertional BP [20, 25, 32]	↑	↑↑
Exertional BP recovery [39]	NS	↓
Heart rate recovery [17, 24, 25]	↑↓	↑↓
Exertional ventricular stiffness [36]	↑↑	↑
Peripheral vessel dilation with exercise [19]	↓	↓
Peripheral blood flow with exercise [19, 38]	↓	NC or ↓

Arrows signify *relative* magnitude of differences in cardiovascular parameters by sex
↓: Worsening parameter
↑: Improving parameter
NC No change in parameter
NS Not studied

changes in certain cardiovascular parameters after exertion, though this is mixed. The second half of this chapter will specifically address the effects of exercise intervention studies.

Sex Differences in Exercise Performance and Cardiovascular Parameters After Exercise Training in T2D

The preceding sections discussed the sex differences in self-reported usual exercise prior to any intervention and/or the effects of single bouts of physical exertion on several factors at baseline. In the second part of this chapter, we will focus on the effects of structured exercise interventions.

There are few studies investigating sex differences in exercise performance after a structured intervention. In one study of obese, middle-aged persons with T2D after a 16-week supervised walking intervention, all participants were noted to have an improvement in VO_2 peak. However, women versus men had a larger increase (10% vs. 2%), though admittedly had a lower baseline VO_2 max [39].

Regarding cardiovascular parameter changes after an intervention, a small study of obese, middle-aged persons after a 16-week exercise intervention found that men alone showed a greater improvement in diastolic blood pressure during recovery. However, post-intervention resting blood pressure did not significantly differ from baseline in either group [39]. Overall, it appears that men with T2D have a higher likelihood for an exaggerated hypertensive response to exercise which may be partially normalized after an exercise intervention. Heart rate variability (HRV), stemming from the effects of the autonomic nervous system on the sinus node, has become a popular, noninvasive marker of increased cardiovascular risk, arrhythmia, and mortality rate in certain populations [40]. A small study of middle-aged patients with T2D explored the effect of 9 months of supervised aerobic activity on HRV and found that men but not women in the exercise group had a significant improvement in HRV compared to controls [41]. Though these studies are provocative, more study is needed to explore sex differences in exercise performance and cardiovascular changes with exercise.

Sex Differences in Body Composition Changes After Exercise Training

Individuals with T2D have unfavorable changes in body composition compared to age-matched controls without diabetes, which may affect metabolic health and overall physical function [42, 43]. Notably, increased visceral adiposity [44], increased intramyocellular lipid accumulation [45], increased ectopic fat including nonalcoholic fatty liver disease (NAFLD) [46], and accelerated decline in skeletal muscle mass [47] may occur. Studies suggest that sex-specific changes in body composition occur in the setting of T2D. As outlined below, although there are limited data, sex-specific changes in body composition after exercise intervention may also occur.

Men and women with T2D likely differ in body composition. In general, men have relatively greater lean muscle mass compared to women, while women have relatively greater adiposity compared to men [48]. Men are also more likely to have central distribution of fat, which is associated with increased visceral adipose tissue (VAT). Women generally have more peripheral distribution of fat with increased subcutaneous adipose tissue (SAT) in the hips and limbs [48, 49]. VAT is associated with insulin resistance [50], atherogenic abnormalities [51], and potentially cardiovascular events [52]. Women may develop an android phenotype after menopause, potentially reflecting the role of estrogen in SAT fat distribution [53]. Decreased testosterone in men [54] and increased testosterone in women [55–57] are associated with increased VAT. Women also have higher intramyocellular triglyceride content, which is associated with lower insulin sensitivity [45, 49].

There are limited data on sex-specific effects on body composition among individuals with T2D

after an exercise intervention. Several studies observed the effects of an exercise intervention on body composition in obese individuals, but not necessarily those with T2D. Kuk and Ross (2009) demonstrated no difference in total fat loss between men and women in an analysis of several weight loss trials, some involving exercise intervention. However, men lost more visceral fat than women for a given reduction in body weight or waist circumference. Men in this study also had smaller reductions in total and lower body SAT. These differences increased in magnitude with loss of body weight or reduction in waist circumference ($P < 0.05$) [58]. McTiernan et al. (2007) demonstrated no significant difference in total body weight or fat loss between men and women after a 12-month aerobic exercise intervention [59].

Among those with T2D, the HERITAGE study, which included a 20-week exercise intervention, demonstrated that aerobic exercise resulted in increases in whole-body fat-free mass and decrease in fat mass and percentage of fat in both sexes, but men lost more abdominal visceral fat, as compared to women [60]. In the Sugar, Hypertension and Physical Exercise (SHAPE) studies, after a 6-month supervised aerobic and resistance exercise program, total abdominal adipose tissue (TAT) loss differed by sex and diabetes status, with men without T2D losing the most (17%), followed by women without T2D (10%), then women with T2D (4%), and lastly men with T2D (1%). Most of this adipose tissue loss came from visceral fat with no significant difference seen in any of the groups in loss of subcutaneous abdominal fat. The study also demonstrated that VAT decreased to a lesser extent among individuals with T2D as compared to those without T2D [61]. The finding of relatively decreased VAT loss among individuals with T2D is contrast with those of Lee et al. [62], and this difference is hypothesized to be due to rigor of physical activity [61]. After 1 year in the Look AHEAD trial, the intensive lifestyle intervention group achieved a 7% and 11% weight loss in women and men, respectively. Regarding adipose tissue, in the intervention group, SAT decreased by 24% in men and 13% in women, VAT decreased by 38% in men and 23% in women, and intramuscular adipose tissue did not significantly change [63].

Regarding changes in lean body mass (muscle), in the SHAPE trials, lean mass increased less in those with T2D and less in women: highest in men without T2D (3.3%), than women without T2D (3.1%), followed by men with T2D (1%) and lastly women with T2D (0.6%) [61]. Jung et al. (2012) demonstrated that vigorous aerobic exercise was associated with increased total skeletal muscle, normal density muscle, and insulin sensitivity in overweight postmenopausal women with T2D [64]. Lee et al. (2005) demonstrated an increase in normal skeletal muscle density with moderate aerobic exercise in men with T2D [62]. Cuff et al. (2003) demonstrated an increased density of muscle in obese postmenopausal women after an aerobic exercise intervention with even greater increase in those undergoing combination aerobic and resistance interventions [65]. These findings suggest that women and men are both likely to improve skeletal muscle function after exercise training, but sex differences need to be further examined in larger studies.

In terms of long-term follow-up, at the 8-year follow-up point in the Look AHEAD trial, the intensive lifestyle intervention group maintained small but significantly lower fat mass and lean mass overall. However, in analyses stratified by sex, differences in fat mass (for males) and lean mass (for females) were not significant at year 8. The authors noted that the lack of significance in these groups might have been due to females having more fat mass to lose than males at baseline and males have more lean mass to lose than females at baseline [66].

Changes in body composition by sex after an exercise intervention were also examined in individuals with prediabetes without significant differences seen in body composition in the Diabetes Prevention Program (DPP) trial of overweight individuals. Intensive lifestyle intervention, achieved through diet and aerobic exercise improvement, resulted in favorable changes in body fat and body fat distribution in both sexes at 1 year [67].

Taken together, these data suggest that T2D is related to potentially unfavorable body composition changes in men and women. The studies have mixed findings regarding sex-specific differences in weight loss and change in body mass after exercise training. Similarly, it is unclear if there are differential benefits of resistance training by sex. Overall, both sexes appear to lose visceral adipose tissue and gain lean body mass with exercise training, though men may have more dramatic and beneficial changes than women.

Sex Differences in Metabolic Parameters After Exercise Training

Exercise training leads to an improvement in glycemic control, insulin resistance, and cholesterol profiles in those with T2D [1]. However, the role of sex in these improvements is less clear.

Pre-intervention data from the Look AHEAD trial of adults with T2D found that HbA1c level was not related to exercise capacity [24]. Vanninen et al. studied adults (mean age 53) with newly diagnosed T2D randomized to standard care or intensified diet education plus continuous encouragement to increase physical activity for 1 year. At 1 year, VO_2 max was inversely correlated with HbA1c in men. This relationship was not significant in women [68].

The Look AHEAD trial also studied the effect of 1 year of diet and aerobic exercise intervention on metabolic control in participants with T2D. As mentioned above, men compared to women in the intervention lost a greater percentage of baseline weight (11% vs. 7%) at 1 year [63]. Fasting glucose was reduced in the intervention group, but significantly more in men (16%) than women (7%). While fasting insulin levels decreased in both sexes after intervention, steady-state insulin measured by clamp only decreased significantly in the women. Fasting free fatty acids decreased significantly in both sexes after intervention, with no sex difference [69]. A Nigerian study found that men had a significant change in fasting glucose more quickly (2 weeks versus 4 weeks after starting an exercise intervention), but the absolute change was similar for men and women. The authors also found that men had significant changes in triglycerides by the fourth week and women not until the sixth week. The absolute change in triglyceride level was larger in men [70]. In the HERITAGE family study (mean age 34), a multicenter exercise training study of the effect of three times weekly cycle ergometry for 20 weeks in sedentary families, baseline insulin sensitivity was 12% higher in women, but women had less of an improvement in this parameter than men (5% vs. 16%) after intervention, though both groups observed statistical improvement. However, it should be noted that the improvement in insulin dynamics was short-lived, with fasting insulin levels improving after 24 h, but returning to baseline by 72 h after the last exercise session [71]. Taken together, these studies demonstrate the beneficial effects of exercise on glucose control and insulin sensitivity, and triglycerides, perhaps with more robust effects in men. However, the studies also suggest that exercise must be sustained in order for benefits to persist.

Leptin is a protein produced by adipose tissue which has hypothalamic effects in the regulation of body mass. While some research has shown that leptin levels are not impacted immediately after exercise, others have shown that there is a late lowering of this hormone [72, 73]. After 24 h of a three repetition maximal weight lifting bout, leptin levels decreased after acute exercise in patients with T2D, but not in controls, and were more extreme for women than men. However, the sex differences did not persist at 72 h [74]. Long-term exercise training effects on leptin have not been studied.

C-reactive protein is a common marker of systemic inflammation, with elevated levels associated with cardiovascular disease. Though an acute rise in CRP can be seen shortly after exercising, chronic exercise is associated with lower CRP levels in the general population and might be a mediator of some of the beneficial effects of exercise [75]. Inactivity during leisure time was not predictive of a higher CRP in women, but was in US men with T2D [76]. In another analysis, while for men there was no statistically significant lowering of CRP with increased activity,

certain subpopulations of women with T2D did see benefit [6].

Endostatin is a proteoglycan which appears to be a negative modulator of angiogenesis and has been shown in mice models to prevent atherosclerotic plaque expansion, presumably by inhibiting intra-plaque angiogenesis [77]. An Austrian study examined the effects of exercise on endostatin levels during a graded bicycle exercise test. Overall at baseline, females had about 40% higher endostatin levels than males. While all groups had an increase in endostatin during exercise, women had higher endostatin levels than males at all times and patients without T2D had higher levels than those with T2D [78]. The long-term effects of exercise training on endostatin and the implications of this on overall cardiovascular health are still speculative.

As summarized in Table 7.3, structured exercise interventions generally lower fasting glucose levels and improve insulin sensitivity, perhaps to a greater extent in men than women. After an exercise intervention, both men and women have improvement in free fatty acids, but men might have a greater improvement in triglycerides with exercise interventions. In terms of inflammatory markers, accelerometry data (which may be more reliable than self-report) only shows a benefit in women. Leptin appears to change acutely, but not chronically, after exercise with a more extreme change in women. The implications of this are still unclear. Lastly, endostatin levels, which may have impact on future atherosclerotic disease, were improved more in those without T2D than with and more in women than in men. However, this marker and its implications for cardiovascular outcomes are still under investigation.

Table 7.3 Changes in clinical and metabolic parameters after an exercise intervention in men versus women with T2D

Parameter	Women with DM	Men with DM
VO_2 peak [39, 116]	↑↑	↑
Exertional BP recovery [39]	NC	↓
Heart rate recovery [34]	NC or ↑	NC
Heart rate variability [41]	NC or↑	↑↑
Weight [61, 63]	↓ or ↓↓	↓ or ↓↓
Abdominal fat [61, 63]	↓ or ↓↓	↓↓
Lean mass [61]	↑	↑↑
Fasting glucose [69, 70]	↓ or ↓↓	↓↓
Fasting insulin [69, 71]	↓↓	↓
HbA1c [117, 118][a]	↓	↓
Insulin sensitivity [71]	↑	↑↑
Free fatty acid [69]	↓	↓
Triglycerides [70, 118]	↓	↓
LDL [118]	↓	↓
HDL [118][a]	NC	NC
Acute leptin change [72, 74]	↓↓	↓
Chronic leptin change [73, 74]	NC	NC
Sex hormones [119][b]:		
Testosterone	NC or ↓	NC
SHBG	↑	↑
Estradiol	NC or ↓	NS
DHEA	NC or ↓	NS
Hepatic fat	↓	↓

Arrows signify *relative* magnitude of change by sex
↑: Improving parameter
↓: Worsening parameter
NC No change
NS Not studied
[a]Changes in parameter are not sex specific in these studies
[b]Studies in obese patients, but not exclusively in those with T2D

Hepatic Fat Content After Exercise Training in Men and Women with T2D

The American Association for the Study of Liver Diseases (AASLD) defines nonalcoholic fatty liver disease (NAFLD) as hepatic abnormalities by imaging or histology in the absence of other causes for secondary hepatic fat accumulation such as alcohol consumption or steatogenic medications. Data from the National Health and Nutrition Examination Survey (NHANES) III and Dallas Heart Study have suggested that the prevalence of NAFLD is higher in men compared to women in the overall US population [79].

Limited randomized controlled trials have examined the effect of exercise in T2D on hepatic fat accumulation [69, 80–83]. The largest of these studies ($n = 96$) utilized the Look AHEAD cohort [81]. The authors demonstrated that with intensive

lifestyle intervention that resulted in 8% weight loss, individuals achieved a 25% greater reduction in hepatic steatosis and thus substantially lowered the incidence of NAFLD vs. the control group [81]. Albu et al. (2010) demonstrated in the Look AHEAD cohort that changes in hepatic fat content (−18%) in response to exercise intervention were similar in men and women [69].

Differences in Sex Hormones Between Men and Women with T2D After Exercise Training

Hypogonadism is common in men with T2D. Kapoor et al. (2007) reported that overt hypogonadism was present in 14–17% (depending on use of total versus bioavailable testosterone) of men with T2D and "borderline hypogonadism" in as many as 42% of men with T2D [84]. Further, higher estradiol and lower SHBG levels have variably been associated with an adverse metabolic profile [85–93]. In men with T2D, trials of testosterone replacement have been associated with favorable body composition changes including decrease in subcutaneous fat and increase in lean mass [94].

In women, elevated estradiol levels have previously been associated with adiposity, elevated inflammatory markers, lipid abnormalities, elevated fasting and 2-h post-challenge glucose, and insulin resistance [85, 95–97]. Though data are inconsistent, DHEA and DHEA-S have been associated with insulin resistance [97–99]. Data have also suggested that SHBG is associated cross-sectionally and prospectively with T2D in men and women, with a larger magnitude of effect in women, most notably in the postmenopausal period [85, 86, 96, 97, 100, 101].

Weight loss, whether by diet, exercise, or surgery, can lead to improvements in hypogonadism [102–111]. There is a paucity of trials specifically in men with T2D that have examined change in sex hormones in response to exercise intervention. A schematic of potential changes in sex hormones that may be observed in obese or insulin-resistant men is shown in Fig. 7.1. Similarly, there are scant studies investigating the association of changes in sex hormones after exercise intervention in women with T2D. A

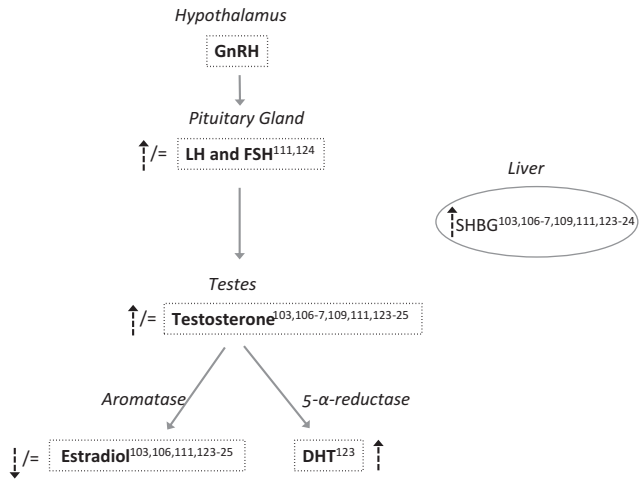

Fig. 7.1 Schematic of proposed sex hormone changes after weight loss in obese, insulin-resistant men with weight loss. Based on the available literature, an increase in gonadotropin levels results in an increase in serum testosterone. With reduction in adiposity, decreased aromatization results in lower estradiol levels. Limited evidence suggests that an increase in testosterone also results in an increase in dihydrotestosterone (DHT) levels. An increase in SHBG is also seen with lifestyle intervention, which has previously been demonstrated to be associated with improvements in insulin resistance. Downward and upward *arrows* denote a decrease and increase in sex hormone/sex hormone-binding globulin (SHBG) levels, respectively, while = represents no change [102, 104–108, 110, 119]

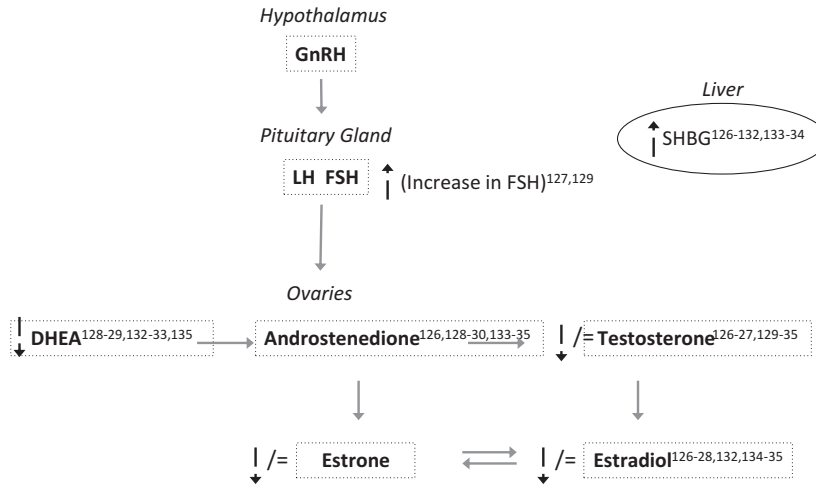

Fig. 7.2 Schematic of proposed sex hormone changes in obese postmenopausal women with insulin resistance after weight loss. Based on the available literature, largely limited to data from the Diabetes Prevention Program (DPP) which included women with prediabetes, lifestyle intervention resulted in weight loss and a small increase in FSH. Increase in FSH is associated with decrease in weight and decrease in estradiol after adjustment for age and race/ethnicity. Although significant changes in testosterone levels were not seen in the DPP trial, limited data from other trials including women without T2D suggest a reduction in testosterone levels may occur after an exercise intervention. DHEA, which is ultimately converted to testosterone, has also been noted to decrease after an exercise intervention. Similar to men, an increase in SHBG is also associated with lifestyle intervention. Downward and upward *arrows* denote a decrease and increase in sex hormone/sex hormone-binding globulin (SHBG) levels respectively, while = represents no change [120–129]

schematic of potential changes in sex hormones that may be observed in obese or insulin-resistant postmenopausal women is shown in Fig. 7.2.

Genetic Factors Related to Sex Differences in T2D and Exercise

It has been demonstrated that approximately 15–20% of persons with T2D fail to improve metabolic health, including glucose homeostasis, insulin sensitivity, and mitochondrial density, in response to supervised exercise intervention [112]. While genetic studies have suggested that the extent of response to exercise training is largely heritable, newer data have shown that DNA hypomethylation is associated with exercise response in the skeletal muscle [112]. It has been postulated that sex differences in hormonal milieu and gene expression can cause differences in cellular environment and thus gene-environment interactions and the penetrance and expression of traits in persons with T2D [112]. Notably, in an analysis of the HERITAGE family study scanning for prediabetes phenotypes, the glycogen synthase gene (GYS1) locus was linked to glucose effectiveness (an insulin-independent effect whereby glucose mediates its own disposal from plasma) in response to endurance [113]. However, it is unclear if this link would be present in those with overt T2D. Fredriksson et al. (2007) demonstrated in their cohort (~30% of individuals with T2D) that the protective effect of exercise and physical activity on cardiovascular mortality in males was attenuated in males carriers of the allele of the Xba1 polymorphism of the GYS1 gene. The polymorphism, however, did not appear to confer risk in women. The authors hypothesized that estrogen, like exercise training, increases Akt phosphorylation and glycogen synthase kinase-3 inactivation, leading to increased glycogen synthase activity via alternate pathways. In contrast, the apolipoprotein E (APOE) gene, important in lipid metabolism, did exert an increase in CV mortality in women but not men [114].

Conclusion

In persons with T2D, exercise clearly has an impact on glycemic control, weight loss, certain cardiovascular measures, the degree of hepatic steatosis, and overall body composition (see Table 7.2). Men with T2D appear to have more self-reported exercise and physical activity prior to an intervention but are less likely to respond to counseling than women. Both sexes appear to have different preferences in exercise type. Prior to training, women with diabetes have lower exercise performance than men with diabetes. After exercise training, women with T2DM tend to have greater improvements in exercise performance and certain cardiovascular parameters, while men have greater improvements in body composition and other measures of cardiovascular parameters. Sex differences in metabolic parameters after an exercise intervention are less clear at this point. Additional research into understanding the pathophysiology and scope of sex differences in exercise among persons with T2D is clearly needed. Further understanding of sex differences in self-reported usual physical activity and physical inactivity, exercise performance before training, and response to exercise training, will allow for individualized care and patient-centered exercise interventions in the future.

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Mitochondria in Muscle and Exercise

8

Lisa S. Chow

This chapter will discuss the role of mitochondria in muscle and how this role may be modified by exercise. The focus will be on human studies, with inclusion of relevant selected animal and cellular studies. We will begin with a general overview of mitochondrial structure and function. Next, the role of mitochondria in muscle and the impact of exercise will be discussed. The goal of this chapter is to highlight the role of mitochondria in muscle function, the extent to which this might be modified by exercise, and identification of critical knowledge gaps for future study.

General Overview of Mitochondria

Mitochondrial Structure

Mitochondria are considered the "powerhouse" in the cell, generating energy from fat and glucose oxidation. Mitochondria can significantly vary in size and number between different cells and tissues. Although the majority of mitochondrial proteins are encoded by the nuclear genome, the mitochondria have its own independent genome (mtDNA) which encodes 37 genes essential to mitochondrial function (13 proteins involved in oxidative phosphorylation, 22 tRNAs, 2 rRNAs) [1]. The components of the mitochondria include the following: the outer membrane, intermembrane space (space between the outer and inner membrane), inner membrane, cristae (formed by foldings of the inner membrane), and matrix (within the inner membrane) (Fig. 8.1).

Mitochondrial Function

The primary role of mitochondria is to generate energy (adenosine triphosphate: ATP) by using oxidative phosphorylation to oxidize hydrogen (NADH, $FADH_2$) derived from carbohydrates (citric acid cycle/Krebs cycle) and fat (beta-oxidation) with oxygen to generate water, carbon dioxide, heat, and ATP. During oxidative phosphorylation, electrons are transferred through a series of linked proteins called the electron transport chain (complex 1–4) to generate a proton gradient across the inner mitochondrial membrane. This proton gradient is then released by ATP synthase (complex 5) to convert ADP to ATP (Fig. 8.2).

Mitochondria influence cellular health beyond energy generation. Mitochondria are involved in generation of reactive oxygen species and cellular function. Reactive oxygen species are generated in the process of moving electrons

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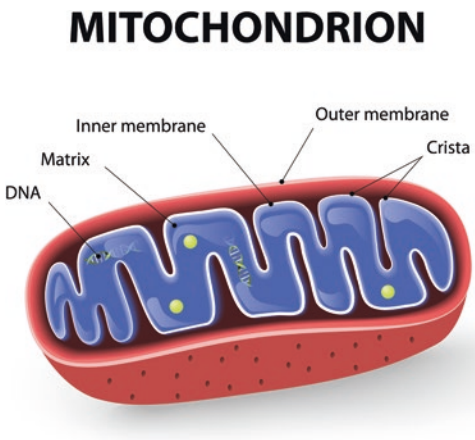

Fig. 8.1 Mitochondrial structure. The mitochondria consist of the outer membrane, intermembrane space (between the outer and inner membrane), and inner membrane. The mitochondria matrix is enclosed by the inner membrane and cristae are formed by foldings of the inner membrane. Mitochondrial DNA (mtDNA) is located within the mitochondrial matrix (Reproduced with permission: Designua/Shutterstock.com)

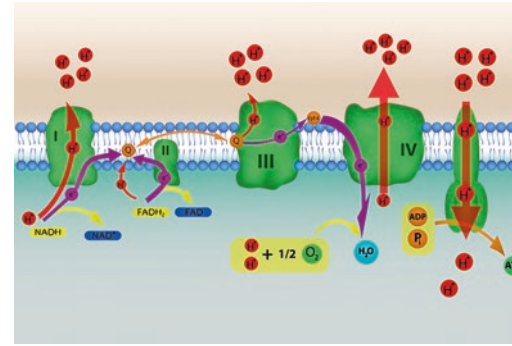

Fig. 8.2 Mitochondria electron transport chain. The mitochondria electron transport chain is involved in oxidative phosphorylation to generate ATP. Electron transfer (e^-) is coupled with proton transfer (H^+) across the inner mitochondrial membrane into the intermembrane space. Complex 2 (NADH coenzyme Q reductase: labeled (I) accepts electrons from NADH, which is generated from the TCA cycle. The electron is then passed to coenzyme Q (Q: ubiquinone) which also receives electrons via $FADH_2$ from complex 2 (succinate dehydrogenase: labelled (II). Coenzyme Q then passes the electrons to complex 3 (cytochrome c reductase: labeled (III). Cytochrome c (cyt c) transfers the electrons from complex 3 to complex 4 (cytochrome c oxidase: labeled (IV) where the electrons reduce molecular oxygen to water. The generated proton gradient moves through complex 5 (ATP synthase) to convert ADP into ATP (Reproduced with permission: extender_01/Shutterstock.com).

through the electron transport chain, which can cause cellular damage by oxidizing proteins and mutating DNA. Consequently, the cell uses protective mechanisms such as uncoupling proteins (to reduce the protein gradient) and antioxidant enzymes, such as superoxide dismutase, catalase, and peroxidases, to detoxify the reactive oxygen species. Uncoupling proteins (UCP) play a key role in mitochondrial function. Uncoupling proteins ameliorate the generation of reactive oxygen radicals by allowing protons to leak across the inner mitochondrial membrane and, thereby, reduce mitochondrial inner membrane potential [2]. Mitochondria also play a complex role in cellular metabolism, growth, differentiation, and death, which are addressed by other reviews [3–5].

Measurement of Mitochondrial Function

Mitochondrial dysfunction has been implicated in a variety of human diseases, ranging from neuropathy [6] to Parkinson's [7] to psychiatric disorders [8] to vascular disease [9] and diabetes [10]. A significant reason for the varying phenotype attributed to mitochondrial dysfunction is due to the various techniques capturing different facets of mitochondrial function which may not overlap phenotypically.

In Vivo Measures

In humans, in vivo mitochondrial measurements generally involve magnetic resonance spectroscopy (MRS). The use of MRS to measure mitochondrial function in vivo in muscle has been well established [11], using either ^{31}P-MRS to measure the ratio of phosphate/inorganic phosphate [12] or phosphocreatine recovery after acute exercise [13]. More recently, ^{13}C-MRS has been used to measure TCA cycle flux [14, 15], which occurs in the mitochondrial matrix, as a surrogate of mitochondrial function.

In Vitro Measures

In contrast to in vivo measures, there are many direct and indirect ways to measure mitochondrial function in vitro [11]. In general, measurements can be performed on frozen tissue, fresh tissue, or isolated mitochondria [16]. For muscle, analysis can also be performed on primary muscle cell cultures derived from isolating satellite cells, allowing proliferation into myoblasts, and then differentiation into myocytes for analysis [17, 18] as well as permeabilized muscle fibers which preserve the mitochondria within their native environment [16]. Quantification of mitochondrial function includes the following: indirect measures (i.e., PGC-1a [19], reactive oxygen species [20], extent of mtDNA mutation [1]), mitochondrial morphology (i.e., size, number [10], fusion/fission [21]), mitochondrial enzyme level (citrate synthase mRNA or protein level) [22], mitochondrial enzyme activity (i.e., citrate synthase activity) [22], and direct measures of mitochondrial function (i.e., oxygen consumption in response to substrate exposure) [23, 24] (Table 8.1).

Mitochondrial Dysfunction and Muscle

In the general population, the relationship between mitochondrial dysfunction and the muscle is often considered within two contexts: (1) mitochondrial dysfunction and aging and (2) mitochondrial dysfunction and insulin resistance/type 2 diabetes (DM2), with the concept that age-associated reduction in mitochondrial function contributes to age-associated declines in insulin sensitivity.

The skeletal muscle is affected by aging, with progressive atrophy and decline in mitochondrial function. Aging is associated with lower mtDNA copy number [25, 26], mRNA encoding Cox3 and Cox 4 [25], citrate synthase activity [25], mitochondrial ATP production [25], and reduction of in vivo synthesis rates of mitochondrial proteins [27]. It has been proposed that the age-associated reduction in mitochondrial function may contribute to the observed age-associated decline in insulin sensitivity.

There is extensive, although still not definitive, evidence suggesting mitochondrial dysfunction is related to reduced insulin sensitivity and DM2. Evidence for reduced skeletal mitochondrial function has been seen both in the context of DM2 [10, 23, 28–33] and in insulin-resistant subjects without DM2 [14, 30, 34]. Specific measures of reduced mitochondrial function in such subjects include smaller mitochondrial size [10], decreased expression of oxidative phosphorylation genes [30, 31], lower levels of mitochondrial enzyme activity [28, 29], lower mitochondrial ATP production [28, 29], lower insulin-stimulated inorganic phosphate (Pi) to ATP flux rates [33, 35], slower TCA cycle flux rates [14], slower postischemic phosphocreatine recovery [32], reduced muscle oxidative capacity [36], and lower abundance of mitochondrial proteins [37] .However, it remains unclear whether the observed mitochondrial dysfunction is related to lower mitochondrial content with maintained function [24, 38], intrinsic mitochondrial differences [39, 40], or a combination of these factors.

Exercise Effects

Exercise exerts a plethora of effects on muscle mitochondria, affecting both structure and function.

Structural Effects

In the muscle, mitochondria can be located either beneath the subsarcolemmal membrane (SS) or the intermyofibrillar (IMF) region between the myofibrils (Fig. 8.3). The SS mitochondria (<20% of mitochondrial mass) [41] are thought to provide energy for membrane-related processes, and the IMF mitochondria are thought to provide energy for muscle contraction [42]. In rat studies, SS mitochondria had lower coupling and oxidative capacity than IMF mitochondria, suggesting that SS mitochondria are less efficient in ATP production [43]. Exercise has been shown to increase mitochondrial enzyme activity along with mitochondrial volume, with a larger increase

Table 8.1 Examples of common ex vivo measures of mitochondrial function

Mitochondrial measurements	Examples	Description[a]
Mitochondrial structure		
	(1) Histology	Examine size, morphology, and localization [10, 41]
	(2) Fusion/fission	Determines formation and breakdown of mitochondria as well as cellular distribution [21]
	(3) mtDNA copy number	Quantify mtDNA content which is a surrogate for mitochondrial number [66]
	(4) mtDNA mutations	Quantify extent of mutations observed in mtDNA [1]
	(5) Cardiolipin	Quantify mitochondrial inner membrane area which is a surrogate for mitochondrial size/number [66]
	(6) Mitochondrial protein synthesis	Quantify synthesis rates of mitochondrial specific proteins [27]
Mitochondrial biogenesis markers		
	(1) Peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1a)	Master regulator of mitochondrial function [19]
	(2) AMP-activated protein kinase (AMPK)	Enhances oxidative energy production [42]
	(3) Mitochondrial transcription factor A (Tfam)	Activator of mitochondrial replication [42]
	(4) Nuclear respiratory factor (NRF-1)	Promotes transcription of many mitochondrial biogenesis and mitochondrial proteins [42]
Fatty acid oxidation		
	(1) Carnitine palmitoyltransferase I	Enzyme in outer mitochondrial membrane which facilitates transport of long chain fatty acids across the membrane [67]
	(2) Beta-hydroxyacyl-CoA dehydrogenase	Enzyme involved formation of acetyl CoA from fatty acid oxidation [68]
	(3) Fatty acid translocase	Long chain transporter of fatty acids found in plasma and mitochondrial membranes
	(4) Direct measure	Feed radioactive-labeled fatty acid and look at radiolabeled CO2 production [67]
Oxidative phosphorylation		
	(1) Citrate synthase	Enzyme in 1st step of TCA cycle (encoded by nuclear DNA) [53, 68]
	(2) NADH dehydrogenase	Enzyme in electron transport chain (Complex 1 – encoded from nuclear and mitochondrial DNA) [66, 68]
	(3) Succinate dehydrogenase	Enzyme in TCA cycle and electron transport chain (Complex 2 – encoded from nuclear DNA) [66, 68]
	(4) Cytochrome c oxidase	Enzyme in electron transport chain (Complex 4 – encoded from nuclear and mitochondrial DNA) [53, 68]

(continued)

Table 8.1 (continued)

Mitochondrial measurements	Examples	Description[a]
Direct Measures of mitochondrial function		
	(1) O_2 consumption	Using either isolated mitochondria or primary muscle culture – measure O2 consumption under various scenarios of substrate/ADP/ATP inhibitor availability [69]
	(2) ATP production	Using either isolated mitochondria or primary muscle culture, measure extent of ATP production given various substrates [69]
Indirect measures		
	(1) Reactive oxygen species	Results from incomplete reduction of O2. Difficult to measure due to instability. Measure H_2O_2 as a surrogate [70]

[a]Included examples of articles which use/discuss the described measurement

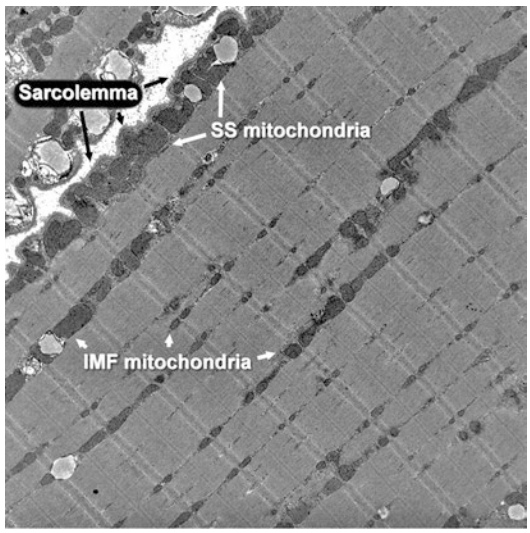

Fig. 8.3 This is a micrograph (*11,400 magnification) of a skeletal muscle cell illustrating subsarcolemmal (SS) and intermyofibrillar (IMF) mitochondria. The SS mitochondria are located between the sarcolemma and the most superficial myofibrils. The IMF mitochondria are located between parallel bundles of myofibrils (Reproduced with permission from Dr. Toledo and the Endocrine Society [45])

in SS volume than IMF [41] .However, whether insulin resistance affects the SS or IMF mitochondria distribution remains mixed, as reduction in SS and to lesser extent IMF mitochondria [44] and, conversely, reductions in IMF but not SS mitochondria [45] have been observed. Aerobic exercise (10 weeks) in obese patients with and without T2DM improved insulin sensitivity and significantly increased median SS mitochondria (124%) than superficial IMF (62%) or central IMF (14%) mitochondria [46].

Functional Effects

Both acute and chronic aerobic exercise have been shown to enhance mitochondrial function. The magnitude of change will depend on intensity and duration of the exercise exposure. However, conceptually, increased mitochondrial content in response to exercise provides many benefits, including increased oxidative capacity, reduced lactate accumulation, and reduced respiration per individual mitochondria to reduce ROS production. The effects of this exercise related enhancement, however, appear to be short-lived, as reduction of activity for even 2 weeks can reduced VO_2 max [47], insulin sensitivity [47], mitochondrial enzyme activity [48], SS mitochondria content [49], and superficial IMF content [49].

Acute Exercise

Within minutes to hours after acute exercise exposure, there are increased mRNA levels of transcription factors associated with mitochondrial biogenesis as well as genes encoding

mitochondrial proteins. In humans, acute knee extensor exercise (3 h) increased mRNA levels of peroxisome proliferator-activated receptor (PPAR) coactivator-1 (PGC-1a), a major stimulator for mitochondrial biogenesis, post exercise (measured at 0,2,6, and 24 h of recovery) peaking within 2 h after exercise [50]. Acute endurance exercise (2 h) increased mRNA levels of PGC-1a post exercise (measured at 0, 1, 4 h of recovery), peaking at 1 h of recovery and returned to basal levels by 4 h of recovery [51]. These findings, however, appear to be blunted by insulin resistance. In lean and obese subjects without diabetes, acute aerobic exercise (interval exercise 10 min exercise, rest for 2 min, repeat four times) increased mRNA and protein levels of PGC-1a and cytochrome c oxidase (at 0.5 h and 5 h recovery) which was either blunted (mRNA and protein levels of PGC-1a) or absent (mRNA and protein levels of cytochrome c oxidase) in the obese subjects [52].

The effect of exercise on PGC-1a appears to be related to exercise intensity. One episode of high-intensity interval training (HIIT: 4*30 s of all out maximal intensity cycling interspersed with 4 min of rest) increased mRNA levels of PGC-1a, citrate synthase, cytochrome c oxidase, and COX IV (at 3 h recovery) which was then followed by increased mitochondrial protein levels of citrate synthase, cytochrome c oxidase, and COX IV (at 24 h recovery) [53]. High-intensity exercise (80% VO_2 max for 36 min) increased PGC-1a mRNA more (at 3 h recovery: 10.2-fold vs 3.8-fold, $p < 0.05$) than low-intensity exercise (40% VO_2 max for 70 min) which was matched for energy expenditure [54]. Extending these findings further, acute high-intensity aerobic exercise (cycling at 60% peak power output in watts for 30 min), but not acute low-intensity aerobic exercise (60 min at 30% peak power output in watts), enhances mitochondrial protein synthesis (24–28 h recovery) [55]. Consequently, there is burgeoning interest in the benefits and applicability of HIIT-based training programs, which promote mitochondrial biogenesis [53, 56, 57] in the context of low-volume exercise and reduced exercise time.

Chronic Effects

The effect of endurance exercise on improving skeletal muscle mitochondrial function has been known since the 1960s [58]. Both cross-sectional [26] and interventional studies [59] have shown that exercise improves the mitochondrial dysfunction associated with aging. Similarly, there has been numerous human studies (Table 8.2) focused on the effects of exercise on muscle mitochondrial function within the context of insulin resistance/T2DM. These studies have generally involved aerobic training over the course of several months (2–6 months), with documented improvement in overall insulin sensitivity/glycemic control. Muscle biopsies performed before and after the training program (generally within 1 week after cessation) show increased mitochondrial content and increased mitochondrial function, particularly with regard to oxidative capacity. In patients with insulin resistance/T2DM, it is clear that chronic exercise increases muscle mitochondrial content and function. However, several knowledge gaps still remain with regard to extent, clinical impact and durability of these findings.

Knowledge Gaps

Several knowledge gaps remain with regard to mitochondrial function and exercise. One knowledge gap is differentiating between responders and nonresponders to a given exercise exposure, although intrinsic blunted oxidative capacity may be a contributing factor [60]. Another knowledge gap is that the relationship between mitochondrial function and insulin resistance remains indeterminate, with varying degrees of correlation observed depending on mitochondrial function measurement and patient selection. Estimates of mitochondrial capacity using in vivo ^{31}P MRS found no differences between subjects with long-standing insulin-treated DM2 (>5 years), subjects with prediabetes, and subjects with recently diagnosed DM2 (<1 month) and

Table 8.2 Examples of exercise interventions in insulin resistance/type 2 diabetes with mitochondrial outcomes

References	Year	Intervention	Duration	Population	Measure of insulin sensitivity	Timing of mitochondrial measure	Mitochondrial measure
Bruce [67]	2006	Cycling (5 days/week, 60 min at 65–70% of VO_2 max)	8 weeks	obese subjects ($n = 9$)	Oral glucose tolerance test – improved by 34%	Bx prior and 36–48 h s/p training program	Increased CPT1 activity, increased fatty acid oxidation
Menshikova [66]	2006	Cycling (4–6 days/week, 30–40 min at 50–70% of VO_2 max)	12 weeks	Overweight subjects ($n = 8$)	HOMA-IR – improved by 23%	Bx prior and at least 48 h s/p training program	Increased cardiolipin, mtDNA, NADH oxidase activity
Hansen [68]	2009	Aerobic (3 days/week) (LOW – 55 min at 50% VO_2 max vs HI – 40 min at 75% VO_2 max)	6 months	Male, obese with T2DM (oral meds only) ($n = 50$)	HgbA1c – decreased by 0.3%	Bx before, 2 month training, 6 months training (4–8 days after last session)	Increased activity of citrate synthase, cytochrome c oxidase
					OGTT – did not change		No change in activity of succinate dehydrogenase, B-hydroxyacyl coA dehydrogenase
							*Similar findings between the LOW and HI group
Meex [39]	2010	Aerobic (2 days/week for 30 min at 55% of peak work load) and resistance training (1 day/week)	12 weeks	Male with T2DM ($n = 18$) or healthy ($n = 20$)	Hyperinsulinemic-euglycemic clamp – insulin sensitivity increased by 63% in T2DM	Bx before and after training program	Improved mitochondrial function as measured by 31P-MRS (28–48%)
							Increase in protein content of ETC complexes
							Increase in mitochondrial content (30%) and ex vivo mitochondrial function [71]

(continued)

Table 8.2 (continued)

References	Year	Intervention	Duration	Population	Measure of insulin sensitivity	Timing of mitochondrial measure	Mitochondrial measure
Mogensen [72]	2010	Aerobic (4–5 days/week cycling, 20–30 min at 60–70% VO_2 max)	10 weeks	Obese patients with T2DM (n = 12) and controls (n = 11)	Hyperinsulinemic-euglcyemic clamp (improved by 17% in T2DM, 20% in control)	Bx before and after training program at least 48 h after last exercise	Increased citrate synthase activity (37–60%)
							Increased mitochondrial content (40%), particularly in the SS region (124%) than superficial IMF (64%) and central IMF (14%) [46]
							Increased ex vivo mitochondrial respiration [73]

sedentary normal controls [61]. In further support of a possible disconnect between mitochondrial ATP synthetic capacity and insulin resistance, comparison between Northern European subjects with DM2 and Asian Indian subjects with DM2 found that Asian Indians with DM2 had higher levels of insulin resistance despite the presence of higher skeletal muscle mitochondrial capacity (as measured by mitochondrial DNA, mRNA of oxidative phosphorylation genes, citrate synthase enzyme activity, and maximal ATP production rate) [62]. There are several examples of mouse models overexpressing muscle-specific PGC-1a, resulting in increased mitochondrial content, and yet are severely insulin resistant [63, 64]. Likewise, a mouse model with muscle-specific PGC-1a knockout displayed higher insulin sensitivity than control mice [65]. Lastly, if the presumption is made that mitochondrial dysfunction is indeed related to insulin resistance, a remaining knowledge gap persists whether this is due to lower mitochondrial content with maintained function [24, 38], similar mitochondrial content with reduced function [39, 40], or a combination of these factors.

Conclusions

The relationship between muscle mitochondrial function and insulin resistance in humans is hindered by the many diverse definitions of mitochondrial dysfunction as well as the various methods and techniques available to determine muscle mitochondrial function. Nevertheless, acute and chronic exercise clearly increases mitochondrial function, with the degree of enhancement depending on exercise exposure. Identifying the mechanism by which exercise improves metabolic health remains clinically significant, as this could lead to therapies capturing the metabolic effect of exercise which will have significant public health impact.

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9 Vascular Dysfunction, Inflammation, and Exercise in Diabetes

Jordan Loader, Matthieu Roustit, Dimitrios Baltzis, and Aristidis Veves

Introduction

The prevalence of diabetes mellitus represents one of the greatest public health issues of the modern era affecting an estimated 347 million people worldwide [1]. Although the causes are complex, this burden is projected to worsen due, in part, to increasingly poor nutritional habits and sedentary lifestyles [2]. Diabetes mellitus has long been considered an independent risk factor for cardiovascular disease (CVD), which remains the single leading cause of mortality among those with type 1 or type 2 diabetes [3]. Evidence suggests that endothelial dysfunction is the earliest discernable pathophysiological precursor to atherosclerotic changes, conferring the importance of considering variables of vascular function when developing a comprehensive understanding of the pathogenesis of CVD in those with diabetes mellitus [4, 5].

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In normal vascular function, the endothelium and vascular smooth muscle (VSM) cells continuously interact regulating vasodilation and vasoconstriction in order to maintain optimal vascular tone and organ perfusion [6]. However, in an environment of chronic hyperglycemia such as that in individuals with diabetes, it has been shown that vascular function is impaired as demonstrated by reduced reactivity to vasoactive agonists, as well as increased expression of plasma and urinary biomarkers representative of general endothelial dysfunction and inflammation [7]. Such inflammatory responses, which compound the impairment of vascular function, are key mechanisms that contribute to atherosclerotic changes and are characterized by lesion formation, plaque rupture, and thrombosis, which ultimately represent important events in the pathogenesis of CVD [8].

Along with diet and medication, physical exercise is considered a cornerstone of the treatment and management of diabetes [9]. Although it has no preventative mechanism in type 1 diabetes, epidemiological studies suggest that regular physical activity can reduce the risk of developing type 2 diabetes by 30–50% [10]. Physical activity also confers a similar risk reduction for CVD, presenting moderate increases in exercise as an efficacious and feasible method for improving cardiovascular health in individuals with type 1 or type 2 diabetes [10]. This chapter will provide an outline of how vascular function is altered from normal to diabetic states and its role in the pathogenesis of CVD, the

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methods utilized for quantifying such changes in vascular function, as well as the role of exercise in attenuating vascular dysfunction and inflammation in diabetic populations.

Normal Vascular Function

The vascular network is typically categorized by size and defined as the macrocirculation, which includes both conduit arteries (>1000 μm) and small arteries (300–1000 μm), or the microcirculation, consisting of smaller arteries and arterioles (10–300 μm) and capillaries (≈6 μm) [11]. As arterial diameter decreases, the proportion of the vessel wall comprised of VSM increases to 70–85% concurrently to a decrease in the vessel's elastic properties illustrating the increased ability of smaller arteries and arterioles to control vessel diameter and thus demonstrate their integral role as resistance arteries that strongly influence vascular hemodynamics [12]. Resistance arteries are also prominently involved in controlling local blood flow throughout the capillary network where nutrients and gas are exchanged between blood and tissue [13], collectively highlighting the microcirculation as a key region of interest when investigating the relationship between vascular dysfunction and CVD in diabetic populations.

Throughout the vasculature, endothelial cells of the intima regularly make contact with VSM cells of the media via fenestrations in the internal elastic lamina [12]. It is here where normal vascular function is maintained by a continuous interaction between the endothelium and VSM cells that is highly influenced by mechanisms such as shear stress, the arteriolar myogenic response, metabolic control, and neural control [7]. Such mechanisms stimulate the balanced synthesis of numerous vasodilators (nitric oxide (NO), prostacyclin (PGI_2), and endothelium-derived hyperpolarizing factors) and vasoconstrictors (endothelin-1, angiotensin II, prostanoids, and isoprostanes), which rapidly diffuse to the VSM cells in order to mediate dilation or constriction of the blood vessel [14]. In addition to modulating vascular tone, vasodilators are also critical in maintaining normal vascular health by regulating platelet aggregation and adhesion, leukocyte recruitment, pro-inflammatory cytokines, angiogenesis, and VSM cell proliferation [15].

Mechanisms of Vasodilation

Although both vasodilators and vasoconstrictors are synthesized simultaneously, the net result of these two antagonistic effects in normal healthy conditions is usually vasodilation [16]. Nitric oxide is the most characterized vasodilator and is continuously synthesized in the endothelium from the amino acid L-arginine by endothelial nitric oxide synthase (eNOS) [17]. Shear stress (the force exerted on the endothelial wall by vascular blood flow), which is the predominant regulator of vasomotion, acts on the endothelium synergistically with several other agonists including insulin, acetylcholine, adenosine triphosphate, adenosine, bradykinin, and histamine to stimulate the synthesis of NO by eNOS in calcium-dependent and/or calcium-independent pathways (Fig. 9.1) [15, 18]. Such agonists activate G protein-phospholipase interactions depleting endothelial cell calcium concentration, which subsequently induces calcium influx via store-operated channels and potassium channel activity [19]. Free intracellular calcium then binds to calmodulin and initiates eNOS activity resulting in NO synthesis [19].

The rate at which NO can be synthesized via this calcium-dependent pathway is limited by the rate of eNOS phosphorylation [20]. Importantly, G protein interactions mediated by the aforementioned agonists also stimulate the phosphatidylinositol 3-kinase pathway, which activates protein kinase B to phosphorylate, and activate eNOS, subsequently synthesizing NO in a calcium-independent manner [21]. Once synthesized, NO diffuses into the adjacent VSM cells where it binds with the enzyme guanylate cyclase resulting in an increase in the formation of cyclic guanosine monophosphate (cGMP) mediating a reduction in intracellular calcium concentrations that, ultimately, induces VSM relaxation and subsequent blood vessel dilation [22].

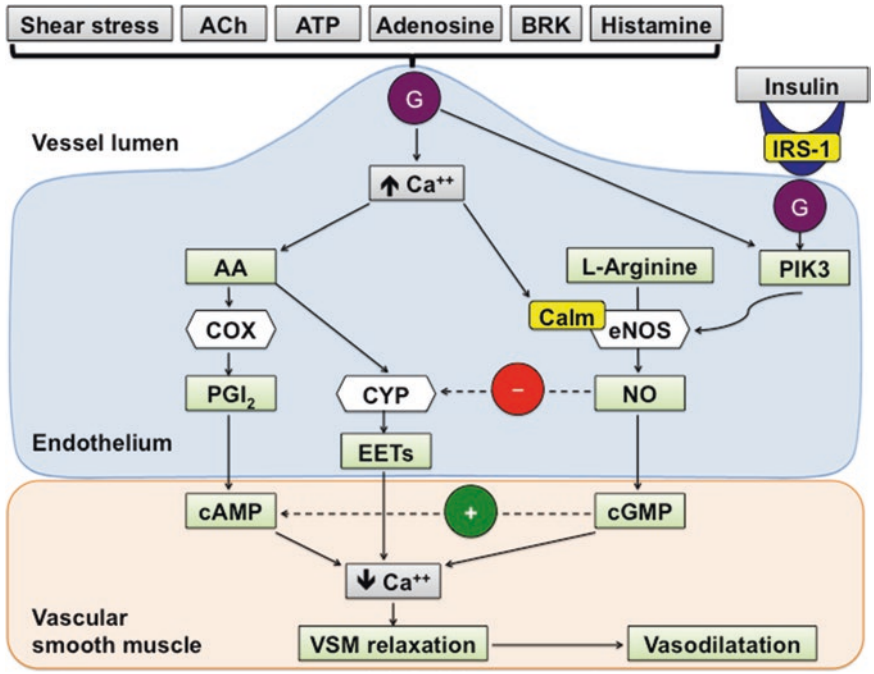

Fig. 9.1 Schematic diagram illustrating the interaction between the three main vasodilatory pathways (NO, PGI_2, and EETs) in normal healthy vascular function. Adapted from [15]. *ACh* acetylcholine, *ATP* adenosine triphosphate, *BRK* bradykinin, *IRS-1* insulin receptor substrate-1, *G* G protein phospholipase, Ca^{++} free intracellular calcium, *AA* arachidonic acid, *PIK3* phosphatidylinositol 3-kinase, *COX* cyclooxygenase, *Calm* calmodulin, *eNOS* endothelial nitric oxide synthase, PGI_2 prostacyclin, *CYP* cytochrome metabolites, *NO* nitric oxide, *EETs* epoxyeicosatrienoic acids, *cAMP* cyclic adenosine monophosphate, *cGMP* cyclic guanosine monophosphate, *VSM* vascular smooth muscle, ↑ increase, ↓ decrease, – downregulates, + upregulates

Indeed, increases in endothelial intracellular calcium concentration resulting from G protein-phospholipase interactions mediated by similar agonists (e.g., shear stress, acetylcholine, adenosine triphosphate, adenosine, bradykinin, and histamine) that activate eNOS also stimulate the synthesis of PGI_2 [15]. Free intracellular calcium liberates arachidonic acid to activate the cyclooxygenase pathway to synthesize PGI_2, which diffuses into the adjacent VSM cells stimulating an increase in the formation of cyclic adenosine monophosphate (cAMP) [23]. Like cGMP, cAMP mediates a reduction in intracellular calcium concentrations that induces VSM relaxation [15]. Importantly, cGMP also promotes cAMP activity increasing the overall sensitivity of the system and explaining the synergistic effect of NO and PGI_2 [15].

Vasodilatory mechanisms are further supported by endothelium-derived hyperpolarizing factors, which are predominantly comprised of epoxyeicosatrienoic acids (EETs) [13]. Increased intracellular concentrations of calcium that liberate arachidonic acids stimulate the synthesis of EETs by several cytochromes [24]. When EETs act on the VSM, they induce hyperpolarization of the VSM cell by opening of potassium channels and closure of calcium channels, which causes a decrease in VSM calcium concentrations and subsequent VSM relaxation [24]. In normal healthy conditions, NO suppresses cytochrome activity and subsequent EET formation, but when NO synthesis is inhibited, cytochrome activity and the influence of EETs increase to maintain normal vascular function [15, 24]. The advantage of this dynamic system that involves multiple regulators of vascular function is that vasodilation or vasoconstriction can still occur even if some pathways are weak [15]. However, impairments in a central mechanism, such as that occurring in CVD, can have substantial deleterious effects on vascular function [15].

Evaluating Peripheral Vascular Function

Given that abnormal vascular function is considered a primary precursor to atherosclerotic changes and the pathogenesis of CVD, evaluation of vascular reactivity may provide a prognostic marker of the progression of CVD and overall cardiovascular health, as well as a valuable method of quantifying the effect of various CVD treatments. Early research into the role of vascular dysfunction in CVD often assessed endothelium-dependent and endothelium-independent function directly in the vascular bed of interest (e.g., the coronary vasculature). Common techniques included intracoronary infusion of vasoactive substances (e.g., acetylcholine, nitroprusside, etc.) performed in conjunction with coronary angiography or intravascular ultrasound to measure coronary macrovascular function and with Doppler wires or cineangiographic frame counts to assess coronary microvascular function [25]. Such tools measure changes in vessel diameter or coronary blood flow in response to aforementioned pharmacological stimuli or even exercise (that induces shear stress), with decreased responses indicating reduced vascular function [25]. These methods are considered highly invasive and technically challenging and are not an option in patients who do not require an angiography. Therefore, noninvasive surrogate markers have been developed, both for conduit arteries and for the microvasculature (Table 9.1).

Methods to Assess Peripheral Macrovascular Function

In recent decades, flow-mediated dilation (FMD) in conjunction with ultrasound measurement of the brachial artery has become the standard noninvasive test to assess macrovascular endothelial function (Fig. 9.2) [26, 27]. Briefly, this test consists of comparing the brachial artery diameter at rest (baseline) to that following occlusion of an artery with the patient remaining in a supine position for the duration of the test. Occlusion is usually of the brachial artery and is achieved by inflating a sphygmomanometric cuff below, or sometimes above, the antecubital fossa. The cuff is

Table 9.1 A description of the advantages and drawbacks of the various technologies available for quantification of macro- and microvascular reactivity

	Advantages	Drawbacks
Macrocirculation		
FMD	Noninvasive	Highly operator dependent
	Standardized methods	Microcirculation influences the stimulus (shear stress)
Intra-arterial injection of vasodilators	Standardized stimulus	Invasive
Microcirculation		
Venous occlusion plethysmography	Provides extrapolated blood flow in the muscle microcirculation	Poor reproducibility
		Difficult to perform
		Requires intra-arterial infusion of drugs (invasive)
Laser-based methods (LDF, LDI, LSCI)	The skin is easily accessible (noninvasive tests)	Only provide an index of blood flow
	Variety of tests that explore different pathways	Lack of standardization of the methods
Digital plethysmography	Easy to use and operator independent	Expensive (marketed proprietary device)
	Noninvasive	Underlying pathways are still poorly understood

FMD flow-mediated dilation, *LDF* laser Doppler flowmetry, *LDI* laser Doppler imaging, *LSCI* laser speckle contrast imaging

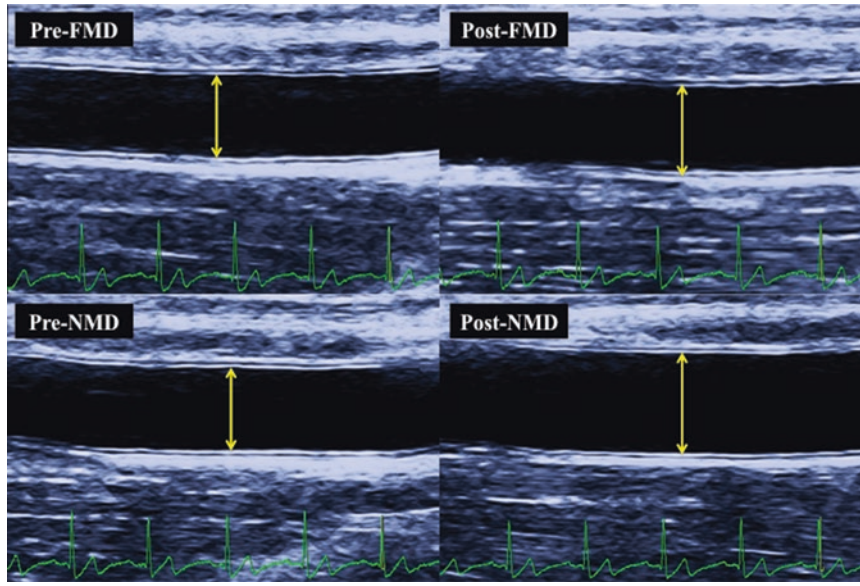

Fig. 9.2 Ultrasound images of the brachial artery. Basal measurements are performed for both flow-mediated dilation (FMD) and nitrate-mediated dilation (NMD) procedures. An increase in diameter of the brachial artery can be observed in response to 5 min of artery occlusion that induces FMD and 4 min after the administration of nitroglycerin that induces NMD. Simultaneous electrocardiogram recordings are performed (illustrated by the green line) during each phase (pre- and post-occlusion/nitroglycerin administration) of FMD and NMD

typically inflated to 50 mmHg above systolic blood pressure for 5 min before being rapidly deflated to induce shear stress by increased blood flow and subsequent vasodilation. Ultrasound images are taken pre- and post-occlusion using a high-resolution ultrasound machine with the ultrasound probe positioned in the longitudinal plane of the brachial artery above the antecubital fossa.

Whereas FMD assesses endothelium-dependent function, nitrate-mediated dilation (NMD) is often used to examine endothelium-independent function in the macrocirculation. Nitrate-mediated dilation is performed using similar protocols to that in FMD, but the occlusion is substituted with a pharmacological stimulus, namely, a NO donor (sublingual nitroglycerine), that bypasses the endothelium and delivers direct stimulation to the VSM cells. To ensure ultrasound image analyses that determine brachial artery diameter are performed at a consistent phase of the cardiac cycle, ultrasound recordings should be acquired in conjunction with electrocardiogram during both FMD and NMD measurements. The percentage change between baseline and post-challenge artery diameter is the key variable of interest in both tests and is considered as the maximal vasodilator response, irrespective of endothelial function, in NMD only [27].

Evidence suggests that mechanisms underlying FMD predominantly involve the NO pathway as infusion of the NO synthase inhibitor N-monomethyl-L-arginine blunted the vasodilation following occlusion; in contrast, aspirin infusion had no effect, suggesting a decreased role of PGI_2 in macrovascular function [28]. More recently, cytochrome P450 (CYP) metabolites, and putatively other hyperpolarizing factors (EETs), have been suggested to closely interact with the NO pathway in the response to artery occlusion [29]. It must also be recognized that FMD does not only measure mechanisms of conduit artery vascular function per se but also, indirectly, the limb microcirculation, due to the stimulus (i.e., shear stress) being highly dependent on maximal forearm resistance [25]. To facilitate between-study comparisons and optimize the evaluation of macrovascular

function, it has been suggested that the change in brachial artery diameter should be normalized to the shear stress stimulus [30]. Despite these efforts to optimize and standardize the test [11, 27, 31], FMD still suffers from a lack of homogeneity and high inter-operator variability.

Methods to Assess Peripheral Microvascular Reactivity

Venous occlusion plethysmography is an old, minimally invasive method that permits extrapolation of blood flow (mL/min), usually from the forearm muscle microcirculation. This test consists of inflating a cuff around the upper arm above venous blood pressure but below diastolic blood pressure (typically 10 s at 40 mmHg). Venous return from the forearm is then briefly interrupted, while arterial blood inflow is preserved, resulting in a linear increase in forearm blood volume. A second cuff placed around the wrist excludes the hand circulation. Changes in forearm blood volume are measured by a strain gauge located between the cuffs and connected to a plethysmograph [32]. Venous occlusion plethysmography is particularly interesting to assess the response to vasodilators, which requires intra-arterial infusion of drugs and makes the procedure more difficult. Finally, heterogeneity in the vascular response due to differences in initial arterial pressures, forearm blood flow, or size of the forearm limits the value of the technique [25].

More recently, the cutaneous circulation has also been proposed as a marker of generalized microvascular dysfunction, mostly because of its accessibility. Subsequently, the use of alternative noninvasive methods assessing skin microvascular reactivity, especially laser-based techniques (laser Doppler flowmetry and laser speckle contrast imaging), has grown substantially in recent decades. Contrary to strain gauge plethysmography, laser-based techniques do not provide a measure of blood flow but an index of blood perfusion usually referred to as *flux*. Given that resting skin blood flux is highly variable, most interest in these techniques has been shown when assessing microvascular reactivity by challenging the microvessels with various tests. The combination of a laser-based technique (i.e., laser Doppler flowmetry, laser Doppler imaging, or laser speckle contrast imaging) with a variety of mechanical, thermal, electrical, or pharmacological stimuli offers a wide range of methods that explore different physiological pathways of the microcirculation, with variable reproducibility [13].

By analogy with FMD, arterial occlusion has been proposed as a test of endothelial microvascular function. This simple test, commonly referred to as post-occlusive reactive hyperemia, involves sensory nerves and CYP metabolites, putatively EETs. Local heating of the skin to a temperature of 42–44 °C is another interesting, reproducible test characterized by a biphasic rise in cutaneous blood flow. The initial peak depends on sensory nerves and involves transient receptor potential vanilloid type 1 channels. This peak is followed by a transient nadir, and after 10–20 min, the flux stabilizes. The delayed plateau is a good indicator of endothelial function, with an involvement of both NO (accounting for approximately two thirds of the response) and endothelium-dependent hyperpolarizing factors (the other third, half of which is dependent on EETs) [13].

Another approach to investigating cutaneous microvascular reactivity consists of local administration of vasoactive drugs by transdermal iontophoresis (Fig. 9.3). This noninvasive technique is based on the transfer of charged molecules across the uppermost layers of the skin under the influence of a low-intensity electrical current. Acetylcholine and sodium nitroprusside are the most widely utilized vasoactive drugs and are used as markers of endothelium-dependent and endothelium-independent vasodilation, respectively. Although easy to perform and inexpensive, this technique suffers from a lack of reproducibility. Moreover, the underlying pathways of vascular function are partly unknown, and the involvement of NO remains debated [33]. Finally, the electrical current itself has an influence on microvascular reactivity, mediated by C-fiber and downstream pathways that would predominantly involve cyclooxygenase-1. Such current-induced vasodilation confounds the assessment of endothelial function. Other

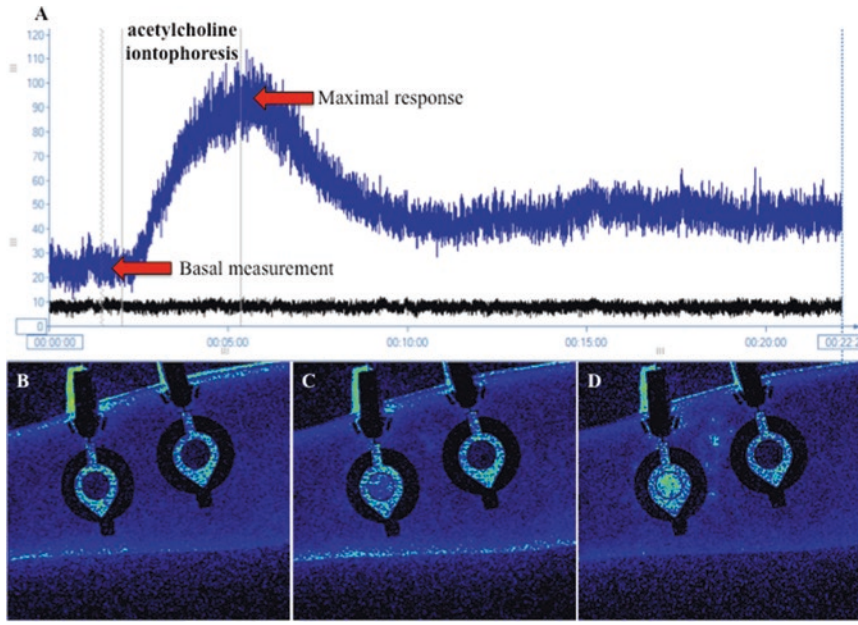

Fig. 9.3 (**a**) The graphed response in perfusion units to transdermal iontophoresis of acetylcholine, which typically induces rapid vasodilation. Laser speckle contrast imaging illustrates the increase in cutaneous blood flow from the (**b**) basal state to the (**c**) intermediate and (**d**) maximal responses to acetylcholine iontophoresis. Note that the speckle pattern color varies by cutaneous region with the brighter green speckles within the electrode during and immediately following acetylcholine iontophoresis indicating increased cutaneous blood flow as compared to the darker (*black* and *blue*) colors within the electrodes during basal measurements

methods do allow direct drug delivery into the dermis, such as microinjections or microdialysis. Although they are free from current-induced vasodilation and permit administration of any kind of vasoactive substance, they can be more invasive and difficult to implement.

Despite these advances in technologies that assess cutaneous microvascular function, the cutaneous vascular anatomy itself presents a challenge for performing reproducible measurements. Organized as two parallel plexuses roughly located at each interface of the dermis connected through ascending arterioles and descending venules, the cutaneous microvasculature is highly innervated and may contain arteriovenous anastomoses, especially in glabrous skin. These anatomical features partly explain the complex regulation of cutaneous blood flow and its heterogeneity according to the skin region.

More recently, a digital form of plethysmography has emerged as a further technique for assessing peripheral microvascular function. Briefly, arterial pulse wave amplitude is measured before and after brachial artery occlusion, and the signal is corrected with simultaneous measurement on the contralateral hand. A marketed proprietary device (Endo-PAT, Itamar Medical) has been used to show that digital vascular dysfunction correlates with metabolic risk factors, including obesity, diabetes mellitus, and ratio of total to HDL cholesterol [34]. Digital plethysmography also has the advantage of being operator independent, but it is only partly dependent on the NO pathway [35].

Vascular Dysfunction and Inflammation in Diabetes

Vascular function in both peripheral conduit arteries and the microcirculation has been shown to be impaired in many, if not all, cardiovascular risk factors, including diabetes. This present section is a non-exhaustive review of the profuse

literature that has correlated the noninvasive tests, detailed above, with diabetes. We will also review the growing importance of biochemical markers and the role of inflammation in the assessment of vascular dysfunction.

Decreased Vascular Reactivity in Diabetes

In recent decades, many studies have demonstrated abnormal vascular function in diabetes mellitus. Impaired reactivity of the brachial artery (FMD) in patients with type 2 diabetes suggests decreased endothelial function in the macrocirculation. Such alteration occurs early in the pathophysiology of the disease, as suggested by abnormal FMD in subjects with impaired glucose tolerance and in normoglycemic individuals with a parental history of diabetes [36]. Impairment of macrovascular reactivity is also an early feature of type 1 diabetes. Decreased FMD has been observed in adolescents with type 1 diabetes diagnosed less than 5 years, while glycemic control over the first years had significant influence on endothelial function [37].

The negative impact of chronic hyperglycemia on vascular reactivity has also been observed in the microcirculation. By using venous occlusion strain gauge plethysmography, an association between chronic hyperglycemia and impaired endothelium-dependent vasodilation has been established in patients with type 1 diabetes [38]. In type 2 diabetes, microvascular dysfunction has also been shown through decreased skin blood flux after iontophoresis of acetylcholine and sodium nitroprusside when compared with matched controls [36, 39]. Consistent with these findings, it is interesting to note that when measured with strain gauge venous occlusion plethysmography, reactivity to a NO donor was impaired, while there was no difference in reactivity to a calcium channel blocker. This suggests an altered NO pathway at the endothelium or the VSM level rather than a loss of functional integrity in the VSM [40].

The mechanisms through which chronic hyperglycemia induces vascular dysfunction are complex and may differ according to the vascular bed. Increased activation of protein kinase C has many repercussions on endothelial cell signal transduction, including not only the NO and endothelium-dependent hyperpolarizing factors pathways but also in endothelin-1 or vascular endothelial growth factors. Chronic hyperglycemia is also associated with elevated production of reactive oxygen species (e.g., superoxide) in the vascular wall and the activation of the polyol pathway [41]. Such oxidative stress reduces NO bioavailability by disrupting several underlying mechanisms involved in NO synthesis [8]. Interestingly, oxidative stress and polyol pathways are also involved in the pathogenesis of diabetic neuropathy which itself impairs microvascular reactivity, the latter dependent on intact sensory nerves [42].

Vascular dysfunction, which itself contributes to the initial pathogenesis of type 2 diabetes, is further compounded by insulin resistance. Postprandial releases of insulin play an integral role in mediating microvascular dilation that is critical for optimal glucose delivery and uptake throughout the skeletal muscular system at rest [16]. However, impaired insulin signaling decreases insulin's influence over stimulating vasodilatory mechanisms, thus contributing to a cycle where there is a decreased ability to metabolize glucose and the existing environment of chronic hyperglycemia that's partly responsible for inducing vascular dysfunction is compounded [22]. Prolonged disruptions of vasodilatory mechanisms also enhance the influence of vasoconstrictive substances, leading to sustained increases in VSM tone that induce adverse structural adaptations including the proliferation and migration of VSM cells at arterial and capillary levels (Fig. 9.4) [43]. Such variances in anatomical structure, characterized by increased intima media thickness, decrease the sensitivity of VSM to vasodilating substances and subsequently increase vascular stiffness [43]. Ultimately, these changes in overall vascular function make the artery susceptible atherosclerotic mechanisms that contribute to the pathogenesis of CVD [41].

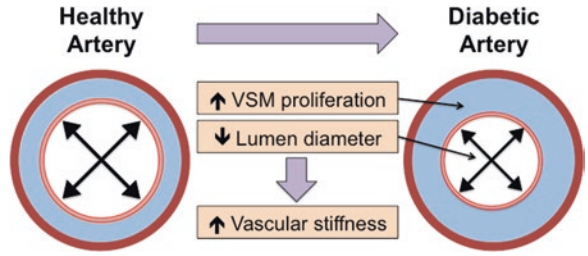

Fig. 9.4 Adverse structural adaptations, including vascular smooth muscle (VSM) proliferation and decreased lumen diameter, in the diabetic artery that decreases vasodilatory capacity and blood perfusion throughout the microvascular nutritive network, as well as increasing arterial stiffness and atherosclerotic mechanisms associated with cardiovascular disease

Inflammatory Cytokines, Growth Factors, and Biomarkers of Endothelial Dysfunction in Diabetes

It's widely accepted that vascular inflammatory responses are key indicators of vascular injury and the atherosclerotic changes that contribute to the pathogenesis of CVD [44]. Previous research demonstrated that serum C-reactive protein (CRP), an inflammatory biomarker, correlates negatively with the forearm blood flow response to acetylcholine, suggesting a relationship between systemic inflammation and endothelial function [45]. Moreover, hyperglycemia and insulin resistance are both known to contribute to microvascular dysfunction through several mechanisms, including the induction of a chronic state of vascular inflammation [46]. Thus, inflammatory biomarkers are often employed as an acceptable surrogate for tests of vascular reactivity to track cardiovascular health in diabetes (Table 9.2).

Increased expression of intercellular cell adhesion molecule-1 and vascular cell adhesion molecule-1 is observed in diabetic populations and has been shown to independently predict myocardial infarction [47–49]. Activated by cytokines and developing atherosclerotic lesions, the endothelium produces cellular adhesion molecules (CAMs) that mediate the attachment and transmigration of leukocytes across the endothelial surface, an important event in atherogenesis, [49]. Found firmly bound to the membrane of the endothelial cell in greatest concentration around the borders of atherosclerotic lesions and lesion prone areas, CAMs may also be released by activated endothelial cells from cell surface adhesions in a soluble form that circulates throughout the plasma [50, 51]. Therefore, the presence of soluble CAMs is thought to reflect their increased expression on the endothelial cell surface and provide a valuable marker of atherosclerotic changes [50].

Further to being acted upon, the endothelium contributes to the inflammatory process and, consequently, to the pathophysiology of vascular complications in diabetes. Indeed, pro-inflammatory molecules such as tumor necrosis factor-α (TNF-α) and CRP may promote endothelial cells to express an atherogenic phenotype [52]. When deciding which inflammatory biomarkers to track, it is important to note that TNF-α, CRP, interleukin-1, interleukin-6, monocyte chemoattractant protein-1, and macrophage migration inhibition factor are the main markers that have been proven to provide prognostic information about the progression and outcome of CVD in diabetic populations [53].

Noting that diabetes is also associated with pro-thrombotic and anti-fibrinolytic states, several molecules such as plasminogen activator inhibitor-1, tissue factor, fibrinogen, P-selectin, and von Willebrand factor may provide an indication of endothelial function [54]. Further to this, assessment of micro-ribonucleic acids and circulating microparticles may reveal the status of endothelial apoptosis,

Table 9.2 Biomarkers of endothelial dysfunction and inflammation in diabetes that indicate key events in the pathogenesis of cardiovascular disease

Biomarker	Status in diabetes	Diagnostic marker of:
ICAM-1	↑	Adhesion of leukocytes
VCAM-1	↑	Adhesion of leukocytes
IL-1	↑	Inflammation
IL-6	↑	Inflammation
TNF-a	↑	Inflammation
CRP	↑	Inflammation
MCP-1	↑	Inflammation
MIF	↑	Inflammation
VEGF	↑	Inflammation
Homocysteine	↑	Inflammation/hyper-coagulation
Adiponectin	↓	Inflammation/endothelial dysfunction
E-selectin	↑	Inflammation/adhesion of leukocytes
P-selectin	↑	Procoagulant state/adhesion of leukocytes
ET-1	↑	Elevated free fatty acids
PAI-1	↑	Altered coagulation process
Fibrinogen	↑	Altered coagulation process
vWF	↑	Altered coagulation process
BH4	↓	Decreased NO bioavailability
EPC	↑	Decreased NO bioavailability
ADMA	↑	Decreased NO bioavailability
miRs	↓↑	Either enhanced or inhibited eNOS activity
MPs	↑	Endothelial apoptosis, mechanical injury, and cellular activation by cytokines

ICAM-1 intercellular cell adhesion molecule, *VCAM-1* vascular cell adhesion molecule, *IL-1* interleukin-1, *IL-6* interleukin-6, *TNF-a* tumor necrosis factor-a, *CRP* C-reactive protein, *MCP-1* monocyte chemoattractant protein-1, *MIF* macrophage migration inhibition factor, *VEGF* vascular endothelial growth factors; *ET-1* endothelin-1, *PAI-1* plasminogen activator inhibitor-1, *vWF* von Willebrand factor, *BH4* tetrahydrobiopterin, *EPC* endothelial progenitor cells, *ADMA* asymmetrical dimethylarginine, *miRs* micro-ribonucleic acids, *MPs* circulating microparticles, *NO* nitric oxide, *eNOS* endothelial nitric oxide synthase, ↑ increased/upregulated, ↓ decreased/downregulated

mechanical injury, and cellular activation by cytokines. Endothelial dysfunction is also associated with elevated levels of homocysteine, which may share a relationship with increased concentrations of asymmetrical dimethylarginine. Elevated asymmetrical dimethylarginine disrupts NO synthesis, decreasing its bioavailability and thus impairing endothelial function. Decreased concentrations of tetrahydrobiopterin, an essential cofactor in the regulation of eNOS, also provide an indication of reduced NO bioavailability and endothelial function. More recently, endothelial progenitor cells, which are of lower concentration in those with diabetes, were also highlighted as viable biomarkers of endothelial dysfunction [52, 55, 56].

Exercise and Vascular Function in Diabetes

A sedentary lifestyle is an important modifiable risk factor for CVD in those with diabetes mellitus, for whom simple-to-follow exercise guidelines have been established by the American Diabetes Association (Table 9.3) [57]. While regular physical activity improves insulin sensitivity and glycemic control in those with type 2 diabetes, it may also inhibit the initiation or progress of CVD via its favorable effects on body weight, blood pressure, lipid profiles, fibrinolysis, and vascular function in both forms of diabetes [10]. The following will provide a brief overview focusing on the effect of exercise on mechanisms of vascular function and the favorable structural adaptations within the artery.

Table 9.3 The American Diabetes Association guidelines for exercise in those with diabetes mellitus [57]

Exercise mode	Frequency	Duration	Intensity	Rest
Aerobic training (e.g., jogging)	At least 5 sessions per week	30 min	Moderate to vigorous	No more than 2 days between sessions
Resistance training (e.g., weights)	At least 2 session per week	–	–	At least 2 days

Effect of Exercise on Vascular Reactivity and Structure

Although acute bouts of physical activity induce positive mechanisms of vascular function, it is habitual exercise that leads to the most favorable adaptations. Evidence suggests that increased exercise-mediated shear stress is initially the prominent mechanism mediating positive functional adaptations to exercise across healthy and diabetic populations [58]. Such vasodilatory potency has been best demonstrated by previous research revealing that exercise-mediated vascular function is preserved even in environments of chronic hyperglycemia such as that in diabetes [59]. Currently, the specific mechanism of vascular function by which vascular reactivity improves in response to habitual exercise is unclear in the human diabetic model. Observed improvements in responses to tests of vascular function such as FMD and arterial infusion of acetylcholine in diabetics following a sustained exercise program suggests increased bioavailability of NO as a possible mechanism [60]. Given that these tests do not entirely differentiate the involvement of NO from PGI_2 and EETs in mediating a vascular response, further research is needed to specify the exact mechanisms.

A unique in vivo study revealing that exercise improves vascular function by upregulating eNOS phosphorylation and protein expression provides some support for the implication of exercise in improving NO bioavailability [61]. It must be acknowledged, however, that reduced degradation of NO by reactive oxygen species and inflammation may also enhance NO bioactivity with training [61]. The attenuation of the deleterious effects of such free radicals may also be partly attributed to the role of exercise in improving antioxidant mechanisms and glycemic control disrupting the state of chronic hyperglycemia that exists in diabetes. Vasodilation mediated by muscular contractions during exercise allows for increased glucose transport to skeletal muscle by GLUT proteins [62]. This process, which is impaired in diabetics at rest, allows for increased glucose metabolism and overall improved glycemic control. With habitual exercise insulin sensitivity also increases in type 2 diabetics further contributing to a return to a normoglycemic state [59]. Finally, improved vasodilatory response to insulin stimulation may be partly attributed to a decrease in endothelin-1 signaling by insulin [16].

Evidence suggests that although positive alterations in endothelial function may be observed after a period of exercise, structural adaptations may not occur concurrently suggesting a delayed mechanism [60]. Decreased arterial stiffness, which may be attributed to improved vasodilatory function and decreased vasoconstrictive influence, may also be attributed to attenuation of VSM proliferation and a return to normal VSM apoptosis [8]. Habitual exercise also promotes pro-angiogenic factors resulting in increased capillary/muscle fiber ratio extending the reach of the nutritive vascular network and enhancing glucose metabolism capacity [58]. Although such structural adaptations can occur with a sustained exercise program and are crucial to reducing the risk of future CVD events, complete restoration of vascular function is unlikely [58].

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Exercise, Adiposity, and Regional Fat Distribution

10

Kerry J. Stewart and Devon A. Dobrosielski

The type 2 diabetes epidemic is largely attributable to being overweight or obese and being physically inactive [1, 2]. The consequences of obesity are severe, affecting the health, quality of life, and economics of the nation [3]. Based on body mass index (BMI), the 2012 National Health Interview Survey [4] reported that 35% of adults were overweight (BMI>25) and 28% were obese (BMI>30). The overall prevalence of obesity significantly increased 4.1% (0.51% annually) between 2004 and 2011 [5]. The June 2007 Consumer Reports health survey indicated that 41% of the adult US population is trying to lose weight. Sixty-three percent of people polled responded that they have dieted at some point in their lives. Besides being a risk factor for type 2 diabetes [6], obesity, one of the ten leading US health indicators, is also associated with increased risk for hypertension, dyslipidemia, coronary heart disease, stroke, and certain cancers [7]. In the Chicago Heart Association Detection Project in Industry study [8], after a mean follow-up of 32 years, individuals with no cardiovascular risk factors and for those with one or more risk factors at baseline, those who were obese in middle age had a higher risk of hospitalization and mortality from cardiovascular disease and diabetes in older age than those who were normal weight. In 2007–2010, the prevalence of diabetes, hypertension, and dyslipidemia was highest among obese (18.5%, 35.7%, 49.7%, respectively) followed by overweight (8.2%, 26.4%, 44.2%, respectively) and normal weight adults (5.4%, 19.8%, 28.6%, respectively) [9]. Some studies have shown that abdominal obesity may be a better predictor than overall obesity for disease risks and all-cause mortality [10]. Data from the National Health and Nutrition Examination Survey between the periods of 1999–2000 and 2011–2012 has shown that the age-adjusted waist circumference increased progressively and significantly from 95.5 cm (95% CI, 94.2–96.8 cm) in 1999–2000 to 98.5 cm (95% CI, 97.5–99.4 cm) in 2011–2012 and that the age-adjusted prevalence of abdominal obesity increased from 46.4% (95% CI, 42.1–50.8%) in 1999–2000 to 54.2% (95% CI, 51.3–57.0%) in 2011–2012. Thus, the mean waist circumference and the prevalence of abdominal obesity among US adults have increased markedly during the past 15 years, and over one-half of US adults had abdominal obesity in the period of 2003–2004. The prevalence of abdominal obesity is still increasing [11].

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Unfortunately, the problem of increasing levels of obesity is also a growing concern in children. In the National Heart, Lung, and Blood Institute Growth and Health Study [12], annual measurements were obtained from girls followed longitudinally between age 9 or 10 and 18 years, and self-reported measures were obtained at age 21–23 years. A total of 1166 Caucasian and 1213 African-American girls participated in the study. The rates of overweight increased through adolescence from 7% to 10% in the Caucasian girls and from 17% to 24% in the African-American girls. Girls who were overweight during childhood were 11–30 times more likely to be obese in young adulthood. Being overweight was significantly associated with an increased prevalence of cardiovascular disease risk factors including systolic and diastolic blood pressure, high-density lipoprotein cholesterol, and triglyceride levels. Similar to adults, the mean waist circumference and waist-height ratio and the prevalence of abdominal obesity among US children and adolescents greatly increased between 1988–1994 and 1999–2004 [13]. Using the 90th percentile values of waist circumference for gender and age, the prevalence of abdominal obesity increased by 65.4% (from 10.5% to 17.4%) and 69.4% (from 10.5% to 17.8%) for boys and girls, respectively. In 2011–2012, 17.95% of children and adolescents aged 2–18 years were abdominally obese defined by waist circumference, and 32.93% of those aged 6–18 years were abdominally obese defined by the waist to hip ratio. Thus, the prevalence of abdominal obesity among US children and adolescents may have leveled off but remains high [14]. This remains an important point since [15] of 9- to 11.5-year-old obese and lean children found that higher levels of total body fat and waist circumference were associated with increased levels of fasting insulin, C-reactive protein, and triglycerides and lower HDL cholesterol. Increased waist circumference and reduced cardiorespiratory fitness were strongly associated with increased insulin resistance. Clearly, interventions are needed to reduce fatness and increase fitness in children as these modifiable risk factors markedly increase their future risk of developing type 2 diabetes.

Nevertheless, whether obesity or fitness and activity level is more important to developing diabetes and diabetes-related cardiovascular complications is not entirely clear. In the Medical Expenditure Panel Survey [1], type 2 diabetes and cardiovascular disease risk increased with a higher body mass index regardless of activity level and increased with inactivity regardless of body mass index. Thus, both physical inactivity and obesity seem to be strongly and independently associated with these conditions. In the Nurses' Health Study [16], sedentary behaviors, especially TV watching, were associated with significantly elevated risk of obesity and type 2 diabetes, whereas even light to moderate activity was associated with substantially lower risk. In a 2007 report from the Nurses' Health Study [17], among 68,907 female nurses who had no history of diabetes, cardiovascular disease, or cancer at baseline, during 16 years of follow-up, the risk of developing type 2 diabetes increased progressively with increasing body mass index and waist circumference and with decreasing physical activity levels. In combined analyses, obesity and physical activity independently contributed to the development of diabetes; however, the magnitude of the risk contributed by obesity appeared to be greater than that imparted by physical inactivity.

Overweight and Obesity Defined

The most prevalent method for determining overweight and obesity classification is the body mass index. Body mass index is calculated as weight in kilograms divided by the square of height in meters and is expressed as kg/m^2. According to the National Institutes of Health's Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults [18], and as shown in Table 10.1, an individual with a body mass index greater than 25 kg/m^2 is considered overweight, whereas the threshold for obesity begins at 30 kg/m^2. Although the body mass index is readily obtainable and widely used in clinical settings and in population studies, it does not specify body fat distribution.

Table 10.1 Classification of weight status by body mass index

BMI	Classification
Below 18.5	Underweight
18.5–24.9	Healthy weight
25.0–29.9	Overweight
30 or higher	Obese

Based on body mass index, this table categorizes individuals into different weight classifications

Fat distribution, particularly the accumulation of abdominal visceral fat, may be a more powerful determinant of metabolic disease and cardiovascular disease risk than being merely overweight or obese. A study in 164 adult patients with established diabetes who have a history of poor glycemic control found that waist circumference by itself, independent of other risk factors comprising the metabolic syndrome, was a strong predictor of future glycemic control [19]. Fat distributed in the arms and legs, however, appears to impose little or no risk [20, 21]. Nevertheless, a study in men found that 6 months of exercise combined with weight loss was efficacious for reducing intramuscular lipids, which correlated with improvements in glucose tolerance [22]. After accounting for intramuscular lipid, the changes in other regional fat depots did not independently add to the prediction of changes in glucose tolerance. Further research is needed to fully clarify these mechanisms.

For abdominal obesity, waist circumference correlates strongly with abdominal fat content as determined by imaging methods [23] and provides a good quality clinical measurement for determining abdominal obesity. Among most adults with a body mass index of 25–34.9 kg/m^2, sex-specific cut points for waist circumference have been identified for an increased relative risk for the development of obesity-associated risk factors [18]. A waist circumference greater than 102 cm (40 in.) among men and greater than 88 cm (35 in.) among women indicates an increased risk. Of note, waist circumference cut points tend to lose their incremental predictive power in individuals with a body mass index ≥35 kg^2 because they will typically exceed the waist circumference cut points noted.

Despite the detrimental effects of abdominal obesity on cardiometabolic health, the Shape of the Nations survey [24], which was performed to assess knowledge and understanding of the increased risk associated with abdominal obesity, showed the need to increase awareness of this health risk. On average, 39% of all people visiting a primary care physician worldwide were overweight or obese. In North America, this proportion was 49%. Abdominal obesity was recognized by 58% of primary care physicians worldwide as a significant risk factor for heart disease; an equal proportion considered high BMI to be a risk factor. Worldwide, 45% of all physicians reported never measuring waist circumference and 52% overestimated the waist circumference that puts their patients at risk. In the general population, 42% were aware of the association between abdominal obesity and risk, but 60% considered high BMI an important risk factor. Only a small proportion of the general population knew their waist circumference or knew the waist circumference that is considered to confer significantly increased risk. More than half (59%) of at-risk patients had not been informed by their physicians about the association of abdominal obesity with heart disease. Another study published in the same year reported similar results [25].

A Brief Review of Mechanisms Linking Obesity with Type 2 Diabetes

A summary of several of the mechanisms leading to the development of diabetes and the risk of developing cardiovascular disease complications from diabetes related to adiposity and inactivity is shown in Fig. 10.1. A key physiological mechanism in this pathway is that increased general and abdominal obesity is strongly associated with insulin resistance, which represents the principal underlying defect leading to type 2 diabetes. Consequently, there is a gradual rise in insulin production, which eventually cannot compensate for increasing levels of insulin resistance. This can lead to a complete halt in the ability to produce

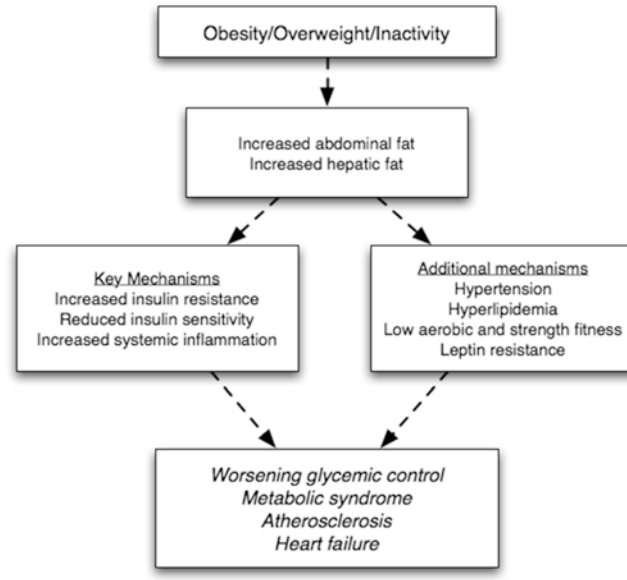

Fig. 10.1 A summary of several mechanisms leading to the development of diabetes and the risk of developing cardiovascular disease complications from diabetes related to adiposity and inactivity

insulin in patients who do not take action such as exercise or weight loss to reduce their insulin resistance. This may not be helpful in some people; they may require medications. According to Lazar [26], the epidemic of obesity-associated diabetes is a major crisis in modern societies, in which food is plentiful and exercise is optional. Arguably, the obesity/diabetes epidemic is the result of the 1977 nutrition guidelines that advocated the reduction in fat, which then resulted in the increased intake of carbohydrates, specifically refined carbs and sugars. Food has been plentiful before the guidelines [27]. This review summarized the evidence for lower-carbohydrate diets and clearly shows the epidemic has taken off over the last 30 years. Diabetes is a form of carbohydrate intolerance. The relationship between obesity and diabetes is of such interdependence that the term "diabesity" has been coined [28]. Insulin resistance is a central pathogenic factor for the metabolic syndrome and is associated with both generalized obesity and the accumulation of fat in the omental and intramyocellular compartments [29]. The accumulation of intramyocellular lipids may be due to reduced lipid oxidation capacity [28]. In the context of the current obesity epidemic, it is imperative to consider interventions that promote weight loss and ameliorate insulin resistance [29].

Adipose tissue is a dynamic endocrine organ that secretes a number of factors that are increasingly recognized to contribute to systemic and vascular inflammation [30–32]. Many of these factors, collectively referred to as adipokines, appear to regulate, directly or indirectly, a number of the processes that contribute to the development of atherosclerosis, including hypertension, endothelial dysfunction, insulin resistance, and vascular remodeling. Several adipokines are preferentially expressed in visceral adipose tissue, and the secretion of proinflammatory adipokines is elevated with increasing adiposity. Biomarkers of inflammation include leukocyte count, tumor necrosis factor-alpha (TNF-alpha), interleukin 6 (IL-6), and C-reactive protein, among others, are associated with insulin resistance, and predict the development of type 2 diabetes and cardiovascular disease [33]. Among 44 men and women, AT IL-18 mRNA content and plasma IL-18 concentration were higher in the obese group than in the nonobese group, and these were positively correlated with insulin resistance [34]. Visceral fat accumulation appears to accelerate the adverse effects of these processes leading to the development of diabetes and atherosclerosis. Adiponectin, a protein that has both anti-inflammatory and insulin-sensitizing effects, is downregulated in

obesity [33]. Many consider adiponectin to be the "common soil" linking type 2 diabetes and coronary heart disease [35]. Among 3640 healthy men aged 60–79 years, lower levels of adiponectin were associated with increased waist circumference and decreased levels of alcohol intake and physical activity. Lower adiponectin level was also associated with increased levels of insulin resistance, triglyceride, C-reactive protein, tissue plasminogen activator, and alanine aminotransferase and with lower levels of HDL cholesterol and factor VIII, factors associated with diabetes. The risk of having of metabolic syndrome status decreased significantly with increasing adiponectin. Among 148 women, aged 18–81 years with a BMI range of 17.2–44.3 kg/m^2, plasma adiponectin did not change with age, but lower levels were associated with increased general and abdominal obesity, insulin levels, and glucose utilization during hyperinsulinemic-euglycemic clamp studies [36]. Taken together, all of these data suggest adiponectin may be a strong marker of risk for diabetes.

Leptin, a protein hormone that plays a central role in regulating energy intake and energy expenditure, is secreted from adipose tissue. Although leptin is a signaling protein that reduces appetite, obese persons appear to be resistant to the effects of leptin. As circulating leptin levels increase, cells that respond to leptin become desensitized to its effects. Thus, a cycle is created which leads to worsening insulin resistance and obesity and eventually diabetes. Hyperleptinemia may be involved in cardiac autonomic dysfunction in patients with type 2 diabetes and visceral obesity [37]. Obesity is also associated with an increase in adipose tissue macrophages, which also participate in the inflammatory process through the elaboration of cytokines [33]. In a 10-year prospective longitudinal study of 748 adults, baseline leptin levels predicted the development of obesity, and after adjustment for obesity, the development of glucose intolerance, insulin resistance, and metabolic syndrome [38] is closely associated with endothelial dysfunction and is recognized as one of the cardiovascular risk factors clustering in metabolic syndrome [32]. Obesity is also associated with oxidative stress, and the oxidation of LDL contributes to the development of atherosclerotic lesions. Among 586 men and women enrolled in a population-based study conducted in Spain [39], increased BMI and waist circumference were each associated with increased levels of Ox-LDL and C-reactive protein, independent of traditional cardiovascular disease risk factors. Of note, the risk of high Ox-LDL was more strongly and independently associated with increased waist circumference independently of BMI in the population. These data further emphasize the high risk conferred by high levels of abdominal fat deposition. The best predictor of microvascular, and to a lesser extent macrovascular complications in patients with type 2 diabetes, is glycemic control (HbA1c) [65–68].

Hepatic Fat

Nonalcoholic fatty liver disease (NAFLD) is a chronic liver disease that can progress to cirrhosis and hepatocellular carcinoma [40]. The incidence of nonalcoholic fatty liver disease (NAFLD) is increasing due to its prevalence in obesity, diabetes, and insulin resistance syndrome [41, 42], though some patients have normal glucose tolerance or body weight [42]. According to the third National Health and Nutrition Examination Survey, more than 6.4 million adults in the United States have nonalcoholic fatty liver disease [43, 44].

The prevalence of NAFLD increases steadily to 70–90% in obesity or type 2 diabetes [45]. Cross-sectional data show that NAFLD is associated with systemic inflammation and insulin resistance [46]. A study of 30 healthy normal and moderately overweight nondiabetic men found that fat accumulation in the liver is independent of body mass index and intra-abdominal and overall obesity, and characterized by several features of insulin resistance [47]. In a 2007 review, Targher [45] notes the association of NAFLD with multiple classical and nonclassical cardiometabolic risk factors, including an association of increased NAFLD with greater carotid artery intima-media thickness and plaque and impaired

endothelial function, independent of obesity and other metabolic syndrome components. These findings suggest that NAFLD might be an early mediator of cardiovascular disease. Overall, there is limited randomized trial data on lifestyle interventions for reducing hepatic fat [40]. In a 12-week study, adolescents with NAFLD at baseline showed significant differences in body mass, BMI, and visceral and subcutaneous fat versus controls [41]. A diet, exercise, and counseling program reduced glucose, abdominal fat, and NAFLD. In a small non-randomized study, ten subjects had significant reductions of hepatic fat in 10 days [48]. In another non-randomized study of eight obese persons with diabetes, dietary weight loss of 8 kg was associated with reduced hepatic fat, hepatic insulin resistance, and normalization of basal glucose production [49]. A 6-month study of caloric restriction with or without exercise found that either intervention leads to reduced lipid deposition in visceral and hepatic tissue and reduced insulin resistance [50]. Clearly, additional research is needed to delineate the role of exercise and weight loss for reducing hepatic fat.

Physical Activity for Managing Obesity and Altering Body Composition

While many individuals with type 2 diabetes need to reduce their overall body weight, not all individuals who are overweight or obese will develop the full range of obesity-related metabolic complications [51]. Variations in body fat distribution, and particularly those with increased abdominal fat accumulation, seem to be at a high risk for developing type 2 diabetes and its complications. It is well established that physical activity improves fitness, reduces cardiovascular and metabolic disease risk factors, and is effective for increasing insulin sensitivity and reducing A1C. Exercise training does not typically result in substantial weight loss in relatively short periods of time. Successful programs for weight loss and maintenance most often rely on a combination of diet, exercise, and behavior modification. Low-carbohydrate diets appear to outperform calorie-restricted diets and low-fat diets in every outcome [27].

Exercise alone, without concomitant dietary caloric restriction and behavior modification, tends to produce only modest weight loss in the range of 2 kg [52]. Weight loss may be modest because overweight and obese persons may not be able to carry out enough exercise to burn a sufficient number of calories to markedly effect energy balance. Furthermore, the caloric expenditure with exercise can be easily counterbalanced by eating more or becoming less active outside of structured exercise sessions [52]. Exercise is associated with numerous health benefits but not from the standpoint of burning calories to achieve marked weight loss by itself, at least in the short-term. Benefits of exercise of particular importance in those with diabetes include improved insulin sensitivity, and glut 4 translocation LPL activity in muscle [53, 54]. Attaining greater amounts of weight loss requires a high volume of exercise, which is difficult to acheive and sustain in most individuals.

[55, 56]. In a randomized study of diet and exercise, exercise of 700 kcal/day, which requires about an hour of moderate-intensity aerobic exercise, produced as much fat loss as what might be expected from a 700 kcal/day dietary deficit [57]. A recent randomized study tested the effect of a 25% energy deficit by diet alone or diet plus exercise on body composition and fat distribution [58]. After 6 months, the calculated energy deficit across the intervention was not different between caloric restriction and caloric restriction plus exercise. Overall, participants lost 10% of their body weight, about 24% of their fat mass, and 27% of their abdominal visceral fat. Rather than the focus of exercise being a tool to "burn calories," Thus, exercise can play an equivalent role to caloric restriction in terms of energy balance but it also has the advantage of increasing aerobic fitness, which has other beneficial effects on cardiometabolic health.

Less appreciated is the fact that maintaining a high level of physical activity will result in favorable alterations in body composition, independent of total weight loss. More specifically,

exercise training has been consistently shown to reduce abdominal obesity, and resistance training will preserve or increase lean mass. This benefit of exercise is of clinical importance since abdominal obesity is at the core of the diabetes epidemic. Among men who participated in 13 weeks of supervised exercise, regular exercise without weight loss was associated with a substantial reduction in total and visceral fat and in skeletal muscle lipid in obese indivduals with and without and type 2 diabetes [59]. Combined with the observation that abdominal obesity conveys a significant health risk, and that increased fitness is associated with reduced morbidity and mortality independent of body mass index, these findings have important clinical and public health implications. Still, it is important to recognize that the presence of diabetes may attenuate visceral fat loss with exercise [60]. The important role of exercise was also shown in a study [61] in which modest weight loss by diet or diet plus exercise for 14 weeks resulted in similar improvements in total abdominal subcutaneous fat and glycemic status in older women with type 2 diabetes; however, exercise was necessary for abdominal visceral fat loss. In healthy persons, exercise reduced abdominal fat [62–65] with some data suggesting a preferential loss of visceral fat [57, 63, 65]. In a randomized controlled trial involving obese, sedentary, postmenopausal women aged 50–75 years, exercisers showed significant differences from controls in baseline to 12-month changes in body weight and total body fat, intra-abdominal, and subcutaneous abdominal [65]. Of note, a dose-response for greater body fat loss was observed with increasing duration of exercise. Conversely, a review of exercise and changes in body composition reported that although well-controlled short-term studies suggest a dose-response relationship between exercise and abdominal fat loss, there is insufficient evidence of such a relationship long term [66]. In a 3-month study involving obese men, weight loss induced by increased daily physical activity without caloric restriction substantially reduced obesity (particularly abdominal obesity) and insulin resistance [57]. Among older persons with hypertension, many of whom had metabolic syndrome, a 6-month exercise training program was associated with reductions in total abdominal fat of 12%, abdominal visceral fat of 18%, and abdominal subcutaneous fat of 9%, despite a modest 2.2 kg weight loss. Changes in abdominal fatness were the strongest determinants of improvements in metabolic syndrome [67]. Among persons with diabetes [68], aerobic fitness increased by 41% and insulin sensitivity by 46% after 2 months of exercise. There was a 48% loss of visceral fat and an 18% loss of subcutaneous fat despite no weight loss. Among lean and obese men with and without diabetes, 13 weeks of supervised exercise, five times per week at a moderate intensity, did not result in a body weight change [59]. However, significant reductions in total, abdominal subcutaneous, and visceral fat were observed in all groups. The reduction in total and abdominal subcutaneous fat was not different between groups; however, the reduction in visceral fat was greater in the obese and type 2 diabetic groups versus the lean group. A significant increase in total skeletal muscle, high-density muscle area, and mean muscle attenuation was observed independent of group. Among men with and without diabetes, a 12-week program of aerobic exercise produced a reduction in waist circumference and fasting IL-6 concentrations, suggesting clinically relevant improvements in cardiometabolic risk factors despite no change in body weight [69].

Type of Exercise

Aerobic exercises entail rhythmic repetitive movements of large muscle groups against small resistance. Such activities can be performed for a relatively long time at a low or moderate intensity. There is an increasing amount of data showing benefits of high-intensity interval training. These include [70–72] walking, jogging, swimming, cycling, rowing, jumping rope, skating, running, and cross-country skiing. These activities increase the demand for oxygen, and the muscles adapt by enhanced extraction of oxygen, which is the reason they are called *aerobic activities*. Sustained slow-movement activity,

often involving small muscle groups against high resistance, is known as *static activity* or *resistive exercise*. Examples are weight lifting, pushups, sit-ups, carrying heavy packages, and handgrips. Most activities requiring lifting and straining, such as shoveling, have a large static component.

While most studies on the treatment and prevention of obesity have focused mainly on aerobic activities, resistance training is a behaviorally feasible choice for weight control [73, 74]. As stated earlier, aerobic exercise by itself does not typically result in marked reductions in weight loss although abdominal fat loss can be substantial. The American Diabetes Association consensus statement on physical activity/exercise and type 2 diabetes says that a program of weight control is recommended, and this should include aerobic exercise and, in the absence of contraindications, should also include resistance exercise [52]. Resting energy expenditure decreases with aging, and this decrease is closely correlated to losses in skeletal muscle mass [75]. Exercise training that includes a resistance component should also preserve or increase lean body mass. This benefit of resistance training is particularly important in older persons since the mechanical stimuli provided by the task of daily living are not sufficient to offset the loss of skeletal mass and function with aging [73].

Reistance exercise can increase muscle mass by 1-2 kg after a few months of training [76]. Theoretically, a gain of 1 kg in muscle mass should result in a resting energy expenditure increase of about 21 kcal/kg of new muscle [77]. Resistance training studies report resting energy expenditure increases in the range of 28–218 kcal/kg of muscle [78–81]. Thus, when sustained over years or decades, this mode of exercise can make clinically important differences in daily energy expenditure.

Resistance training can also reduce total body fat mass in men [82, 83] and women [82, 84–86], independent of dietary caloric restriction. Several studies have demonstrated decreases in visceral adipose tissue after resistance exercise [82, 83, 86–88].

Treuth and coworkers assessed body composition in older men using dual-energy x-ray absorptiometry (DXA) [83] and in older women using computed tomography (CT) [86] and observed significant decreases in visceral fat following 16 weeks of resistance training. Ross et al. [87, 88] used magnetic resonance imaging to measure regional fat losses after exercise combined with diet interventions. In their first study [87], both diet plus aerobic exercise *and* diet plus resistance training elicited similar losses of visceral fat that were greater than losses of whole body subcutaneous fat. In a follow-up study [88], they isolated the effects of endurance exercise training and resistance exercise by comparing the responses to diet alone and diet combined with each training modality in middle-aged obese men. All three groups lost significant amounts of total body fat, and all three groups experienced a significantly greater visceral fat loss compared with whole body subcutaneous fat loss. The changes amounted to a 40% reduction in visceral fat in the RT and diet group, 39% in the endurance training and diet group, and a 32% reduction in the diet-only group.

As reviewed by Braith and Stewart [73], resistance training plays an important role in glycemic control. Muscle contraction increases glucose uptake in skeletal muscle. While aerobic exercise uses large muscle groups for long periods of time, resistance training that uses the major muscle groups may provide comparable or even greater recruitment of muscle mass during an exercise workout session. Although there is little data that resistance training prevents type 2 diabetes, this mode of exercise reduces acute insulin responses during oral glucose tolerance testing in healthy persons and in men and women with diabetes and improves insulin sensitivity in persons with diabetes and insulin resistance. Among older men who were overweight or obese [89], participation in aerobic versus resistance exercise for 6 months resulted in comparable improvements in glucose metabolism, whereas an increase in insulin activation of glycogen synthase occurred only with aerobic exercise.

The American College of Sports Medicine has recommended the use of progressive resistance

training as part of a well-rounded exercise program for individuals with type 2 diabetes. ACSM now has a joint position stand with ADA on exercise and type 2 diabetes [90, 91]. Similarly, in the absence of contraindications, the American Diabetes Association [52] also recommends resistance training for those with type 2 diabetes. These recommendations are supported by evidence that resistance is an integral component in the therapeutic management of glycemic control in type 2 diabetics [92, 93], particularly if the resistance training is performed in a supervised versus a home-based program [94]. Among older men with type 2 diabetes who participated in a 16-week supervised resistance training program [93], though there was no weight loss, there were reductions in visceral and subcutaneous fat which were accompanied by increased insulin sensitivity and decreased fasting blood glucose.

Though performing resistance training by itself rather than in combination with aerobic exercise appears to contribute to some aspects of improving body composition such as reducing abdominal fatness and increasing lean tissue, the available evidence does not support its exclusive use without aerobic exercise. Thus, for the overweight or obese individual with type 2 diabetes whose goals include improved glycemic control, a combined exercise routine consisting of both aerobic and resistance remains the primary recommendation for most patients. Guidelines for medical screening for participation in exercise training can be found in Chapter 16.

Summary

Being overweight or obese and physical inactivity markedly increase the risk of developing cardiovascular and other complications in persons with type 2 diabetes. Growing evidence highlights the particularly adverse effect of having abdominal obesity on cardiometabolic health. There is also an increasing prevalence of nonalcoholic fatty liver disease, which also contributes to increased cardiometabolic risk among persons with diabetes. Many studies show that increasing levels of physical activity and participation in exercise training programs contribute to weight reduction, along with dietary interventions. However, independent of total body weight loss, exercise reduces abdominal obesity and, along with the concomitant benefits on multiple cardiometabolic risk factors such as hypertension, insulin resistance, and hyperlipidemia, among others, plays a central role in reducing the complications of diabetes. There is some but not entirely conclusive evidence, mainly because of the lack of randomized, controlled trials, that exercise also reduces hepatic fat. Though exercise has been widely recognized as an important component of the overall medical management for type 2 diabetes, its benefits go beyond the established benefits on fitness levels. The evidence as discussed in this chapter clearly notes the benefits of exercise on favorable altering body composition, which can occur independent of weight change. The resulting reduction in regional fat depots is an especially important result of regular physical activity. For most individuals with diabetes, participation in both aerobic and resistance exercise is recommended to maximize benefits on body composition. These benefits consist of reduction in fat and increased in lean mass.

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11 Exercise, Blood Flow, and the Skeletal Muscle Microcirculation in Diabetes Mellitus

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Introduction

Any attempt to understand limitations in exercise function with diabetes would be incomplete without considering the influences of the cardiovascular system and blood flow regulation. Exercise capacity (VO_{2max}) is impaired both in type 1 diabetes (T1DM) and type 2 diabetes (T2DM) [1–6], and this impairment is predictive of mortality [7–11] and cardiovascular complications [12–15]. These relationships suggest that exercise capacity is a sensitive measure of early changes in cardiovascular function with diabetes. This notion is further supported by the associations of cardiac output and skeletal muscle blood flow (SMBF) with VO_{2max} in healthy individuals [16–18]. Limitations in both cardiac output and SMBF have been reported in diabetes [19–22], indicating that blood flow may be a component of exercise limitations in diabetes. In addition to reduction of total blood flow, increased heterogeneity of microvascular blood flow distribution [23–26], loss of capillary perfusion [27, 28], and reduced whole-body oxygen extraction [29] have also been reported, indicating that heterogeneous distribution of blood flow may also play a role in limiting aerobic capacity in diabetes. In this chapter, we will explore known changes to both blood flow and its distribution in diabetes, beginning with changes in cardiac function and progressing to the capillary level.

Cardiac Output

Both T1DM and T2DM are associated with left ventricular diastolic dysfunction [30, 31]. Diastolic dysfunction in diabetes is associated with fibrotic remodeling of the myocardium [32]

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and eventually leads to heart failure. As fibrotic remodeling progresses, the contractile ability of the heart is not necessarily impaired, sometimes but not always allowing for maintenance of systolic function [33]. The result of these changes is that stroke volume (SV) is reduced in diabetes [19], and cardiac output is impaired under conditions in which the heart cannot compensate with increased heart rate (HR), such as in maximal exercise [19, 21]. It is not entirely clear from the literature whether the subclinical cardiac dysfunction observed in diabetes contributes to limitations in exercise capacity. Baldi et al. found using an inert gas rebreathing technique that whole-body arteriovenous oxygen difference during exercise is reduced in diabetes and that reductions in oxygen extraction are associated to reductions in VO_{2max} [29], whereas Gusso et al. found using a similar CO_2 rebreathing technique that arteriovenous oxygen difference was not altered by diabetes, but that reductions in CO and VO_{2max} were associated [19]. This juxtaposition of results suggests that differences in blood flow distribution (e.g., greater fractional perfusion of non-muscle tissues in diabetes) or mitochondrial demand are co-determinants of exercise capacity in diabetes along with CO. Given the substantial similarities between the cardiac and skeletal muscle, it is probable that impaired cardiac function is itself a manifestation of muscle functional limitations in diabetes rather than their root cause.

Reduced cardiac output in diabetes is further compounded by the association between diabetes and hypertension [34, 35]. In particular, large arteries become less responsive to vasomotor stimuli in diabetes, and this effect is particularly pronounced in assays of nitric oxide (NO)-mediated endothelium-dependent vasodilation resulting from pharmacological agonists [36, 37] and fluid shear stress [38, 39]. Reduction in vasomotor (and especially vasodilatory) function tends to occur in conjunction with fibrotic remodeling of large arteries [40], and vessel stiffness itself may contribute to reduced dynamism in vessel tone. In people without diabetes, hypertension causes impairments in both cardiac output and VO_{2max} [41]. The rate of hypertension is significantly elevated in both T1DM and T2DM relative to the general population [36, 37], which suggests that hypertension and the associated reductions in cardiac output may contribute to population-level differences in exercise capacity with diabetes. It is worth noting, however, that limitations in VO_{2max} are observed in diabetes even in the absence of hypertension or any other overt cardiovascular disease state [2, 31]. Although hypertension likely contributes to exercise limitations at the population level, hypertension alone cannot fully account for the exercise limitations observed in diabetes.

Skeletal Muscle Blood Flow

Independently of cardiac and large vessel function, oxygen delivery to the skeletal muscle could be impaired by inappropriate distribution of blood flow among organs. As previously discussed, the vasomotor dynamism of large blood vessels is reduced in diabetes [37–40]. It is likely that this effect would interfere with redistribution of blood flow from inactive organs (e.g., mesenteric blood flow) to the active skeletal muscle, but this hypothesis has not yet been directly tested. In addition to possible differences in the dynamism of blood flow distribution, lean body mass as a fraction of total body mass is reduced in T2DM [42, 43]. This effect would be expected to impair whole-body oxygen extraction by increasing blood flow to non-oxidative tissues as a fraction of total blood flow [44]. However, body composition is not necessarily altered in T1DM [45, 46], and impaired VO_{2max} is found not only when comparing of T2DM and lean, healthy individuals [1] but also in T1DM [3, 4] and even when comparing of T2DM and obese, sedentary individuals without diabetes [47]. It is therefore likely that the contributions of macrovascular blood flow distribution to reductions in aerobic capacity can occur independently of changes in body composition.

Regardless of whether these differences stem from cardiac dysfunction, vascular dysfunction, or something else entirely, SMBF measured at the whole-limb level is often but not always reduced in diabetes [20, 22, 48–51]. Even if SMBF were to reach normal steady-state levels, the hyperemic

response to exercise is often slowed in diabetes [48, 49, 52, 53]. It is likely that slowed blood flow kinetics contribute to the increased discomfort the onset of exercise reported in diabetes [53–55]. Interestingly, there are some studies in which steady-state SMBF is not reduced in diabetes and yet aerobic exercise capacity is still impaired [56–58]. This juxtaposition of findings implies that organ-level (as opposed to whole-body) oxygen extraction is impaired in diabetes in addition to reductions in SMBF. True to form, human MRI studies by Zheng et al. [59] and animal catheterization studies by Frisbee et al. [60] show an impaired ability to increase skeletal muscle oxygen extraction fraction (SMOEF) following muscle contraction. This effect of diabetes does not appear to be unique to the skeletal muscle, given that tissue-level oxygen extraction is also reduced in diabetic retinopathy and neuropathy [61, 62]. As is also true of impaired cardiac function and hypertension, it appears likely that reduced SMBF contributes to but is not necessary for diabetic exercise dysfunction.

Microvascular Perfusion Heterogeneity

Impairment of oxygen delivery independently in T2DM of SMBF is likely caused by increased heterogeneity of microvascular perfusion. Frisbee et al. have shown in the obese Zucker rat (OZR) model of T2DM that microvascular perfusion heterogeneity is increased [25], that this perfusion heterogeneity contributes to peripheral vascular disease [23, 26], that reversal of this perfusion heterogeneity with a cocktail of anti-adrenergic and endothelium-targeting drugs acutely normalizes skeletal muscle function [24, 25, 60], and that these effects can be predicted from first principles in mass transport and anatomy [63]. Importantly, microvascular perfusion heterogeneity in the OZR model of Frisbee et al. caused impaired muscle oxygenation in part through heterogeneous red blood cell (RBC) distribution at the capillary level [24, 63]. This result is further recapitulated by the intravital microscopy results of Poole et al. in the Goto-Kakizaki (GK) rat model of T2DM [28] and in the streptozotocin-treated model of T1DM [27]. Not only are microvascular perfusion heterogeneity and a resulting impairment in oxygen availability observed in all these animal models of diabetes, it has also been shown that microvascular perfusion heterogeneity leads to impaired oxygen extraction independently of total blood flow on both theoretical [63–66] and empirical bases [26, 67, 68]. The mechanism for this impairment (some capillaries are underperfused, while others are overperfused and effectively saturate their capacity for oxygen delivery) is not tissue specific, consistent with observations of oxygen extraction limitations not only in the skeletal muscle [59, 60] but also in other peripheral tissues [61, 62]. In addition to increases in the heterogeneity of microvascular perfusion, reduced capillary density is also observed in diabetes [69, 70], further reducing oxygen availability independently of SMBF. Combined, the effects of microvascular perfusion heterogeneity and reduced capillary density can account for discrepancies between SMBF and aerobic capacity [63].

Microvascular dysfunction and perfusion heterogeneity in diabetes may be caused by degradation of the endothelial glycocalyx. The endothelial glycocalyx is a semipermeable, space-filling layer of glycoproteins and glycosaminoglycans lining the luminal surface of the endothelium. Glycocalyx degradation has been reported in both T1DM and T2DM [71–73], and glycocalyx degradation is associated both in diabetes and in health with increased risk and early signs of future cardiovascular morbidities [74–78], as is exercise capacity [7–11]. Degradation of the endothelial glycocalyx causes a similar redistribution of RBCs within the capillary network to that observed in diabetes whether glycocalyx degradation is achieved by enzymatic means [79, 80] or as a result of oxidative stress stemming from acute hyperglycemia or infusion of oxidized LDL [81, 82]. Furthermore, physiologic glycocalyx degradation during sepsis or adenosine infusion has been shown to cause reductions in tissue oxygen extraction [83, 84]. Although the connection between glycocalyx degradation and reduced aerobic capacity in diabetes has not yet been directly tested, it is noteworthy that glycocalyx

degradation is involved in glomerular hyperfiltration (an early sign of diabetic nephropathy) [85, 86], glycocalyx degradation causes acute insulin resistance [87], and insulin resistance, glomerular hyperfiltration, and reduced aerobic capacity are all mutually correlated in diabetes [15, 88]. Mass transport analysis reveals that insulin resistance and impaired exercise capacity can both be predicted from perfusion heterogeneity [66], and so it is likely that the perfusion effects of glycocalyx degradation contribute to these phenotypes. Simulation studies indicate that glycocalyx charge density (as a determinant of permeability) modulates the heterogeneity/homogeneity of microvascular perfusion [89], providing a plausible mechanism for increased microvascular perfusion heterogeneity in diabetes. Ongoing studies within our group seek to clarify the relationship between the endothelial glycocalyx and diabetic exercise dysfunction.

Considering Causality

Because blood flow and its distribution are altered at every level of the circulation in diabetes from the heart to the smallest capillaries, it is useful to consider precisely which effects might play a causal role in reducing aerobic capacity. Studies in which CO, SMBF, or both are normal in diabetes and yet aerobic capacity is reduced show that changes in macrovascular parameters are not necessary for diabetic exercise dysfunction [2, 31, 56–58]. Although similar macrovascular changes are sufficient to reduce aerobic capacity in the general population [16–18], the fact that they are not necessary for reduced aerobic capacity in diabetes indicates that the root cause of diabetic exercise dysfunction may lie elsewhere. Antioxidant therapy normalizes many macrovascular parameters in diabetes [90, 91] and yet has not been shown to normalize exercise capacity (and would be expected to interfere with exercise training [92, 93], whereas the microvascular dysfunction reported by Frisbee et al. is acutely reversible and its reversal improves skeletal muscle function [25, 60]. This combination of results indicates that microvascular dysfunction might play a causal role in diabetic exercise impairments. Given that the heart and the vessel walls of microvessels are themselves heavily vascularized and therefore subject to microcirculatory influence, it is plausible that cardiac and macrovascular dysfunction in diabetes are themselves caused by microvascular dysfunction.

In this overview of changes in blood flow and its distribution in diabetes, we sought to assess the possibility that exercise dysfunction in diabetes might be an early detector of impaired cardiovascular dysfunction. Blood flow is often (but not always) reduced at the whole-body level [19, 21], at the whole-limb level [20, 22, 48–51], and at the capillary level [27, 28] in diabetes. However, reduced aerobic capacity is sometimes observed even when blood flow is maintained [2, 31, 56–58]. This apparent discrepancy may be explained by microvascular alterations including increased perfusion heterogeneity [24, 25, 60] and reduced capillary density [69, 70]. Microvascular perfusion heterogeneity is itself a plausible contributor cardiac and macrovascular dysfunction due to its effects on tissue oxygenation [64, 65, 67, 68] and can be recapitulated by glycocalyx degradation [79–82], which also occurs in T1DM [72], in T2DM [71], and more generally in states of acute nutrient stress [75, 81, 82]. Further studies will be required to clarify the relationships between glycocalyx degradation, blood flow, and microvascular perfusion. It is even possible that the etiology of impaired exercise capacity varies from individual to individual, but it is clear that oxygen delivery limitations resulting from impairments in blood flow or its distribution play a central role.

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Part III

Management and Treatment

12 Diabetes Prevention Program (DPP) and the Action for Health in Diabetes (Look AHEAD) Study: Lessons Learned

Bethany Barone Gibbs and John M. Jakicic

The Diabetes Prevention Program (DPP) and the Action for Health in Diabetes (Look AHEAD) Study were large, randomized trials that evaluated the effects of a lifestyle intervention, including diet and physical activity, in persons at risk for or with type 2 diabetes. This chapter will review the study design, primary findings, and lessons learned about the health benefits of increasing physical activity and cardiorespiratory fitness in these seminal clinical trials.

The Diabetes Prevention Program (DPP)

DPP was a landmark clinical trial that investigated whether an intensive lifestyle intervention or the drug metformin could prevent or delay type 2 diabetes in adults at high risk for developing the disease (Table 12.1). The study included 3234 adults at 27 sites in the United States with both impaired glucose tolerance (2-h plasma glucose 140–199 mg/dL based on a 75-g oral glucose tolerance test) and elevated fasting plasma glucose (95–125 mg/dL, except in American Indian participant sites). Other inclusion criteria were age ≥25 years and body mass index ≥24 kg/m^2 (≥22 kg/m^2 for Asian participants) [1]. The randomized participants had an average age of 51 years and average body mass index of 34 kg/m^2 and were 68% female. Also, because minority populations are at elevated risk for developing type 2 diabetes, the DPP recruited a diverse sample with 45% minorities (black, Hispanic, American Indians, Asian, and Pacific Islander) [2]. The study was planned to recruit for just under 3 years and follow all participants until the trial end date which was 5 years after recruitment began [1].

DPP Intervention

The study included three arms: (1) metformin (850 mg, twice daily), (2) placebo, or (3) an intensive lifestyle (diet + physical activity) intervention. We will focus on the lifestyle intervention in this chapter. The behavioral intervention targeted a ≥7% weight loss and ≥150 min/week of physical activity by 6 months after randomization. This was followed by an individualized maintenance phase for the remainder of the study period. Weight loss was achieved by focusing on reducing dietary fat intake and reducing calories by 500–1000 kcals/day [3]. The dose of physical activity that was prescribed in DPP helped inform the current recommendations for physical activity in general populations [4] and among persons

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Table 12.1 DPP at a glance

Participants	Adults with impaired glucose tolerance and elevated fasting glucose who were overweight or obese
Study design	Three-arm randomized clinical trial comparing the effects of an intensive lifestyle intervention, metformin, or placebo on type 2 diabetes incidence
Lifestyle intervention	Lifestyle coaches delivered an individualized intervention targeting a ≥7% weight loss and ≥150 min/week of physical activity (i.e., brisk walking or similar intensity)
Primary finding	Incident type 2 diabetes was significantly reduced by 58% with intensive lifestyle intervention and 31% with metformin as compared to placebo

with type 2 diabetes [5]. The intervention utilized an individual coach for each participant, an initial core curriculum of 16 lessons, and a flexible toolkit approach for achieving and maintaining weight loss and physical activity after the initial intensive period [3]. If participants needed help reaching or maintaining the physical activity goal, one use of the toolkit was to facilitate engagement in this component of the intervention (e.g., exercise videos, personal training, or exercise class registration), and centers could additionally offer group exercise programs (e.g., exercise classes, organized group walks) [2].

Primary Findings of DPP

The DPP was stopped 1 year prior to the scheduled end date because efficacy had been demonstrated [2]. Compared to placebo, and over an average 2.8 years of follow-up, the lifestyle intervention decreased the incidence of type 2 diabetes by 58%, and metformin decreased the incidence of type 2 diabetes by 31%. Moreover, the lifestyle intervention was superior to metformin for decreasing type 2 diabetes incidence. Metformin and the lifestyle intervention resulted in similar benefits to fasting plasma glucose, but the lifestyle intervention was more effective at reducing post-load glucose [2].

After DPP was stopped, follow-up of participants continued in the DPP Outcomes Study (DPPOS). DPPOS continued unmasked metformin treatment in participants randomized to that arm; all participants were offered a lifestyle intervention based on the efficacy demonstrated in the initial trial. Though similar across groups during the DPPOS follow-up period where all participants received the same lifestyle intervention, cumulative incidence of type 2 diabetes through 10 years after DPP randomization remained significantly lower in the intensive lifestyle (−34%) and metformin groups (−18%) vs. placebo [6]. Though cardiovascular risk factors were similar across groups at the 10-year follow-up, the lifestyle intervention group was using significantly less antihypertensive and lipid-lowering medications, suggesting a durable effect of the initial intervention [7]. Analyses of cost-effectiveness demonstrated good value for both interventions from a payer and societal perspectives at the end of DPP and 10 years into the DPPOS [8, 9].

Lessons Learned About the Effects of Physical Activity in DPP

Within the highly efficacious DPP lifestyle intervention arm, there was natural variation in the level of physical activity participation. Lifestyle intervention participants self-reported an average of 224 ± 141 min/week of physical activity at 6 months and 227 ± 212 min/week of physical activity at the study end [10]. This high level of participation in physical activity, well above the 150 min/week target, suggests that the intervention was highly effective at engaging physical activity participation among DPP participants. However, it also could suggest that more than 150 min/week of physical activity might be necessary to observe a similar magnitude of diabetes risk reduction in a weight loss intervention context. In terms of goal achievement, 74% and 67% of lifestyle intervention participants met the ≥150 min/week goal at the 6-month and final study visits, respectively. These rates of meeting physical activity goals were higher than the rates

of achieving the weight loss goal (≥7%), which was 49% at 6 months and in 37% at the last study visit [10]. The odds of achieving the physical activity goal at 6 months or at the study end in the DPP lifestyle intervention were significantly higher in men, with older age, and with lower BMI. The odds also differed by race, with Hispanic participants being more likely than whites to achieve physical activity goals at the end of the study. Self-monitoring of diet was associated with achieving physical activity goals at 6 months and the study end. Lastly, meeting the physical activity goal at 6 months increased the likelihood of meeting the physical activity goal at the end of the study by 50% [10].

Individual achievement of physical activity goals within the DPP lifestyle intervention arm also had an independent effect on the primary outcome of incident type 2 diabetes. In an analysis that looked at individual changes in weight, diet, and physical activity within the lifestyle intervention arm [11], change in weight was the strongest predictor of decreased type 2 diabetes risk with a 16% reduction in risk for each kilogram of weight lost. The change in continuous, self-reported physical activity did not independently predict the development of type 2 diabetes [11], but this could be a reflection of high levels of physical activity at the beginning of the study [12]. However, the change in physical activity predicted greater weight loss, such that each 100 min/week of brisk walking or equivalent intensity activity was associated with a weight loss of 0.43 kg in the third year of DPP [11].

Further analyses stratified lifestyle intervention participants into groups based on meeting weight loss, fat intake, and physical activity goals after the first year of the intervention. Figure 12.1 displays the proportion of participants meeting each combination of physical activity, dietary fat intake, and weight loss goals. Importantly, after the first year of follow-up, the most common pattern of goal attainment was to be meeting only the physical activity goals (and not the dietary fat intake or weight loss goals). In addition, most individuals meeting the dietary fat and weight loss goals were also meeting the physical activity goals. These findings highlight that increasing physical activity might be especially achievable in this population at risk for the development of diabetes, even among individuals who are not able to achieve a weight loss of at least 7%.

Achieving physical activity goals, with or without weight loss, was associated with a decreased risk of diabetes over the average 3.2 year follow-up. Compared to individuals who did not achieve physical activity, dietary fat, or weight loss goals, those achieving only the physical activity goal had a 46% reduction [95% confidence interval (CI): −16%, −66%] in diabetes; this reduction was similar even after adjustment for continuous weight change (Fig. 12.2). Even more striking, achieving the physical activity, weight loss, and fat intake goals together resulted in a reduction in diabetes incidence of 89% [95% CI:−76%, −95%] when compared to lifestyle participants who did not achieve any goals [11]. Thus, achieving the recommended levels of physical activity appears to be an important strategy both with and without weight loss for diabetes prevention. Because physical activity goals were more commonly met than the targeted weight loss among DPP lifestyle intervention participants [10], physical activity may be a particularly important strategy for preventing or delaying diabetes among at-risk individuals struggling to achieve weight loss.

In addition to the primary outcome of incident diabetes, changes in health-related quality of life were also evaluated in DPP. Participants in the intensive lifestyle intervention, but not the metformin group, had clinically (≥3% improvement) and statistically significant improvements in self-reported physical function and general health as measured by the 36-item Short-Form (SF-36) [13]. Though a further mediation analysis suggested that the change in weight and not physical activity was primarily responsible for the observed quality of life improvements in the intensive lifestyle group, the group effects remained statistically significant even after adjustment for the individual lifestyle changes, and differences in measurement error between weight and self-reported physical activity might explain this result [13].

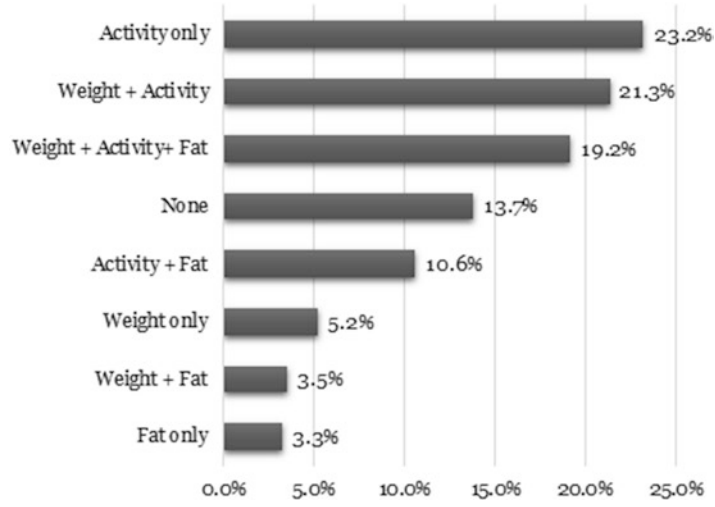

Fig. 12.1 Proportion of DPP intensive lifestyle intervention participants ($n = 975$) meeting activity (physical activity ≥150 min/week), fat (dietary fat <25% of calories), and weight (weight loss ≥7%) goals at 1 year of follow-up (Adapted from Hamman et al., *Diabetes Care*, 2006 [11])

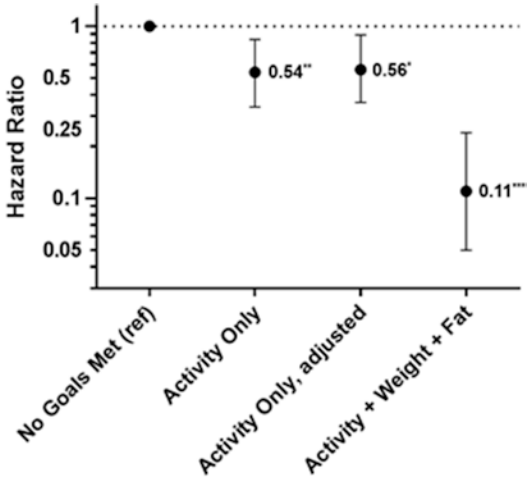

Fig. 12.2 Hazard ratios for diabetes onset over 3.2 years of follow-up in the DPP intensive lifestyle intervention among participants meeting physical activity goals only (Activity Only, $n = 226$), subjects meeting physical activity goals only with statistical adjustment for weight change over time (Activity Only, adjusted, $n = 226$), and in participants meeting physical activity, weight loss, and dietary fat intake goals (activity + weight + fat, $n = 187$) vs. participants meeting no goals (reference, $n = 134$). $p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ (Adapted from Hamman et al., *Diabetes Care*, 2006 [11])

The Action for Health in Diabetes (Look AHEAD) Study

After the clinically important results from DPP that found a lifestyle intervention was effective and superior to a pharmacotherapy for preventing and delaying type 2 diabetes, the Look AHEAD Trial was designed to evaluate whether a lifestyle intervention could reduce major cardiovascular events in a population with type 2 diabetes [14]. For an overview of the study, please see Table 12.2. Look AHEAD recruited 5145 adults aged 45–74 years at 16 clinical sites in the United States who had preexisting type 2 diabetes, BMI ≥25 kg/m^2 (≥27 kg/m^2 if using insulin), systolic blood pressure <160 mmHg and diastolic blood pressure <100 mmHg, triglycerides <600 mg/dL, and HbA1c <11%. Though participants were allowed to enroll in the study if they had a history of a cardiovascular event to increase generalizability, all participants were required to complete a maximal exercise test to ascertain that there were no contraindications to participating in the exercise program. In the final study sample, participants were on average 59 years old and had an average BMI of 36 kg/m^2. Sixty percent of randomized participants were women, and the racial composition was 63% white, 16% black, 13% Hispanic, and 8% other. The primary endpoint was the first occurrence of a composite of major cardiovascular events including cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and hospitalization for angina. The Look AHEAD Study was planned to follow participants for these outcomes over a maximum of 13.5 years [15].

Table 12.2 Look AHEAD at a glance

Participants	Adults with type 2 diabetes who were overweight or obese
Study design	Two-arm randomized clinical trial comparing the effects of an intensive lifestyle intervention vs. an education and support control group on major cardiovascular events
Lifestyle intervention	Individual- and group-based intervention targeting a ≥7% weight loss and ≥175 min/week of moderate-intensity physical activity (i.e., brisk walking or similar intensity)
Primary finding	The intensive lifestyle intervention did not reduce major cardiovascular events over a 9.6 year average follow-up as compared to the control group

Look AHEAD Intervention

Participants were randomized to either the intensive lifestyle intervention or the diabetes education and support (control) group. The Look AHEAD intensive lifestyle intervention used a combination of group and individual counselling that occurred weekly during the first 6 months but then declined in frequency for the remainder of follow-up. The intervention targeted a ≥7% weight loss through caloric restriction to 1200–1800 kcal/day, dietary fat restriction to <30% of calories, at least 15% of calories from protein, the use of meal replacements, and ≥175 min/week of moderate-intensity physical activity (e.g., brisk walking). If needed, the drug orlistat was added to the standard behavioral modification plan to achieve the initial weight loss goals. Like DPP, a toolbox approach was available for participants having difficulty achieving the weight loss goal [16]. The comparison control group, diabetes education and support, was offered educational sessions on weight loss, exercise, and social support three times per year during the first 4 years and then annually thereafter [17]. Participants in both groups continued to be medically managed by their health care provider, except for temporary glucose-lowering medication adjustments to avoid hypoglycemia among intervention participants. The laboratory results from annual assessments in the Look AHEAD Study were shared with each patient's identified health care provider [15].

Primary Findings of Look AHEAD

Like DPP, the Look AHEAD Study was stopped prior to completion of the planned follow-up. However, unlike DPP, Look AHEAD was stopped prematurely for futility. This judgment was based on an interim analysis by the data safety and monitoring board that determined that, if the study continued, the chance of finding the intensive lifestyle intervention decreased the risk of the primary composite cardiovascular endpoint was 1% [15]. Thus, after an average follow-up of 9.6 years, the intensive lifestyle intervention was not shown to decrease the risk of major cardiovascular events compared to the control group (HR = 0.95, 95% CI: 0.83, 1.09). Prespecified secondary outcomes, including overall mortality, other cardiovascular composite scores, and the components of the composite scores, were also not different between groups. These null findings were observed in the context of significantly lower weight among intervention participants throughout the trial, with a between-group difference of 7.9% at 1 year and 2.5% at the study end. Other cardiovascular risk factors differed by group across the trial in favor of the intervention group including lower waist circumference, lower HbA1c, and higher cardiorespiratory fitness (through year 4, the last measurement). Participants in the intervention group were also less likely to use insulin, statins, and antihypertensive medications as compared to the control group [15]. Benefits were observed comparing the intervention group to control for other outcomes including urinary incontinence in women [18], depression and health-related quality of life [19], autonomic function [20], and physical function [21]. The lifestyle intervention was also found to be cost saving with respect to medications, hospitalization, and selected outpatient services. Over 10 years, the health care savings was estimated to be over $5000 for a participant in the lifestyle intervention vs. control [22].

The null findings for the primary and secondary endpoints of Look AHEAD suggest that the intensive lifestyle intervention was not effective for reducing major cardiovascular events in this population as compared to an education control group. One contributing factor could have been the provision of yearly assessment results to each patient's health care provider, which may have led to enhanced medical management in the control group. This is consistent with the higher use of medications and the lower than expected event rate in the control group [23]. Another potential reason for the lower than expected event rates in the control group may have been the selection of healthier participants at baseline who passed the initial maximal graded exercise test and had better controlled cardiovascular risk factors [24]. A further salient point is that secular changes in the medical management of patients with diabetes that occurred during the trial, such as a marked increase in statin use, could have been responsible for the negative findings [23]. Lastly, focus on weight loss achieved through a low-fat diet or, in cases, meal replacements might have been less effective for controlling cardiovascular risk than a Mediterranean diet which has been shown to confer cardioprotection [15, 24]. The possibility of inadequate power is less likely because the study was very large with excellent retention (<4% lost to follow-up) [15].

Lessons Learned About the Effects of Physical Activity in Look AHEAD

Though the Look AHEAD Study did not confirm the hypothesis that an intensive lifestyle intervention could reduce major cardiovascular events, assessment of physical activity as well as cardiorespiratory fitness in this study allows for a greater characterization of the impact of increased physical activity and fitness on health outcomes in Look AHEAD. The intensive lifestyle intervention effectively increased physical activity and cardiorespiratory fitness as compared to the control group. Intensive lifestyle participants in whom self-reported brisk physical activity was assessed significantly increased activity by 872 kcal/week at the 1-year follow-up and by 348 kcal/week at the 4-year follow-up; by comparison, the control group increased by activity by ~100 kcal/week at both time points. Cardiorespiratory fitness, assessed by a graded exercise test and after multivariable adjustment for baseline characteristics and weight change, was also significantly higher in the lifestyle intervention vs. control by 6.6% at 1 year, 5.8% at 2 years, and 1.9% at 4 years [25].

Greater participation in physical activity and greater gains in cardiorespiratory fitness were associated with greater weight loss among Look AHEAD participants [25–27]. Over the first 4 years, each percentage point increase in cardiorespiratory fitness was associated with a − 0.1 kg decrease in weight ($p < 0.001$) [25]. Changes in physical activity were similarly, inversely related to weight change ($p = 0.02$) [25]. Physical activity participation was also important for weight loss maintenance. When restricted to intervention participants achieving at least a 10% weight loss in the first year, participants who maintained that 10% weight loss at 4 years had significantly higher self-reported physical activity vs. participants with <10% weight loss maintained at 4 years (Fig. 12.3) [26].

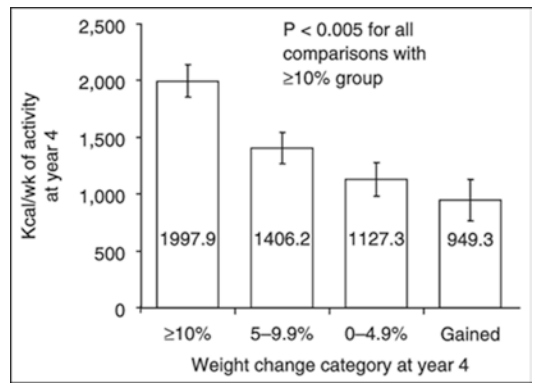

Fig. 12.3 Self-reported weekly calorie expenditure from physical activity in year 4 for intensive lifestyle intervention participants who had lost ≥10% of weight at 1 year and completed the Paffenbarger Activity Questionnaire at year 4, lost ≥10% of initial weight ($n = 186$), lost 5–9.9% ($n = 120$) or 0–4.9% ($n = 79$), or gained above baseline weight ($n = 45$) (With permission from Wadden et al. [25])

Within the Look AHEAD Study, whether increased physical activity or weight loss was associated with better glycemic control has also been evaluated. Participants in the lifestyle intervention were more likely to achieve partial or full remission of type 2 diabetes during the first 4 years of the Look AHEAD Study, but associations with changes in fitness were attenuated to nonsignificance after adjustment for weight change [28]. However, when HbA1c was evaluated as a continuous variable, individuals achieving >10% increase in fitness had significantly greater declines in HbA1c as compared to individuals with a smaller increase (0–10%) or with a decline in fitness ($p < 0.001$). The effect remained statistically significant even after adjusting for weight loss, which was a more powerful predictor of improvements in HbA1c. However, over the first 4 years, increased self-reported physical activity was not related to changes in HbA1c after adjustment for weight loss [25].

Beyond weight loss and glycemic control, increases in cardiorespiratory fitness were also related to independent improvements in cardiovascular risk factors. In an analysis evaluating joint associations of changes in cardiorespiratory fitness and weight on 1-year changes in cardiovascular risk factors, change in each weight and submaximal fitness were associated with improved systolic and diastolic blood pressure, fasting glucose, HbA1c, HDL cholesterol, and triglycerides when included one at a time in regression models (see Table 12.3). When added to models simultaneously with changes in weight, change in fitness remained independently associated with small favorable changes in fasting glucose, HbA1c, HDL cholesterol, and triglycerides. For example, with each metabolic equivalent (MET) increase in fitness during a graded exercise test, triglycerides decreased by 9.0 mg/dL without adjustment for weight loss and decreased by 3.3 mg/dL after adjusting for weight loss [29]. Because increased fitness was associated with greater weight loss, the latter adjusted results likely underestimate the effect of increasing fitness on changes in these cardiometabolic risk factors. One other study evaluated the combined effects of weight loss and increased fitness on heart rate recovery following the graded exercise test, a measure of autonomic function. This study found that the intervention improved heart rate recovery (autonomic function) and observed a dose-response effect where greater gains in fitness or greater weight loss each predicted greater improvements in heart rate recovery. Moreover, the effects of weight loss and fitness gains were additive in that the greatest improvement in autonomic function was observed in participants in the highest categories of weight loss *and* fitness gains [20].

Another benefit attributable to the physical activity component of the lifestyle intervention in Look AHEAD was improved health-related quality of life. At 1 year, the physical component scores from the SF-36 and the Beck Depression Inventory II were better in the intervention vs. control group. It was found that the change in fitness was a significant mediator of these effects, suggesting that increased fitness contributed to these quality of life benefits [30]. Lastly, among participants reporting knee pain at baseline ($N = 2203$), the lifestyle intervention improved self-reported knee pain, physical function, and stiffness at 1 year based on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). This benefit was also found to be mediated by changes in fitness [21]. Thus, in addition to clinical health benefits, increased fitness resulted in improved quality of life among intervention participants in the Look AHEAD Study, which is another important outcome in populations with type 2 diabetes.

In Look AHEAD, changes in fitness were consistently related to health benefits, while changes in physical activity were not. Though the reasons are not entirely clear, there are several possible explanations for this result. One explanation is that cardiorespiratory fitness, a physiological parameter, is measured with less error than physical activity behavior and this improved the ability to detect associations with health outcomes. Another possibility is that only those participants engaging in physical activity of sufficient intensity and duration to elicit changes in fitness achieved greater health benefits. It is further possible that the ability to improve fitness was a marker of healthier participants who were more able to benefit from the lifestyle intervention. Regardless of the reason, the results from Look AHEAD suggest that improving fitness should be a goal in patients with diabetes.

Table 12.3 Change in cardiometabolic risk factors associated with changes in weight (per kg) and submaximal fitness (per metabolic equivalent (MET)) among lifestyle intervention participants in the Look AHEAD Study (*n*-2256)

		Weight change only	Fitness change only	Weight + fitness change
Systolic blood pressure (mmHg)	β weight change (kg)	0.4**	–	0.4**
	β fitness change (METS)	–	−1.0**	−0.2
Diastolic blood pressure (mmHg)	β weight change (kg)	0.2**	–	0.2**
	β fitness change (METS)	–	-0.5***	−0.1
Fasting glucose (mg/dL)	β weight change (kg)	1.4**	–	1.2**
	β fitness change (METS)	–	-5.3**	−3.0**
HbA1c (%)	β weight change (kg)	0.04**	–	0.04**
	β fitness change (METS)	–	-0.2 **	-0.08**
LDL cholesterol (mg/dL)	β weight change (kg)	0.1	–	0.06
	β fitness change (METS)	–	-0.7	-0.6
HDL cholesterol (mg/dL)	β weight change (kg)	−0.2**	–	−0.2**
	β fitness change (METS)	–	0.7**	0.4*
Triglycerides (mg/dL)	β weight change (kg)	3.0**	–	2.8**
	β fitness change (METS)	–	−9.0**	−3.3*

Adapted from Barone Gibbs et al. [29]. Data are presented as β coefficients (*p*-value). Models were adjusted only for weight change and only for fitness change and then mutually adjusted for weight change + fitness change. All models are adjusted for age, race, gender, change in medication, and baseline outcome value

*$p < 0.01$

**$p < 0.001$

Conclusions

DPP and Look AHEAD have been critical in understanding the role of lifestyle intervention in persons at risk for or with type 2 diabetes. The DPP lifestyle intervention was highly effective at reducing or delaying the incidence of type 2 diabetes in a high-risk population. Though weight loss was a stronger predictor of decreased incidence of diabetes within the lifestyle intervention group, achieving the targeted 150 min/week of physical activity predicted greater weight loss, was easier for participants to achieve (vs. the ≥7% weight loss target), and decreased the risk of diabetes by 44% even when weight loss and dietary fat intake goals were not achieved. Thus, these findings support the role for physical activity in diabetes prevention. In patients at risk for developing diabetes, clinicians should provide education on the results of the DPP study and facilitate lifestyle intervention that targets weight loss through caloric restriction and physical activity. DPP also informs some areas in need of more research. Though DPP provides evidence that recommending 150 min/week of physical activity can reduce the risk of diabetes as part of lifestyle change, the high levels of physical activity achieved by DPP lifestyle participants suggest that a larger dose of physical activity (200–250 min/week) might be the more appropriate target. Also, whether prescribing physical activity in the absence of a weight loss intervention can produce clinically significant risk reduction was not addressed by the DPP. Thus, continued research about dose-response relationships and the isolated effect of increasing physical activity on diabetes risk will be helpful for clarifying these relationships.

Despite the failure to find a reduction of the lifestyle intervention on major cardiovascular events among participants with preexisting type 2 diabetes in Look AHEAD, increases in physical

activity and cardiorespiratory fitness were independently related to improved weight loss, glycemic control, cardiovascular risk factors, and health-related quality of life among study participants. In particular, increased fitness was more strongly related to these health benefits. Thus, as part of an overall behavioral weight loss intervention, these findings provide strong evidence that physical activity is an important part of the treatment recommendations for adults with type 2 diabetes. For patients with existing diabetes, it appears that physical activity of sufficient duration and intensity to produce increases in cardiorespiratory fitness should be recommended. Thus, consistent with current public health recommendations, physical activity should be accumulated across bouts that are at least 10 min in duration and at the intensity of brisk walking or greater (i.e., ≥3 metabolic equivalents [METs]) [5]. Patients with little or a lack of recent experience in physical activity may need specific counselling and the assistance from a certified health-fitness professional to adopt a lifestyle that includes sufficient engagement in this important behavior to prevent and treat diabetes. Moreover, even in the absence of weight loss or ideal diabetes control, clinicians are encouraged to recommend physical activity to their patients to elicit numerous health benefits that may extend beyond cardiometabolic health.

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Exercise and Nutritional Concerns

13

Sheri R. Colberg

Introduction

Nutrition is undoubtedly one of the more controversial and hotly debated topics related to diabetes, health, and weight loss. In addition, athletes and recreational exercisers have to deal with many controversies related to the best nutritional practices to optimize performance. Even the American Diabetes Association (ADA) has lately backed away from making definitive nutrition recommendations, stating that, "There is not a one-size-fits-all eating pattern for individuals with diabetes [1]." In light of these ongoing controversies, a discussion of possible and recommended nutritional best practices for diabetes and health management, weight control and maintenance, and athletic endeavors and sports participation with diabetes is warranted and covered in the rest of this chapter.

Management of Overall Health and Blood Glucose

For health and blood glucose management, the ADA recommends that "individuals with diabetes should be encouraged to replace refined carbohydrates and added sugars with whole grains, legumes, vegetables, and fruits [1]." Dark chocolate and cocoa, red wine, green and black tea, and coffee also have large amounts of disease-fighting antioxidants, which potentially benefit health by lowering systemic inflammation and cardiovascular disease risk [2]. Most diabetes complications, such as peripheral neuropathy and cardiovascular disease, are likely related to unchecked oxidative stress in various tissues and organs, thus eating foods with the potential to provide antioxidant protection may at least in part mitigate the potentially negative impact of hyperglycemia [3]. The remainder of this section will focus on nutritional practices that promote enhancements in overall health and more effective blood glucose management.

Macronutrient Effects on Health

All three macronutrients—carbohydrates, protein, and fat—as well as total daily calories are likely important in determining overall health and type 2 diabetes risk. High intake of certain types of fat can contribute to the development of insulin resistance and cause deleterious changes in blood fats as much as an excess intake of refined carbohydrates [4]. For example, a high-fat breakfast that contains mostly a more healthful fat like olive oil instead of sausage allows blood glucose and insulin levels to stay lower [2],

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whereas a higher intake of highly processed meats has been associated with an elevated risk of type 2 diabetes [5, 6]. Polyunsaturated omega-6 fats abundant in the corn, sunflower, peanut, and soy oils may lower inflammation [7] and decrease type 2 diabetes risk [8]. A diet with 30–40% of total calories derived from protein, with a lower intake of carbohydrates and fats, may assist in blood glucose management, weight loss, and prevention of weight gain or regain, although a high intake of protein from processed meats actually increases type 2 diabetes risk [6].

Fiber and the Gut Microbiome

In the human diet, natural plant fibers remain largely undigested in the intestinal tract, but the healthy gut microbiome thrives when more dietary fiber is consumed, and it is likely that this very microbiome has a critical important role in human health [9]. In fact, a high-fiber diet may help reduce the chances of developing heart disease, insulin resistance and type 2 diabetes, obesity, stroke, colorectal and other types of cancer, diverticulosis, and hemorrhoids [10]. Oats in particular may have a strong anti-inflammatory effect by increasing the healthful bacteria in gut [11], but their higher carbohydrate content requires adequate insulin coverage to keep blood glucose levels from rising excessively in people with diabetes.

Glycemic Index and Glycemic Load

Carbohydrate-based foods vary in their actual immediate impact on the rise in blood glucose levels after consumption, known as the *glycemic index*, or GI. The amount of digestible (non-fiber) carbohydrate consumed, the *glycemic load* or GL, also impacts the full blood glucose response, not just the rapidity of it [12]. A low-GL, high-fiber diet raises circulating levels of adiponectin, an anti-inflammatory hormone released by fat cells that can increase insulin action and lower blood glucose [13], making it likely that dietary inclusion of fiber-containing carbohydrates is critical for lowering GI and optimizing blood glucose responses and overall health. Fiber also lowers the GL of foods containing it and increases their satiety; furthermore, foods with a higher fiber content are generally lower in added sugars, fat, and calories.

Carbohydrate Counting and Glycemic Impact of Other Macronutrients

To deal with the rapid influx of blood glucose derived from high-GI carbohydrates, a functional pancreas releases a large amount of insulin. When individuals have diabetes or prediabetes, however, their pancreases may not be able to release enough insulin to effectively control these glucose spikes [14]. For this reason, many people—especially insulin users—count carbohydrates and dose insulin accordingly to cover the carbohydrate content in meals and snacks, as well as adjust food intake and insulin doses to prevent hypoglycemia or hyperglycemia associated with physical activity [15].

For insulin users, the ADA agrees that nutritional guidelines need to provide more specific guidance. For example, their 2017 Standards of Care state, “For people with type 1 diabetes and those with type 2 diabetes who are prescribed a flexible insulin therapy program, education on how to use carbohydrate counting and in some cases fat and protein gram estimation to determine mealtime insulin dosing can improve glycemic control [1].” They add that “individuals with type 1 or type 2 diabetes taking insulin at mealtimes should be offered intensive education on the need to couple insulin administration with carbohydrate intake [1].” However, carbohydrate counting can be difficult to do accurately—particularly given differences in GI among carbohydrate sources and the glycemic impact of mixed meals—and is associated with higher daily blood glucose variability in adults with type 1 diabetes [16]. Some of the difficulty with carbohydrate counting may arise because greater intake of high-GI carbohydrate foods increases insulin resistance even in people without diabetes [17], and lower GI foods may require less insulin and doses that peak and provide coverage at different times.

Recent studies have shown the importance of not only carbohydrates in determining total insulin requirements but also protein and fat intake [18, 19]. These latter macronutrients can cause a rise in blood glucose levels 3–6 h after a meal, a time when most rapid-acting mealtime insulin has waned; therefore, simply counting carbohydrates is not always an effective strategy in insulin dosing. In fact, when postprandial glucose variability (the maximal amplitude after meal) was measured in adults with type 1 diabetes, variability was significantly lower when they administered insulin doses based on the GL of carbohydrates rather than the actual number of carbohydrates eaten both after lunch and dinner meals [20].

Effective management of blood glucose levels and insulin sensitivity after both meals and exercise is also affected by the macronutrient composition of meals [18, 19]. This critical point was aptly made in a recent review of all studies done to date, which reported that high-fat and high-protein meals both require more total insulin than a meal with less fat or protein and an identical carbohydrate content [18]. Moreover, a high-GI carbohydrate meal consumed after 90 min of moderate walking in the evening appears to cancel the beneficial effect of exercise on stimulating fat oxidation and lowering plasma triglycerides after a subsequent high-fat meal the next morning, whereas consuming a postexercise meal with low-GI carbohydrates retains the positive effect of prior exercise [21]. One benefit of understanding the delayed glycemic effects of various macronutrients is that insulin users can eat protein (and even fat) strategically to prevent later-onset hypoglycemia [22, 23].

Food Insulin Index

Related to the effects of macronutrient consumption, the food insulin index (FII) has been studied in normal and diabetic populations related to ingestion of mixed meals [24]. The initial FII study done on healthy adults without diabetes reported that the relative insulin demand evoked by mixed meals is best predicted by a physiologic index based on actual insulin responses to isoenergetic portions of single foods [24]. Consuming mixed meals with the same calorie—but varying macronutrient—content suggested that carbohydrate counting was of limited value in predicting insulin needs. Based on the FII algorithm, meals can be predicted to result in a high or low insulin demand. Overall, it provides another potential tool for reducing postprandial hyperinsulinemia in adults with type 2 diabetes, thereby potentially improving insulin resistance and beta-cell function [25]. In adults with type 1 diabetes, the use of the FII algorithm significantly decreased their glucose incremental area under the curve over 3 h and peak glucose excursions while improving by 30% the time glucose levels were in a normal range compared to carbohydrate counting [26].

Health and Glycemic Effects of Other Diets

Changing up the composition of the diet can also impact health and diabetes management. A recent systematic review and meta-analysis of 20 randomized, controlled trials (RCTs) in adults with type 2 diabetes that lasted at least 6 months assessed the effects of differing diets on glycemic control, lipids, and weight loss [27]. The authors concluded that low-carbohydrate, low-GI, Mediterranean, and high-protein diets all led to a greater improvement in glycemic control compared to the control diets in each study. Both the low-carbohydrate and Mediterranean diet led to greater weight loss, and all resulted in improved HDL-cholesterol with the exception of the high-protein one. Others have shown that adults with type 2 diabetes who follow a low-GI diet (<40) improve their blood glucose control, enhance insulin action, lower bad blood fats, and lose weight [12, 13].

Weight Loss and Maintenance

The ADA 2017 Standards of Care state, “Modest weight loss achievable by the combination of reduction of calorie intake and lifestyle modification benefits overweight or obese adults with type 2 diabetes and also those with prediabetes.” These individuals are counseled to lose weight to

help manage or potentially reverse these conditions. Many with type 1 diabetes ultimately battle weight gain and insulin resistance as well, and preventing excessive weight gain in these individuals can assist in keeping insulin action heightened and insulin needs minimized. Exercising regularly and increasing fitness allow insulin to work more efficiently to control blood glucose levels [28].

Weight Loss and Maintenance Through Lifestyle Changes

A lower-carbohydrate diet, in addition to decreasing blood lipids and blood glucose, may help people lose weight and keep it off [13], as can a low-GI/GL diet plan [13]. Likewise, weight loss can frequently be accomplished through lifestyle changes that include a modest reduction (500–750) in daily intake of kilocalories, along with regular physical activity of varying types. Although weight loss can be accomplished without exercise as a means to increase caloric deficits, most successful losers who maintain weight loss have incorporated regular exercise into their daily routines to keep it off long term, as documented through participants in the National Weight Control Registry (NWCR), all of whom have lost at least 30 lb (13.6 kg) and kept it off for at least a year [29–31]. Moreover, sustaining a weight loss of as little as 5–7% of the total body weight can lead to a decrease in insulin resistance and improvements in blood glucose levels and, therefore, allow for a reduction in the required doses of diabetes medications [32].

Even in a follow-up of participants who lowered their risk of developing type 2 diabetes in the Diabetes Prevention Program [33], the ones who maintained weight loss over time were almost exclusively those who exercised regularly [34]. Physical activity during weight loss is particularly important for maintenance of lean body mass (i.e., muscle mass) and achievement of a greater loss of body fat overall [35]. Many people who regain lost weight after dieting gain primarily fat, resulting in a higher body fat percentage than prior to dieting, but continued physical activity participation can mitigate or prevent fat weight regain [36]. For individuals with type 2 diabetes or obesity, a recent meta-analysis suggested that weight loss exceeding 5% is needed to produce beneficial outcomes in glycemic control, lipids, and blood pressure, and maintaining a sustained weight loss equal to or more than 7% over time is optimal [37].

Hypoglycemia and Weight Gain

For all who wish to lose weight, keep lost weight off, or maintain current body weights using regular physical activity, nutrition becomes an important component of being able to achieve those body weight goals. A diabetes regimen that results in frequent hypoglycemia may actually lead to weight gain [38], however, even among regularly training athletes who are insulin users [39]. Inability or failure to reduce circulating insulin levels during exercise frequently results in the intake of additional carbohydrate and calories to prevent and treat hypoglycemia [40]. Moreover, weight loss is harder to achieve when circulating insulin levels are higher since insulin is an anabolic hormone that stimulates glucose uptake into fat cells even when muscle cells are resistance to its effects. It is more effective to keep insulin needs as low as possible by enhancing insulin action with physical activity.

Low-Carbohydrate Diets and Weight Loss

Although low-carbohydrate diets have frequently resulted in greater short-term weight loss, a systematic review of RCTs lasting longer than 12 weeks in adults with type 2 diabetes found no consistent differences in body weight or glycemic balance between low-carbohydrate, low-fat, low-GI, and usual care diets in this population [41]. In adults with type 1 diabetes, following a low-carbohydrate diet (defined as 75 daily grams) may result in lower A1C values, lesser insulin use, and greater weight loss [42]. The exact percentage of carbohydrates that constitutes all

"low-carbohydrate" diets is not well defined overall and subject to interpretation. Moreover, macronutrient intake may or may not differentially affect the ability to reverse visceral adiposity and metabolic syndrome. For instance, in adult males with central adiposity, consuming energy primarily as carbohydrate (53% of calories) or fat (73% of calories) for 3 months did not differentially influence visceral fat and metabolic syndrome, even though chosen foods were minimally processed, lower GI ones. Intake of dietary fat per se does not appear to greatly impact central adiposity and metabolic syndrome [43].

Optimizing Athletic Performance

Sports participation and athletic performance are both positively and negatively impacted by a number of nutritional factors. Carbohydrate is important as a fuel during aerobic activities that are moderate or higher, and dietary patterns and nutritional supplements have the potential to impact the ability to exercise in varying ways. A number of these factors and their effects on performance are discussed in this section.

Use of Carbohydrates (Glycogen and Glucose) for Exercise

Carbohydrate is the body's preferred metabolic fuel during moderate exercise and its almost exclusive fuel during intense activities. Supplementing with carbohydrates is recognized as an effective strategy to increase endurance capacity in athletes [44]. Uptake of glucose arising from carbohydrate supplementation can occur through a contraction-mediated, insulin-independent mechanism during physical activity, making the use of carbohydrates as a metabolic fuel possible even in individuals who are insulin resistant at rest [45].

Skeletal muscles and the liver have a limited glycogen storage capacity, and repletion of these stores after physical activity is dependent on the availability of blood glucose, which can come directly from ingested carbohydrates or de novo glucose production from alternate substrates like lactate, pyruvate, alanine (an amino acid), and glycerol (the backbone of triglycerides in stored and dietary fat) [46]. Maintenance of blood glucose levels at more normal physiological levels improves exercise performance [47], and in many instances, supplementing with carbohydrates before and during activities improves endurance performance [48]. However, adequate repletion of muscle glycogen following exercise requires effective management of blood glucose levels under conditions of carbohydrate ingestion, particularly in insulin users who must match carbohydrate intake with insulin dosing [49]. When carbohydrate intake is limited after glycogen use, it will be restored over time, albeit much more slowly than normal [46].

Effects of Low-Carbohydrate Diets on Performance

The requirement for higher carbohydrate availability during moderate and intense activities may make it difficult for exercisers with diabetes to perform well when they voluntarily limit their carbohydrate intake, especially prior to, during, and after exercise [50]. Given that prolonged (>90 min), continuous, endurance exercise is limited by endogenous carbohydrate stores, a low-carbohydrate diet can have an even greater negative impact on athletic performance during these and other activities that result in muscle glycogen depletion [51]. Some adults following low-carbohydrate or ketogenic diets to prevent post-meal spikes in blood glucose levels arising from carbohydrate consumption impair their exercise performance by limiting muscle glycogen storage before exercise [52]. By way of example, in elite adult walkers without diabetes, a recent RCT demonstrated that although a low-carbohydrate, high-fat diet for 3 weeks increased their exercise fat oxidation, performance was not enhanced overall like it was when they were following either an isocaloric high-carbohydrate diet during training or one that alternated between high- and low-carbohydrate intake [53].

Other athletes chronically following a low-carbohydrate, high-fat diet (7% carbohydrate, 72% fat, 21% protein) over 8 months were unable to increase production of blood glucose via gluconeogenesis or fully compensate for reduced glucose availability compared to athletes on a mixed diet (51% carbohydrate, 33% fat, 16% protein) [54]. Despite a low intake of carbohydrates, their gluconeogenic ability remained relatively stable but was unable to increase during physical activity to compensate for reductions in muscle glycogen content. Individuals starting out in a low-glycogen state will undoubtedly have to supplement with carbohydrates during extended activities and may also suffer declines in endurance performance related to excessive depletion of muscle glycogen stores.

Carbohydrate Intake and Glycogen Repletion

Adequate insulin delivery and blood glucose management are critical to faster recovery of carbohydrate stores postexercise. In addition, greater intake of carbohydrates (e.g., 1.2 $g \cdot kg^{-1} \cdot h^{-s1}$) supports rapid glycogen repletion during acute recovery from exhaustive exercise in most individuals. Intake of higher-GI/GL carbohydrates like bagels or bananas immediately following exercise facilitates initial muscle glycogen repletion, which is most rapid early in recovery. Co-ingesting a small amount of protein (0.2–0.4 $g \cdot kg^{-1} \cdot h^{-1}$) with less carbohydrate (0.8 $g \cdot kg^{-1} \cdot h^{-1}$) may provide a feasible option to achieve similar muscle glycogen repletion rates [50] and in individuals with diabetes proves to be an easier way to simultaneously manage blood glucose levels.

In individuals requiring insulin, rapid restoration of glycogen is still somewhat dependent on insulin availability, although less so than compared to glycogen repletion past the "window of opportunity" that lasts for 2 or more hours after exercise [55]. Interestingly, adults with type 1 diabetes can end up with higher glycogen stores during carbohydrate loading when they maintain better blood glucose control by ingesting slightly less carbohydrate (50% of total calories instead of 60%), which suggests that loading with higher carbohydrate intakes may be counterproductive in their case [56]. For optimal liver glycogen stores, maintenance of more normal blood glucose levels has also been shown to be the most effective repletion strategy [57]. Regularly using muscle glycogen by engaging in bouts of physical activity is also important for reducing and limiting insulin resistance that results from having maximal glycogen storage [46].

Carbohydrate Intake and Hypoglycemia Prevention

An individual's starting blood glucose levels can affect exercise performance, as can levels during the activity. The target range for blood glucose before exercise should ideally be 90–250 mg/dL (5.0–13.9 mmol/L). During exercise, carbohydrate intake may or may not be required, depending on the use of insulin or other medications, exercise timing, activity undertaken (intensity, duration), and other factors, but also based on starting blood glucose levels [58]. Frequent blood glucose monitoring is recommended to determine appropriate carbohydrate supplementation and prevention of hypoglycemia and hyperglycemia both during and after activities (Table 13.1).

To prevent hypoglycemia during 30 min or more of exercise, additional carbohydrate intake and/or reductions in insulin are typically required for insulin users. For low-to-moderate-intensity aerobic activities lasting 30–60 min undertaken when circulating insulin levels are low (i.e., fasting or basal conditions), as few as 10–15 g of carbohydrate may prevent hypoglycemia [59]. When exercising with relatively higher levels of circulating insulin (after bolus insulin), however, a more realistic requirement may be 30–60 g of carbohydrate each hour of exercise [60], which is similar to carbohydrate requirements to optimize performance in athletes with [61] and without [48] type 1 diabetes. Particularly during longer workouts or a long event like a marathon, carbohydrate supplementation both before and during the activity is beneficial to performance and maintenance of blood glucose levels.

Table 13.1 Suggested carbohydrate intake or other actions based on blood glucose levels at the start of exercise

Preexercise blood glucose	Carbohydrate intake or other action
<90 mg/dL (<5.0 mmol/L)	Ingest 15–30 g, of fast-acting carbohydrate prior to the start of exercise, depending on the size of the individual and intended activity; some activities that are brief in duration (<30 min) or at a very high intensity (weight training, interval training, etc.) may not require any additional carbohydrate intake. For prolonged activities at a moderate intensity, consume additional carbohydrate, as needed (0.5–1.0 g/kg body mass per hour of exercise), based on blood glucose testing results
90–150 mg/dL (5.0–8.3 mmol/L)	Start consuming carbohydrate at the onset of most exercise (~0.5 to 1.0 g/kg body mass per hour of exercise), depending on the type of exercise and the amount of active insulin
150–250 mg/dL (8.3–13.9 mmol/L)	Initiate exercise and delay consumption of carbohydrate until blood glucose levels are less than 150 mg/dL (8.3 mmol/L)
250–350 mg/dL (13.9–19.4 mmol/L)	Test for ketones: do not perform any exercise if moderate-to-large amounts of ketones are present
	Initiate mild-to-moderate-intensity exercise. Intense exercise should be delayed until glucose levels are less than 250 mg/dL because intense exercise may exaggerate the hyperglycemia
≥350 mg/dL (19.4 mmol/L)	Test for ketones: do not perform any exercise if moderate-to-large amounts of ketones are present
	If ketones are negative (or trace), consider conservative insulin correction (e.g., 50% correction) before exercise, depending on active insulin status
	Initiate mild-to-moderate exercise and avoid intense exercise until glucose levels decrease

Adapted from Zaharieva and Riddell [94] (Reprinted with permission from Colberg et al. [95]. All rights reserved)

If exercise-related hypoglycemia should occur, different options are available to treat it effectively. Given that the GI of glucose is high (100) and the GI of fructose is low, glucose-based sports drinks, gels, and supplements are more ideal to treat hypoglycemia that occurs during physical activity. PowerBars, Clif Bars, and other sports bars contain some longer-lasting protein and fat along with the carbohydrate, which can help prevent blood glucose levels from decreasing as much during longer workouts or sporting events. Some rapidly absorbed carbohydrates recommended for physical activity are given in Table 13.2.

Exercise Timing with Meals and Blood Glucose Maintenance

The timing of exercise relative to meals may also affect blood glucose management. For example, undertaking a bout of activity in the morning in a fasted state results in relatively more stable blood glucose levels in adults with type 1 and type 2 diabetes compared to the same bout of activity done later in the day. Adults with type 2 diabetes have also been shown to exhibit improved postprandial glycemic profiles over the following 24 h after prebreakfast activities compared to exercise performed post-breakfast [62]. In type 1 diabetes, days where exercise was performed before breakfast resulted in less frequent hypoglycemia and a greater percentage of continuous glucose monitor readings in a near-normal range compared to afternoon exercise [63]. However, prebreakfast resistance exercise has resulted in increases in blood glucose in adults with type 1 diabetes [64]; resistance exercise in the afternoon may instead lead to declines in blood glucose later on [65].

Macronutrient Intake, Sports Performance, and Recovery from Exercise

Other important dietary aspects affecting performance include adequate intake of other macronutrients (besides carbohydrates), vitamins,

Table 13.2 Recommended sports drinks, gels, and other carbohydrate sources

Product	Carbohydrate content	Other ingredients
Gatorade	14 g per 8 oz. (240 ml)	Sodium, 110 mg; potassium, 25 mg
	(6% carbohydrate solution)	
PowerAde	21 g per 8 oz (240 ml)	Sodium, 55 mg; potassium, 30 mg
	(8% carbohydrate solution)	
All-Sport	21 g per 8 oz (240 ml)	Sodium, 55 mg; potassium, 55 mg
	(9% carbohydrate solution)	
Cytomax	19 g per 8 oz (240 ml)	Sodium, 10 mg; potassium, 150 mg
	(8% carbohydrate solution)	
Ultra Fuel	50 g per 8 oz (240 ml)	None
	(21% carbohydrate solution)	
Accel Gel	20 g carbohydrate per 41 g pouch	Protein, 5 g (whey protein from milk); fat, 0 g; sodium, 100 mg; potassium, 50 mg; vitamins E and C (100%); various flavors
Gu Energy Gel	25 g carb (85% maltodextrin, 15% fructose) in 1.1 oz (31 g) pouch	Sodium, 50 mg; potassium, 35 mg; vitamins C and E, 100% of daily value
Hammer Gel	23 g carbohydrate per 36 g serving (about 2 tablespoons, or 30 ml)	Amino acids (L-leucine, L-alanine, L-valine, L-isoleucine); sodium chloride; potassium
PowerBar	43 g carbohydrate in one 65 g bar	Protein, 9 g; fat, 2.5 g; fiber, 2 g; sodium, 200 mg; potassium, 115 mg; vitamins; minerals; essential amino acids; various flavors
PowerBar Gel	27 g carbohydrate per 41 g packet	Sodium, 200 mg; potassium, 20 mg; chloride, 90 mg; many flavors with 25 or 50 mg of caffeine added
Clif Bar	45 g carbohydrate per 68 g bar	Protein, 10–11 g; fat, 3–6 g; fiber, 5 g; sodium, 125 mg; potassium, 310 mg; vitamins; minerals; various flavors
Clif Shot Bloks Chews	24 g carbohydrate per three pieces (30 g)	Sodium, 70 mg; potassium, 20 mg; various flavors, some with more sodium or caffeine
GlucoBurst	15 g glucose in 1.3 oz. (37 g) pouch	Sodium, 30 mg; potassium, 10 mg
Dex4 Glucose Gel or Liquid Blast	15 g glucose per tube or container	None
Dex4 Glucose Tablets	4 g glucose per tablet	None

(continued)

Table 13.2 (continued)

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minerals, and water. For most regularly training individuals, daily protein requirements are roughly 1.1–1.5 mg of protein per kg of weight (roughly 15–20% of total calories). Although aging by itself increases the need for quality protein, its intake is particularly critical in strength training athletes and individuals engaging in long-duration aerobic training. Taking in inadequate daily calories also increases protein needs in all exercising individuals with and without diabetes.

Recovery foods and drinks are frequently considered optimal for muscle glycogen repletion when they contain carbohydrates and protein in a 3:1 or 4:1 ratio. Interestingly, chocolate milk has become an affordable recovery beverage for many athletes, taking the place of more expensive commercially available recovery beverages and sports drinks. Low-fat chocolate milk consists of a 4:1 ratio (similar to many commercial recovery beverages) and provides fluids and sodium to aid in post-workout recovery [66]. The protein assists in reducing the risk of and preventing later-onset hypoglycemia in insulin users by providing an alternate source of blood glucose a few hours after ingestion [67]. It may also help to have some protein in a bedtime snack (along with fat and carbohydrate) for insulin users trying to prevent nighttime hypoglycemia after a day of strenuous or prolonged activity [22, 23, 68].

Micronutrient Intake and Sports Performance

As far as micronutrients are concerned, a number of vitamins and minerals are critical for optimal sports performance. For example, almost all of the B vitamins function in the metabolism of exercise fuels, and deficiencies in some or all of them can compromise normal fuel (carbohydrate and fat) turnover during physical activity. Vitamin B12 has been widely abused by (nondiabetic) athletes in the past (without any gains in performance); however, it is often deficient in people with diabetes [69], particularly those taking metformin long term [70], and taking it as a supplement can positively impact athletic endeavors in that case.

With regard to minerals, the most important ones related to exercise and sports performance in people with diabetes are likely magnesium, iron, and calcium. Magnesium is involved as a coenzyme in over 300 metabolic reactions, and hyperglycemia and insulin use may promote the loss of magnesium and lead to muscle cramping and other symptoms during physical activity [71, 72]. Chronic magnesium deficiency has been linked to high blood pressure, stroke, plaque formation and heart disease, cardiac arrhythmias, insulin resistance and type 2 diabetes, alterations in blood fats, platelet stickiness, inflammation, oxidative stress, asthma, chronic fatigue, and depression [73]. Since many people with diabetes experience hypomagnesemia, it could potentially limit their ability to be active [74], and supplementation will likely provide some benefit in those cases. Iron is, of course, important to all exercisers due to its inclusion in hemoglobin and its importance for the binding and delivery of oxygen to working muscles during physical activity. Calcium is also critical for effective muscle contractions, bone mineral density, and other metabolic functions. These and other nutrients and supplements that may enhance physical activity participation in people with diabetes are listed in Table 13.3.

The Importance of Hydration and Electrolyte Replacement

Adequate hydration is also required for both maintenance of blood volume (and hence delivery of oxygen and fuels to working muscles and removal of acids and other waste products) and thermoregulation. Hydration status affects a person's ability to sweat and cool the body during physical activity, and overheating can occur more easily in a dehydrated state [75]. Due to greater body water losses through urine with hyperglycemia, people with diabetes are more likely to experience mild-to-moderate hydration during exercise than normal [76]. It is recommended that they take in adequate fluids during exercise bouts, with plain water effective during most activities lasting an hour or less. For longer work-

Table 13.3 Supplements of potential benefit to diabetic athletes

Nutritional supplement	Potential beneficial effect
Antioxidants	Reduction of oxidative damage to cell membranes induced by exercise and hyperglycemia
Caffeine	Increased release of fatty acids, better hormonal response to hypoglycemia during exercise
Carbohydrate, glucose intake	Intake of appropriate amounts of carbohydrate before, during, and after exercise to prevent exercise-induced hypoglycemia
Chromium, vanadium, and zinc	Improvement in insulin sensitivity (especially in type 2 diabetes)
Glycerol	Hyperhydration and prevention of dehydration with exercise and hyperglycemia
Sports drinks[a]	Prevention of hypoglycemia (if drink contains glucose fructose), as well as dehydration and electrolyte imbalance during prolonged exercise, especially in the heat
Water, fluid replacement	Prevention of dehydration, especially because of hyperglycemia or exercise in the heat when perspiration is greater

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[a]Sports drinks can also cause hyperglycemia if carbohydrate intake exceeds the necessary amount during exercise

outs, exercisers can consume sports drinks or diluted fruit juices to replace both water and carbohydrate. All individuals are advised to continue drinking more after an activity because it takes up to a day to restore fluids and electrolytes lost through sweat and ventilation [77].

Nutrient-deficient diets are likely the cause of high blood pressure associated with taking in excess sodium and being deficient in potassium [78]. Their interaction, along with a lower intake of magnesium, likely contributes to elevations in blood pressure, not just sodium intake alone [79]. Replenishment of these and other electrolytes (chloride and calcium) during most activities is not usually required. All of these minerals can be replenished naturally on a daily basis by eating more vegetables, fruits, nuts, whole grains, and legumes (all plant-based foods), and their replenishment during exercise is only recommended during ultra-endurance types of events, particularly when undertaken in hot and humid environments [76].

During longer events, water alone will keep people hydrated, but taking in sports drinks or other substances with carbohydrate will prolong endurance by preventing declines in blood glucose and providing muscles with an alternative source of carbohydrate (besides muscle glycogen) [80, 81]. Exercise ingestion of sports drinks and other fluids that are 5–10% carbohydrate solutions (i.e., 5–10 g of carbohydrate per 100 ml of fluid) will allow faster emptying from the stomach than more concentrated solutions. Fluids in the 5–10% range are absorbed as rapidly as plain water, making them effective for hydration, but they should only be used by people with diabetes if additional carbohydrates are required during activities. Most sports drinks have been formulated to contain only 6–8% carbohydrates and contain a mixture of glucose and fructose because each one is absorbed through a different mechanism in the small intestine; consuming some of both may optimize carbohydrate entry into the blood during exercise. However, straight fruit juice is usually more concentrated than 10% and should be diluted for faster absorption during exercise. Only use more concentrated solutions before or after exercise because their emptying from the stomach is somewhat delayed.

Supplementing with Caffeine and Coffee

Exercisers are likely to use sports supplements and drinks that have caffeine since they are very popular among athletes and sports enthusiasts. Caffeine occurs naturally in some foods and drinks, such as chocolate, coffee, and tea, but it has been added as a stimulant by the manufacturer to most sports products. While some observational studies have suggested that drinking coffee may lower the risk of type 2 diabetes [82, 83], in reality, caffeine makes the body more insulin resistant. In lean, obese, and type 2

Table 13.4 Supplements of potential harm to diabetic athletes

Nutritional supplement	Potential harmful effect
Amino acid supplements	Amino acid imbalance in the body, added stress on kidneys because of excess nitrogen excretion
Caffeine	Potential for greater water loss and dehydration, especially during exercise in the heat
Carbohydrate loading[a]	Hyperglycemia before, during, or after exercise, as well as reduction in insulin sensitivity; hypoglycemia if consumed before exercise and too much insulin is taken for carbohydrate
Creatine[b]	Added stress on the kidneys, especially if kidney disease is present, because of excess urinary excretion of creatinine
Fat loading	Slower carbohydrate absorption rates during exercise if consumed before or during activity, increased insulin resistance, ketone production, and obesity long term
Protein supplements	Added stress on kidneys because of excess nitrogen excretion, especially with diabetic kidney disease

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[a]Carbohydrate loading can also be beneficial to ensure proper replacement of muscle and liver glycogen levels before and after exercise. Adequate insulin must be available to prevent hyperglycemia and facilitate glucose uptake into muscle

[b]Creatine will create the greatest kidney stress during the initial loading period (5–7 days). During the ensuing maintenance period of supplementation, added stress on the kidneys may be minimal if their function is normal

diabetic adults equally, caffeine ingestion equivalent to two to three 8-ounce cups of coffee (5 mg per kg of body weight) per day reduces insulin action by about a third, and the caffeine-induced decrement is still present after as many as 3 months of moderate aerobic exercise [84]. In adults with type 2 diabetes managed with diet, exercise, and oral medications only, drinking two cups of coffee daily caused their blood glucose levels to rise by 8% [85]. Caffeine intake also exaggerated the rise in their blood glucose after meals: by 9% after breakfast, 15% after lunch, and 26% after dinner. People with type 2 diabetes who took caffeine before doing an oral glucose tolerance test were also more insulin resistant [86]. Fortunately, any insulin resistance related to caffeine use will be minimized during exercise, and caffeine ingested naturally in coffee likely has a lesser effect on insulin action than straight caffeine (Table 13.4).

Caffeine also potentially exerts a diuretic effect, which could cause dehydration, particularly when accompanied by water losses related to hyperglycemia in individuals with diabetes. However, caffeine consumed right before or during exercise has a minimal diuretic effect. In addition, consuming caffeine with carbohydrates after exercise may increase how quickly muscle glycogen is restored [87]. In addition, during exercise undertaken by adults with type 1 diabetes, caffeine ingestion (via capsule) has been shown to assist in maintenance of more normal blood glucose levels, but with an increased risk of later-onset hypoglycemia [88]. However, caffeine-containing energy drinks have been shown to potentially elevate blood pressure in young adults with type 1 diabetes [89].

Safety and Efficacy of Creatine Supplementation

There have been some concerns about the safety of supplementing with creatine (Table 13.4), a substance present in all muscle cells both in its free form and as creatine phosphate (CP), a main component of the phosphagen (ATP-CP) energy system. Normally, daily dietary intake of creatine in the diet is 1 g, and another gram is synthesized by the body to reach the 2-g amount required by the body. Creatine monohydrate supplements taken to build greater strength and power from resistance training are generally considered safe and effective, even in older adults, and may help them regain lost muscle mass more rapidly than by doing training alone [90]. A potential concern is that excess breakdown products of creatine must be excreted by the kidneys and may cause undue stress on them. However, short-term use of creatine supplements appears to be harmless, even in older adults with type 2 diabetes [91, 92],

and overall protein intake is unrelated to the worsening of urinary markers of kidney function in individuals at risk for diabetic kidney disease. Thus, taking creatine as a supplement, at least over the short term, is likely safe for people with diabetes [93]; however, it will likely only benefit sports performance that relies heavily on muscle stores of phosphagens and rapid muscle glycogenolysis (via the lactic acid energy system), not endurance activities.

Knowledge Gaps

There remain many factors that are not fully understood with regard to nutrition and exercise in people with all types of diabetes. It requires a balancing act to maintain normal blood glucose levels during physical activity to optimize performance, particularly in insulin users, but many other diabetes-related factors may impact participation that have not been fully studied. Few studies have been done on youth with diabetes, and none have investigated why some individuals with diabetes experience a higher incidence of muscle cramping during physical activity and diminished physical fitness levels. Are such changes related to micronutrient deficiencies, changes in hydration status, or blood glucose levels themselves? Is glycogen repletion normal in individuals who effectively control their blood glucose levels during recovery? How deleterious to performance is following a lower-carbohydrate diet in these populations specifically? Are hepatic glycogen levels restored to and maintained at normal levels in those with type 1 diabetes who must deliver insulin peripherally as opposed to through the portal circulation directly to the liver? These and many other relevant questions remain unanswered.

Conclusions

Exercise truly cannot be undertaken without consideration of nutritional status, and this is even more true for individuals with type 1 or type 2 diabetes. Whereas nutrition can be used to optimize health, glycemic balance, and weight loss, it is critical to ensuring the availability of metabolic fuels during physical activity and optimizing sports performance and participation in all athletic endeavors. Special consideration should be given to nutritional status in all individuals with diabetes who are regularly active or plan to become so, including macronutrient intake, micronutrient status, hydration, and potential use of nutritional supplements to enhance sports performance. More quality clinical research is needed in many areas related to exercise and nutritional status in people with diabetes.

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14 Behavior Change Strategies for Increasing Exercise and Decreasing Sedentary Behaviors in Diabetes

Daniel Bessesen and Audrey Bergouignan

Introduction

Strong evidence exists to support the physiological health improvements that result from increased physical activity and exercise for those with type 2 diabetes (T2D) and prediabetes separate from its role on body weight [1]. Often in combination with dietary changes and weight loss, physical exercise has been shown to actively contribute to the prevention of diabetes in persons with impaired glucose tolerance [2–4] and to improvements in cardiovascular fitness, insulin sensitivity, glycemic control, and hemoglobin A1c measures in patients with T2D [5–10] and reductions in all-cause mortality [11–16]. Structured exercise programs have shown to be equally efficacious as pharmacotherapy for improving both glycemic control and cardiovascular risk [17, 18].

Based on these observations, it is now widely recommended by governments that adults accumulate at least 30 min of moderate-to-vigorous-intensity physical activity (MVPA) on most, preferably all, days of the week [19]. However, national surveys have revealed that over 79% of adults fail to achieve the 30 min per day goal and less than 15% regularly engage in vigorous physical activity [20]. Objective measurements using portable sensors (accelerometers) indicated that only 5% of the US population achieve recommended levels of activity [21]. Westernized adults spend about 55–70% of their waking hours engaged in sedentary behaviors [3, 5, 6, 22] with one study reporting 9 h/day sitting on average [23]. Furthermore, approximately 50% of adults who initiate an exercise program drop out the first 6–12 months [24, 25]. Unlike many of the lifestyle features that behavioral modification strategies have been used to address (e.g., eating, drinking, sleep, and sexual behaviors), there is no human biological drive to exercise, especially now that predation has disappeared and food is available in abundance. In fact, intentional exertion for the explicit purpose of expending energy seems almost counter to the human physiological tendency to

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conserve. As such, one of the compelling behavioral challenges in increasing exercise is that an individual considers this behavior change because they "should" or that "it will be good for them" rather than in response to a biological or physiological urge or sensation.

Physical activity guidelines and recommendations for T2D, impaired tolerance, dyslipidemia, and general health gains emphasize moderate-to-vigorous PA (MVPA) or activity greater than approximately 45% VO_2max [26, 27], yet recent findings have added further corroboration to the argument that sedentary behaviors are a separate cluster of behaviors that require distinctive behavioral strategies. For the purposes of this chapter, the following definitions will be used: *Physical activity* is typically defined as bodily movement that substantially increases energy expenditure above resting energy expenditure; *Exercise* is generally defined as intentional, structured, repetitive bodily movements performed with the goal of improving or maintaining physical fitness; *Sedentary behavior*, too much sitting as distinct from too little exercise, is defined by low-energy expenditure (ranging 1,0–1.5 METs; metabolic equivalents of the basal metabolic rate) in a sitting or reclining position during waking hours [28, 29]. In this chapter, we will briefly review the available data showing how increase in exercise and decrease in sedentary time allow people with diabetes to achieve and maintain optimal blood glucose, lipid, and blood pressure levels to prevent or delay chronic complications of diabetes. We then will discuss the strategies to adopt and maintain these behavioral changes.

Environmental Influences on Physical Activity and Sedentary Behaviors

Contemporary societal changes in lifestyle behaviors have resulted in a widespread deficiency in daily life activity and a general adoption of sedentary behaviors [30]. Factors contributing to these changes include decreased physical labor in employment, motorized transportation, increased leisure time use of computers, Internet, video-games, increased television viewing, decreased availability of and emphasis on physical education in schools, decreasing convenience of walking space, and increasing safety concerns which restrict access to walking, playgrounds, and other outdoor pursuits [31–34]. Not surprisingly, the convenience of local destinations and "walkability" of neighborhoods has been shown to associate with higher pedometer readings. Adams MA et al. [35] reported that high-walkable recreationally dense neighborhoods differed significantly from other neighborhood types by as much as 13 MVPA min/day, almost 60 min/week of walking for transportation and 75 min/week of leisure time activity. By contrast, residents of low-walkable neighborhoods spend more time sitting in cars [36]. Watching television, sitting at one's work desk, working on a computer, and seating in a car comprise the majority of daily activities for many US adults. While the health benefits of consistent MVPA are well known, the significant challenge to motivate and sustain long-term behavioral change against these environmental obstacles remains [37]. The beneficial effects of MVPA may furthermore be attenuated or otherwise undermined against this backdrop of normalized and ubiquitous inactive living.

Sedentary Behaviors and Type 2 Diabetes

A meta-analysis (ten studies) suggests that there is a 112% greater relative risk associated with a large duration of sedentary behaviors for development of T2D, independent of time spent in exercise [38]. Time spent sitting in cars, particularly over 1 h/day, has been associated with higher total and central adiposity and a more adverse cardio-metabolic risk profile [39]. Time spent watching television has been reported to be significantly associated with the risk of developing T2D independent of BMI [40]. Hu et al. reported that each 2 h/day increment that females watch television poses a 14% risk for development of T2D [41]. This would grossly equate to a 34% increased risk of diabetes for women at the estimated average of 36 h of television viewing

per week. In contrast, even minimal activity change such as standing or walking in one's home can reduce this risk by more than 10%. One hour per day of brisk walking was shown to associate with a 34% risk reduction for developing T2D. The authors conclude that 30% of new cases of obesity and 43% of new cases of T2D could be prevented by making modest lifestyle changes including <10 h of television per week and at least 30 min of brisk walking per day [41].

Behavioral Conceptualization of Daily Physical Activity and Exercise Recommendations

In order to develop explicit behavioral recommendations to increase physical activity and decrease sedentary behaviors in the general public, many specifics of the proposed exercise guidelines must be articulated. For example, clarifying the most desirable type of activities to pursue, specifying both the amount of time and intensity required, and identifying acceptable derivations of exercise that will achieve the overall goal. The terms of physical activity (dose, type, intensity, volume, and timing) have been fully reviewed in Chaps. 15 and 16. Only a brief summary on daily physical activity and exercise program specifics shown to be efficacious in improving glycemic control are therefore presented here.

Exercise

In regard to cardiorespiratory health, the most recent position stand states: "The American College of Sports Medicine recommends that most adults engage in moderate-intensity cardiorespiratory exercise training for >30 min/day on >5 days/week for a total of >150 min/week, vigorous-intensity cardiorespiratory exercise training for >20 min/day on >3 days/week (75 min/week), or a combination of moderate and vigorous intensity exercise to achieve a total energy expenditure of >500–1000 MET/min/week." The national recommendations for exercise accumulation previously cited suggest some lack of consensus as to the ideal amount of exercise per day to maximize health benefits. The simple conceptualization of "some is good and more may be better" appears to apply.

In regard to T2D, engaging in physical activity of any intensity (including low activities) likely positively impacts insulin action and blood glucose control acutely. Chronic MVPA (6–12 months) reduces insulin resistance [42, 43]. However evidence suggests that the duration of exercise is more important than intensity for eliciting favorable response in insulin action [42]. The frequency of exercise (>5 days/week) is supported for persons with diabetes by research suggesting improved insulin sensitivity in insulin-resistant individuals for 16–24 h after a single exercise training bout and up to 48–72 h after exercise with extended physical training [27, 44–46]. In other words, as long as total caloric expenditure during exercise is matched (total exercise dose), daily exercise may be done every other day instead of every day with the same glycemic results, although at least 150 min/week of physical activity is recommended. As for the type of exercise to prescribe, both aerobic and resistance training are important for individuals with diabetes, and ideally a program that combines the two types of training should be undertaken to achieve maximal glycemic and other benefits. Multiple short bouts (e.g., at least 10-min duration) can be accumulated within an exercise day to meet the 30 min goal and produce health improvements. These short bouts may be easier to incorporate into busy schedules and may formulate the cornerstone of health behavior change strategies at the outset of attempting to develop and integrate exercise into a daily schedule for sedentary individuals.

Daily Physical Activity

In addition to the favorable metabolic effects associated with regular structured exercise, epidemiological data from large prospective cohort studies indicate that light-to-moderate physical activity, such as walking, is the most readily available and cost-effective resource available to most

people and protects against the development of T2D. Research supports health improvements with brisk walking for at least 30 min on most days per week [12, 47]. A synthesis of results from cohort studies [47–49] indicates that brisk walking for at least 150 min/week, when compared to minimal amounts of weekly walking significantly lowers risk of T2D. A prospective study of 37,828 women from Women's Health Study found that self-reported walking for 2–3 h/week was associated with a 34% reduction in the incidence of T2D over almost 7 years of follow-up [48]. It is however important to keep in mind that incrementally higher amounts of exercise provide greater protective benefits against T2D [47].

Reducing and Breaking Up Sedentary Time

There is now an empirical basis for advocating the reduction of overall sitting time as part of the treatment and management of T2D patients. While displacing sitting time with light activity breaks may be an effective management tool by itself, it is also plausible that such standing up and moving around more could provide a further behavioral stepping stone toward participation in light intensity and MVPA. Concurrently reducing total sedentary time and interspersing frequent, short bouts of standing and physical activity between periods of sedentary activity seems to lower metabolic risk, even in physically active adults [50–52]. In addition, frequent breaks in sedentary time was beneficially associated with waist circumference, BMI, triglycerides levels, and 2-h postmeal plasma glucose, highlighting the importance of avoiding prolonged uninterrupted periods of sedentary time [53]. Frequent breaks from sitting may also assist in controlling postprandial spikes prevalent throughout the day in many individuals with T2D, even in those with a glycated hemoglobin (HbA1c) level below 7.0% [54]. Additionally, a recent randomized crossover study in 20 men with T2D reported that three 15-min bouts of light-intensity walking compared with a day of prolonged sitting reduced postprandial glucose (17%) and insulin (11%), highlighting the potential of more regular bouts in T2D blood glucose management [55]. Only 3-min bouts every 30 min of light-intensity walking or of simple resistance activities like half-squats, calf raises, gluteal contractions, and knee raises attenuate acute postprandial glucose, insulin, C-peptide, and triglycerides response in adults with T2D [56].

Self-reported sedentary behaviors, such as television viewing time and objectively assessed sedentary time, are only weakly associated with the amount of time spent in MVPA [17, 18, 57], supporting the idea that being sedentary is not the same as being physically inactive (i.e., not meeting the current guidelines for physical activity). Moreover a recent study in young healthy participants showed that increasing MVPA is not linked to lower sedentary time [58]. Therefore, strategies need to be developed to concurrently decrease sedentary time and increase physical activity. In addition, once individuals have successfully implemented more daily movement into their lifestyle, they will be more likely to participate in structured forms of physical activity to gain additional benefits. All clinicians working with people with T2D or prediabetes should consider incorporating these suggestions into care plans to improve their patient's glycemic management.

Behavior Modifications and Exercise

Behavior modification is a specialized area of psychology that utilizes specific theory-based strategies to analyze and modify behavior. The "functional analysis" of behavior involves specifying the relationship between environmental variables and specific behaviors, and "behavioral modification" occurs via the implementation of strategies to modify environmental, cognitive, or affective factors to facilitate the development of adaptive new behaviors. Behavioral modification techniques form the cornerstone of intentional lifestyle change and have been proven effective in improving exercise habits, dietary change, alcohol and drug misuse, and sleep problems. For

decades, applying behavioral change tactics to increase exercise, change diets, and adhere to pharmacotherapy has comprised the foundation of diabetes treatment [59].

The basic premise of health behavior change is that graded efforts to increase awareness of maladaptive behavioral patterns and to increase adaptive health behaviors can result in health improvement. This premise has been widely supported by recent large-scale, multiyear, multicenter investigations of people with prediabetes [3, 4] and T2D [60, 61]. The Diabetes Prevention Program [62] was a multiyear, multicenter investigation of the differential effectiveness of an intensive lifestyle intervention, medication, and placebo to delay or prevent the diabetes onset in at risk adults. The goals of the lifestyle intervention were to achieve at least 7% total body weight reduction via dietary modification and at least 150 min/week of moderate-intensity walking. Over a 2.8-year follow-up, the incidence of diabetes was 11.0, 7.8, and 4.8 cases per 100 person-years in the placebo, medication, and lifestyle arms, respectively. The lifestyle intervention was found to reduce the incidence of diabetes by 58%, which was significantly greater than all other arms. These impressive results were created by modest lifestyle changes over 2–3 years in which participants lost an approximate average of 10 lb and increased walking (e.g., nearly three-quarters of lifestyle participants achieved the goal of 150 min or more). The results of the Diabetes Prevention Program study [62] are similar to those reported by Thomilehto et al. [3], who randomized 522 Finish adults with impaired glucose tolerance to either a similar intensive lifestyle intervention (e.g., supervised exercise and personalized dietary counseling) or a control group (e.g., oral and written information about dietary change and increasing exercise but with no personalized instruction). At an average follow-up of 3.2 years, participants in the intensive lifestyle intervention group showed significantly greater weight loss and improved metabolic measures, and a significantly greater number achieved the physical activity goal of more than 240 min/week. Amazingly, the risk of developing diabetes in intervention subjects was reduced by an identical 58% compared to control subjects as previously reported [4]. In the Look AHEAD study, people with established diabetes, underwent and intervention of combined weight loss and exercise in over 5000 individuals, achieved a mean weight loss of 8.6% and a fitness improvement of 21% [63]. The results of these large-scale trials are of high clinical importance as they support a beneficial impact of small-to-moderate lifestyle changes for health improvement and can fortify self-efficacy.

Behavior Change Strategies to Promote Physical Activity

The benefits of regular physical activity for people with diabetes are often clear to healthcare providers, and yet most patients do not get recommended levels of activity. While trained behaviorists may be available to some patients, physicians, advanced practice providers, exercise physiologists, and other healthcare professionals are often called upon to use counseling approaches and behavior modification strategies to help their patients adopt new health habits. Over the last 20 years, studies have predominantly used strategies that are based on theoretical models of how behavior change occurs, as well as examining the most effective counseling strategies for achieving behavior change. These theoretical models may initially seem esoteric and impractical for clinician implementation without formal training in psychology or counseling. Yet, given the challenges in helping patients make real lasting behavior changes, understanding the broad principles of some of the more widely studied models can be very helpful. The theoretical models can help clinicians form a deeper understanding of factors that underlie human behavior and enable them shape the language they use when talking to individuals about their behaviors. At the end of the day, the goal is to help patients with the "nuts and bolts" of exactly what they are being asked to do and how they can go about becoming more active. In this section, the importance of counseling will be discussed followed by general descriptions of several of the most commonly studied models of behavior change.

The Importance of Talking to Patients About Physical Activity and Lifestyle

For behavior change to occur, a patient needs to see a compelling need for change, feel like the change that is being suggested will be helpful to them, and believe that they will be able to make the recommended changes. These steps do not occur unless they are exposed to a prompt to make achange. While a prompt to become more active may come from family members, the media, or the worksite, a discussion about the importance of physical activity that comes from a healthcare provider can be particularly impactful. Berning used data from the Behavioral Risk Factor Surveillance System (BRFSS) survey to see if advice from a physician or healthcare to make lifestyle changes had an impact on a person's weight [64]. He found strong evidence that physician's advice was associated with weight loss. Dorsey and Songer [65] used data from the National Health Interview Survey (NHIS) to look specifically at physician's advice to change diet and increase physical activity in people with prediabetes and diabetes. They found that 50–60% of people wanted to increase their physical activity levels. They found that one third of those looking to change their behaviors had not discussed this with their doctor, but those that did were significantly more likely to make changes. Rose and coworkers performed a meta-analysis of 13 studies that examined the effects of physician's advice of lifestyle change and they too found a strong and significant effect [66]. One caveat, physician's advice is not consistently provided and may have pragmatic limitations. A recent review of 41 studies of physician's advice around diet and physical activity given to obese patients found that advice about diet was given more often than advice about physical activity and that advice given about physical activity was typically quite general ("be more active") and often was based on the providers personal experience as opposed to being evidence based [67].

Introduction to Several Commonly Studied Theoretical Frameworks

For a clinician without much formal training in behavioral science, the large number of theoretical frameworks published can be daunting. There can be an understandable desire to learn the "best one." The science of behavioral change is a young and evolving field. As such, there is controversy, a lack of consensus, and inconsistencies with nomenclature. Behavior change is difficult and important, so having a general knowledge of the core ideas underlying some of these theories can help practitioners navigate the growing literature and more effectively counsel their patients. The theories we will review are not mutually exclusive, and there are areas of overlap, yet each has a particular focus and may be most useful in particular situations [68]. *One limitation of these theories is that while they seek to explain how behavior change happens or how best to communicate with patients about behavior change, they often do not give specific advice about the details of the behavior change (For example, "Ms. Jones you should walk at a moderate intensity for 10 min 5 days a week.").*

Social Cognitive Theory (SCT) SCT is one of the models most studied in the context of behavior change involving physical activity. Described by Bandura, there are two central ideas in SCT: self-efficacy and outcome expectations [69]. Self-efficacy can be thought of as the level of confidence that a person has that they can exercise control over their health habits [70]. *Self-efficacy* has been found in many studies to be the factor most consistently associated with and individual achieving recommended levels of physical activity [71, 72]. The second factor in SCT is *expectations* about outcomes. This idea is that a person's judgments about the likely consequences of engaging in a particular behavior, good or bad, will play an important role in whether or not they will engage in that behavior. The theory is that a person will do those things that they believe will be good for them and avoid those things that will be harmful [73]. While these ideas may seem like

common sense, to the extent that many patients lack self-efficacy or positive expectations about engaging in physical activity, they will tend to be less active. The theory then suggests that effective behavioral interventions will be those that build people's self-efficacy and positive expectations.

Transtheoretical Model (TTM) or Stages of Change The TTM proposed by Prochaska and Diclemente in 1983 [74] provides a framework for thinking about whether a patient is ready to change their behavior. The theory hypothesizes that individuals go through a series of sequential steps in their thinking before making a change in their behavior. The specific stages of change hypothesized are:

Precontemplation: This person is happy with their current levels of activity and does not see a compelling need for changes.

Contemplation: These people have some concerns about how little activity they currently get, but they are not confident about starting an exercise program. These people are ambivalent about change. They typically mostly see barriers to change and need help resolving their ambivalence about trying something new.

Planning: The person sees a compelling need to change their level of physical activity and is making specific plans about what they are going to do. These people are the most open to input about the details of what to do.

Action: These people have begun a physical activity program. They need help with problem-solving and sustaining the new behaviors.

Maintenance: This is the goal state. These people have successfully adopted new activity habits for at least 6 months.

Relapse: People in relapse tried to be active but were not able to sustain it and have gone back to their previous habits. These people are typically frustrated and sad.

Determining readiness for behavioral change has been suggested as a useful factor in predicting participation with behavior change efforts [75, 76], and the readiness for change construct has been specifically applied to exercise [77, 78]. Available data suggest that individuals in the precontemplation stage report the lowest levels of physical activity, while those in the action and maintenance stages reported the highest. Cowan et al. [79] assessed 182 primary care patients and found 15% in the precontemplation stage, 26% in contemplation, 50% in preparation, 7% in action, and 13% in maintenance, suggesting that only a small percentage of medical patients may be actively engaged in exercise at a given time. Recent reviews of the utility of the TTM in promoting physical activity have concluded that the evidence in support of the effectiveness of this model is quite limited and of poor quality [80]. However, this is not surprising given that the TTM is essentially a diagnostic strategy that allows the clinician to get a sense of how ready the patient is to make behavior changes. The model does not provide guidance on how to then help the person to advance to the next stage. TTM can be quite useful to a clinician who is trying to decide if it is worth bringing up the topic of physical activity with a particular patient and what topic to discuss (e.g., the value of exercise for the precontemplative individual as opposed to relapse prevention for a person in maintenance).

Motivational Interviewing (MI) Introduced by Miller and Rollnick in 1991 [81] initially as a strategy for counseling individuals struggling with addiction. They defined MI as a "directive client centered counseling style for eliciting behavior change by helping clients explore and resolve ambivalence" [81]. The primary purpose of this interviewing style is the examination and resolution of ambivalence. They suggested that the motivation to change must come from the individual and cannot be imposed from the outside. They suggest that the physician's job is to have the patient talk about their ambivalence and try to resolve it. They suggest that direct persuasion is not an effective method for resolving ambivalence. In MI, the counselor focuses on ambivalence as opposed to teaching specific skills. They point out that an individual's readiness to change may be reflected in the resistance

that they give to suggestions or demands that the physician makes. The goal is to have the patient assume *responsibility* for their progress and help them build a sense of *self-efficacy*.

There are a number of other strategies that are part of MI. These include:

Reflection: This means repeating back to the patient what you hear them say while providing empathy but highlighting discrepancies.

Rolling with resistance: When change is suggested and the patient is resistant to that suggestion, it means that they are not ready to change and it is best to not push the idea. A better approach is to come back to the idea when the person is more receptive.

Highlighting discrepancies: Sometimes, patients will say that they want to increase their activity, but then when it comes to actually following through, they do not. In this situation, the counselor can non-judgmentally point out the inconsistency between these two.

Alternative futures: In this strategy, the provider suggests that the patient play their behavior forward in time and imagine what the consequences might be of their current level of physical activity verses an adopting a more active lifestyle.

Pros and cons to current and future behaviors: In this strategy, the patient can use a 2 × 2 table to help explore pros and cons of their current behaviors which can be compared and contrasted with the pros and cons of an alternative behavior.

MI strategies used in combination with other behavioral interventions have shown promise in increasing reported levels of physical activity [82–85]. A recent review of the applications of MI concluded that the current literature supports a modest effect of adding MI to a physical activity intervention in people with chronic health conditions [86]. Outcomes for patients with diabetes who are counselled about diet and weight using MI also are promising but small [87]. Here again though, it is not surprising that MI does not have a larger effect as this is an approach to counseling, not a specific strategy for getting people to be more active. MI) does not help a provider define a good exercise program, it just helps the provider communicate with the patient who wants to change but is having trouble actually making progress.

Core Behavioral Strategies for Increasing Physical Activity and Decreasing Sedentary Time

Self-Monitoring Self-monitoring has consistently been found to be a key factor in promoting behavior change. Self-monitoring is the systematic recording of behaviors selected for change. In exercise adoption, numbers of steps accumulated via pedometer recordings, minutes of intentional daily exercise, number of stairs walked, increases in lifestyle activities (e.g., minutes spent raking leaves, mowing the lawn), and amount of time spent watching television, sitting at a desk, or working on a computer may all be targeted for self-monitoring. Daily monitoring of additional factors which influence exercise intention (e.g., mood states, perceived obstacles, weather, time availability) can also provide critical information that can be addressed to increase the likelihood that a person will sustain an exercise program.

Goal Setting Using information obtained from the daily recording of activity levels, the development of realistic, achievable, and measurable goals for the progressive graded increase in activity is critical to long-term success. Overall goals can be divided into individual weekly goals, and these weekly goals can be sequentially increased over an extended time period. Initial behavior change goals may include setting a minimum number of minutes per day to walk or meeting a step goal or reducing the amount of time watching television or working on a computer. Ideally the person will express a high level of confidence in their ability to achieve the goal. Social support and reinforcement for persistent effort is critical as it realistically may take weeks or months to increase activity levels to achieve the desired number of minutes per day and/or the number of days per week.

Behavioral Contracts and Reinforcement Planning Behavioral contracts are an "effort agreement" between two parties (e.g., the person attempting behavior change and a family member, healthcare professional, or peers also attempting to be more active) in which the goal behavior and the time frame for completion are defined. This contract should also include the identification of very specific rewards which will be provided when the contingencies in the contract are achieved. Self-reward is an important part of exercise contracts that can be an important strategy in motivating patients to maintain efforts over time [88, 89]. Long-term behavior change may be facilitated by a gradual change in the way an individual perceives and defines their identity, gradually seeing themselves as a person who is active rather than a person who is sedentary.

Problem Solving Problem-solving techniques generally include five steps which are identifying and defining specific obstacles to long-term behavioral performance, brainstorming a number of potential solutions to each challenge, considering the ease of applicability of each option, selecting and implementing a high-probability option to navigate a given obstacle, and evaluating the success of the chosen option. This problem-solving algorithm can be flexibly applied to both overt/environmental challenges (e.g., winter weather, transportation, financial issues, physical injuries, and schedule conflicts) and covert/intrapersonal obstacles (lack of motivation, depression, and negative self-statements).

Stimulus Control/Prompting Stimulus control is the behavioral strategy designed to identify and modify environmental cues or prompts associated with increasing activity. Multiple environmental cues are present each day which may prompt inactivity (e.g., television remote controls and easy access transportation) and a commitment to increase activity comes with an inherent acknowledgment that behavior change is not initially convenient. Multiple prompts can be strategically placed in one's home and work environment to cue activity increases. For example, placing exercise clothes in readily available carry bags for work, keeping walking shoes in sight at both home and work, charting of walking days and times, or using electronic schedule prompts to remind of exercise times.

Cognitive Restructuring Just as humans develop a variety of daily physical habits that become increasingly "automatic" determinants of behavior, we are equally prone to developing cognitive "habits" that influence our perceptions of ourselves, our world, and our daily behavior. Most people contemplating activity increases have made multiple prior unsuccessful attempts to exercise. Ideas and negative thoughts that come from these previous attempts to be active can become self-defeating and adversely impact a person's motivation to attempt future exercise. Conversely, focusing on positive previous efforts to be active and successes at meeting goals following the introduction of a physical activity plan can "restructure" the person's ideas around their ability to be active.

Social Support Involving influential others in behavior change efforts can have a significant effect on long-term motivation and productivity. Individuals attempting activity increases are encouraged to keep social support members aware of their goals and to involve others whenever possible in exercise sessions [90]. Wallace et al. [91] reported that individuals who began a fitness program with their spouse had higher levels of adherence at 12 months than those who joined alone. In an interesting report of the potential influence of social others on exercise performance, Brekke et al. [92] reported that brief educational interventions with nondiabetic relatives of people with diabetes had a positive and statistically significant influence on producing increased physical activity in sedentary family members with diabetes.

Relapse Prevention More than 50% of individuals who begin exercise regimens discontinue within 3–6 months [93, 94]. Sallis et al. [95] reported that among women adopting either moderate- or vigorous-intensity activity,

discontinuation rates were 30% and 50% for moderate and vigorous exercisers, respectively, between 6 and 12 months. Waning motivation, significant schedule changes, loss of exercise partners, or physical injury may all contribute to an episodic hiatus from activity. Among the factors shown to associate with behavior change adherence is maintaining long-term contact with treatment providers and/or peers [96, 97]. Follow-up contacts can be efficiently accomplished via episodic individual or group meetings, telephone, or Internet [98–100].

Table 14.1 summarizes these commonly used behavioral strategies.

The Utility of mHealth and eHealth Tools to Promote Physical Activity

Self-monitoring has consistently been found to be an important element in successful behavior change. In addition, prompts to action appear to also be important components. Electronic tools offer the hope of more convenient and as a result more effective approaches for self-monitoring and reminder prompts. Over the last few years, the number of apps devoted to lifestyle change has exploded. Unfortunately, high-quality research on these electronic tools has lagged behind commercial investment. One easy way to monitor physical activity is with an *electronic app* such as the popular MyFitnessPal. A recent study [101] examined the utility of giving patients being seen in a primary care setting this tool. While users of the app reported high levels of satisfaction with the tool, their use of it dropped off markedly after the first month. In addition, there was no effect of using the app on self-reported levels of physical activity or weight as compared to the control condition. These finding suggest that an electronic tool given broadly to people without considerations of their readiness to change or without other supports for behavior change has minimal effects.

Text messaging could provide a very low-cost approach to providing patients with prompts and simple timely advice around physical activity. A recent systematic review of this strategy [102] examined 55 studies using this approach for a range of behaviors and found that text messaging resulted in significant positive behavioral outcomes for participants. Very few of these studies however focused on physical activity and few provided detailed rationales for the timing of prompts and the theoretical underpinnings of the interventions.

Telephone interventions might allow for not only behavioral prompts but also problem solving and social support at a lower cost than traditional face-to-face interventions. A recent systematic review of 17 studies using telephone intervention strategies [103] found moderate evidence for the effectiveness of this approach for initiating physical activity behavior. A smaller number of studies examined the effects of telephone interventions on weight maintenance and the effects here were positive but less compelling.

A recent meta-analysis examined the relative effectiveness of *web-based* physical activity interventions as compared to face-to-face interventions versus remote and web 2.0 interventions for promoting physical activity [104]. While they did not find sufficient data to conclusively answer the question, the evidence they reviewed suggested that web-based interventions could be as successful as face-to-face interventions [105]. While promising, further studies are clearly needed using evidence-based approaches combined ideally with direct measures of physical activity.

Evidenced-Based Strategies to Promote Physical Activity

Recently a number of meta-analyses and systematic reviews of numerous trials have been published in an effort to more specifically summarize the specific intervention strategies that have been found to be associated with increases in measured physical activity, improvements in HbA1C levels, or increases in self-efficacy for physical activity. One meta-analysis examined 27 studies designed to promote physical activity in a range of individuals [106]. This study found

Table 14.1 Examples of behavioral modification strategies in exercise adoption and maintenance

Behavioral technique	Purpose(s)	Target uses/examples
Self-monitoring	Increase awareness of behavior patterns	Daily activity minutes/steps
		Time spent sitting
	Reinforce changes in target behaviors	Factors influencing activity pattern
		Mood, negative thoughts
		Weather, pain
		Television/computer/driving time
		Glucose before/after exercise
Goal setting	Specify realistic, measurable, obtainable incremental goals for target behaviors	Graded activity increases
		Walking more
		Achieving moderate intensity
		Minutes per day/week
		Number of days per week
	Decreasing sedentary behaviors	Reducing time spent watching television, working on a computer, or driving
		Frequently interrupting prolonged sitting time
Behavioral contracting	Specify criteria for increases in target behaviors, decreases in maladaptive behaviors	Activity amount/type/frequency
		Time management schedule
		Incremental goals
Reinforcement planning	Specify rewards for contract fulfillment	Reinforcement/rewards
	Extrinsic	Positive comments from others
		Buying new shoes, clothes
		Entering walks, fun runs
		Pleasurable activities, massage
	Intrinsic	Self-perception (“a walker”)
		Positive self-esteem changes
		Changes in body appearance
		Improved mood, less fatigue
Problem-solving	Stepwise algorithm to modify challenges to consistent efforts at behavior change	Obstacles to exercise adherence
		Adverse weather
		Mall walking
		Minor injuries
		Apathy
		Mood challenges
		Walking partners/social support
		Walkability and parks
Stimulus control/cues	Prompt occurrence of target behaviors	Color dots to prompt awareness
		Exercise goals
		Increase visual cues to prompt activity
		Equipment, clothes, shoes
		Electronic calendar prompts to exercise
Changing the environment	Make changes in home/work environments to support performance of the target behavior	Keep walking shoes in sight at home/office
		Packing exercise clothing for work
		Preparing exercise equipment for easy use
		Using standing desk station

(continued)

Table 14.1 (continued)

Behavioral technique	Purpose(s)	Target uses/examples
Cognitive restructuring	Identify/modify self-defeating thoughts	Inaccurate self-perceptions
		Too out of shape to start
		Won't do any good
		Lack will power
	Increase self-rewarding thoughts to motivate change efforts	Encouraging thoughts
		I can do it this time
		Little changes will help
		A lapse is not a crisis
		Proud of myself for trying again
Social support	Identify positive resources	Enlist family/friends in efforts
		Medical treatment providers
	Identify new/extended resources	Community/public resources/clubs
		Exercise groups
		Professional organization exercise classes (e.g., Arthritis Foundation)
Relapse prevention	Define lapse and relapse	Set explicit criteria to reengage
	Develop plans to reengage	Identify multiple resources to assist reengagement efforts
	Develop resources to contact to assist with reengaging	Multiple community resources for activity, continued contact, and support

that "action planning," "'provide instruction," and "reinforcing effort toward behavior" were associated with significantly higher levels of both self-efficacy and physical activity. Six specific techniques were associated with higher physical activity. These were as follows: "provide information on consequences of the behavior in general," "action planning," "reinforcing effort or progress toward behavior," "provide instruction," "facilitate social comparison," and "time management."

Another recent analysis systematically reviewed 21 behavior change techniques used in clinical studies of 1975 subjects enrolled in physical activity interventions conducted in patients with diabetes [107]. They found that four techniques were associated with increases in physical activity. These were (1) prompt focus on past success, (2) barrier identification/problem-solving, (3) use of follow-up prompts, and (4) provide information on where and when to perform physical activity. Two behavior change techniques were associated with improvements in HbA1c. These were to prompt review of behavioral goals and providing information on where and when to perform physical activity. Surprisingly, the use of a pedometer was found to be associated with lower levels of physical activity. This finding highlights how simply using a self-monitoring tool may not actually increase physical activity. The strength of this analysis is that it was conducted on studies performed in patients with diabetes who tend to be older and have physical challenges with exercise.

A meta-analysis of 17 studies that sought to increase physical activity in people with diabetes [108] found that behavioral interventions resulted in increases in physical activity when compared to usual care. Several of the studies reviewed also demonstrated improvements in HbA1C levels. Several specific behavioral strategies were associated with success. These included the use of follow-up prompts, prompt review of behavioral goals, provide information on where and when to perform PA, plan social support/social change, goal setting (behavior), time management, prompting focus on past success, barrier identification/problem-solving, and providing information on the consequences specific to the individual. These authors highlight

the lack of consistency in the nature of the theoretical framework used in these studies, lack of reporting on the fidelity of the interventions, and lack of consistency in the specific intervention strategies used.

An Ecological Perspective on Changing Physical Activity and Sedentary Behaviors

Changing behavior at the individual level, although needed, poses barriers and limitations beyond the individual's control. By considering extrinsic influences on behavior, multilevel ecological approaches applied to sedentary behaviors and physical activity interventions have the potential to produce sustainable health behavior change and larger-scale effects [61, 109, 110]. The "drivers" of sedentary behaviors and physical activity include both elements of conscious/decision-making and habitual responses cued or required by the milieu or the public policy. Thus interventions should take advantage of changes in the built and social environments, the use of social networks, and the promotion of relevant public policy changes in addition of the proven behavioral strategies (e.g., incorporating messages to build awareness, adopting new technology, etc.). Two recent workplace sitting interventions have included organizational (management consultation, workshop, and brainstorming), environmental (sit-stand workstations), and individual (one-to-one health coaching, self-regulation strategies, and motivational interviewing) elements. One trial reported successful reductions in sitting time by 125 min/day over 4 weeks [111]. Two longer 12-week randomized controlled trials reduced sitting time 94 min/day [112] and 59 min/day [113], respectively, with reductions in waist circumferences compared to the control condition. The French 'Intervention Centered on Adolescents' Physical activity and Sedentary behavior' (ICAPS) combined approaches of personal, educational, social, environmental, and organizational changes in school and outside school, to target adolescents in their environment [114]. Implemented in schools, the program was based on student's perception, motivation, and knowledge of physical activity, social environment (family, teachers), and physical and political environment, but also on the perception of this environment (accessibility of sports facilities, transport, media). ICAPS showed that it was possible to promote physical activity, reduce sedentary lifestyles, and prevent excessive weight gain in adolescents (50% decrease in risk of being overweight) [115, 116]. The self-confidence of the students had increased, which is recognized to be one of the long-term behavior change predictors. Four years following the end of the intervention, behavioral changes (decreased sedentary lifestyle, active transport) have been maintained, especially mediated by a positive attitude toward physical activity, social support around students, and changing self-perception of their environment [115]. These lasting changes are a major factor when we know that the practice of physical activity and its benefits during childhood are predictive of the behavior and health in adulthood.

Summary and Future Work

The American Diabetes Association/European Association for the Study of Diabetes treatment algorithm for new T2D states that "at diagnosis, highly motivated patients with a HbA1c level of <7.5% should be given the opportunity to engage in lifestyle changes for 3–6 months before embarking on pharmacotherapy (usually metformin)" [117]. In the clinical setting, however, very few patients with T2DM even see a certified diabetes educator prior to the institution of glucose-lowering medications much less embark upon a serious and intense long-term program of exercise and weight loss. Exercise needs to be seen as prescribed treatment.

Healthcare professionals are typically highly motivated to help their patients adopt healthy lifestyle behaviors. There can be a tendency for office visits to consist of a good deal of advice giving. If as often happens the patient does not adopt the practices suggested, the clinician can become frustrated with the patient and feel a sense of futility. Ultimately, behavior change

needs to come from the patient. The clinician cannot adopt an exercise program for the patient. All the care provider can do is have a conversation with the patient that is honest, supportive, and hopefully helpful as they consider their current physical activity habits and health risks and whether they want to make changes. If they are ready to make changes the conversation can focus on steps that are realistic, specific, and measurable and that the patient is confident that they can actually accomplish. Small gradual steps may build a sense of self-efficacy and promote further progress. Having a basic understanding of a number of theories about behavior change can help a clinician respond to clinical circumstances with tailored strategies that are more likely to promote the adoption of lifestyle changes than a "one size fits all" approach. Having honest conversations with patients about changing physical activity behaviors will help the clinician appreciate the challenges involved and allow them to provide more specific and useful advice to the patient. Using evidence-based approaches that are informed by an understanding of the factors that underlie behavior change can make the clinical interaction more successful and rewarding for both the patient and the provider.

Improving health outcomes via exercise has become a combination task of reducing daily sedentary activity and increasing activities designed to intentionally expend energy. Making efforts to increase lifestyle, leisure, and recreational activities in addition to structured activity has been shown to produce health improvement. Since simply avoiding sedentary behavior appears to have a large impact on glycemic management, individuals with T2D should at least be encouraged to minimally engage in frequent daily movement to better manage their diabetes and body weight. While daily movement is not as effective as most structured exercise programs in increasing fitness levels, it is important for expending extra calories, breaking up prolonged sitting time, and building a fitness base in sedentary individuals. Once increased daily movement is implemented, individuals will likely feel more confident, ready, and able to participate in structured forms of physical activity, including both aerobic and resistance training of varying intensities, which can greatly enhance their health and diabetes management. Individuals with diabetes seeking improved cardiorespiratory fitness should exercise as many times per week as possible but with a minimum goal of 4–5 days/week to maintain enhanced insulin sensitivity. Daily exercise quotas can be accumulated via multiple short bouts as well as extended single sessions of activity. Accumulating 30 min of exercise has shown to produce fitness improvements, and additional health benefits may be achieved by increasing exercise duration to 60 min/day. As it is known that more than half of people initiating behavior efforts to increase exercise discontinue within 6 months, longer-term and sustainable behavioral strategies must be emphasized in treatment planning. Implementing readiness for change and MI strategies have shown promise in maintaining efforts and must be consistently utilized in future programs.

Profound environmental challenges exist to increase the activity level of the general public. Increasing the availability of behavioral skill instruction to larger numbers of individuals via their introduction in naturalistic work-site programs, computer-based programs, or web-based behavior change programs is therefore recommended. The development of large-scale interventions including improved community development to increase activity convenience (e.g., sidewalks and improved lighting) and community program development (e.g., walking programs) to address the broad need to increase the general publics' participation in regular physical activity is also encouraged.

Significant behavioral challenges exist in improving the physical activity levels of adults, adolescents, and children in the USA. Epidemiological data suggests that population rates of obesity and diabetes are rapidly increasing and that sedentary lifestyle is independently related to chances of developing diabetes. Fortunately, the data reviewed in this chapter supports the benefits of increasing physical activity even by a relatively small amount and holds promise that both small- and large-scale activity programs might improve the fitness levels of the general population and someday reverse the alarming health trends of the last two decades.

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Exercise and Quality of Life

15

Willy Marcos Valencia and Hermes Florez

Introduction to Exercise

Exercise is a fundamental intervention for any patient with diabetes or at risk for it. The joint position statement by the American College of Sports Medicine (ACSM) and the American Diabetes Association (ADA) highlights the multiple benefits from exercise, not only to control blood glucose but also to reduce the risk from metabolic abnormalities and diabetes-related comorbidities and complications [1]. The recommendation for *exercise* is to participate in at least 150 min/week of moderate to vigorous aerobic exercise spread out over at least 3 days, and, in addition, at least 2–3 days/week of moderate to vigorous resistance training. With regard to *physical activity*, the recommendation is to increase their total daily unstructured physical activity. Flexibility training may be included, but it does not replace the abovementioned.

Nevertheless, recent US data shows that only 41% of patients comply with the recommendations for aerobic exercise and a dismal 12% comply with the recommendations for resistance exercise [2].

Hereby, in order to proceed with recommendations, we need to clearly distinguish between physical activity and exercise. *Physical activity* is any bodily movement produced by contraction of skeletal muscle that substantially increases energy expenditure (including occupation and leisure time activities). *Aerobic exercise* involves large muscle groups in dynamic activities that result in substantial increases in heart rate and energy expenditure. *Resistance exercise* is an anaerobic training designed specifically to increase muscular strength, power, and endurance by varying the resistance [3].

Exercise and QOL in Diabetes

There is a large body of evidence on the positive benefits from exercise to prevent and control type

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2 diabetes: control glucose and improve insulin sensitivity and myocardial and vascular function [4], among others. Clearly, engagement in physical activity has well-established health benefits and decreases prevalence and severity of common chronic health conditions, as described more than 20 years ago [5]. To list recommendations from major organizations regarding the importance of exercise in diabetes is beyond the scope of this chapter. However, it is clear that for most interventions, the effect of exercise is related to adherence, and long-term patient compliance represents a major limitation, especially when translating results from studies into clinical practice.

In type 2 diabetes, lower physical and mental HRQOL are independent markers for mortality, associated with higher rates of overall and cardiovascular mortality [6–8]. There has been an increasing interest in addressing QOL as a patient-related outcome in diabetes. Consequently, there is a growing body of literature addressing the impact of exercise on QOL. However, there is discrepancy between definitions for QOL, tools and instruments to assess it, and their applicability to patients with diabetes (displayed and exemplified in the Tables 15.1, 15.2, and 15.3).

Furthermore, this is particularly important given the heterogeneity of this population and the variability of exercise intervention protocols.

We present a review of the most relevant publications, to our perspective, without the attempt to provide an exhaustive review, examples of which have been published in different systematic reviews:

(A) The *Italian Diabetes and Exercise Study (IDES)* was a multicenter parallel randomized, controlled, open label study on the impact of exercise in QOL (using SF-36) in sedentary patients with diabetes [23]. All participants received structured individualized counseling, aiming to reach 150 min/week of physical activity, with additional reinforcing counseling every 3 months. The intervention group ($N = 303$) received supervised 150 min/week progressive training (aerobic and resistance) in two supervised sessions. The control group ($N = 303$) received only counseling. The investigators found that improvements in physical and mental domains were related to the volume of physical activity, with supervised exercise training providing volume-independent benefits. A follow-up study (IDES-2) is underway, with the purpose to address the long-term behavioral intervention for adoption and maintenance of a physically active lifestyle [24].

(B) The *Health Benefits of Aerobic and Resistance Training in individuals with type 2 diabetes*

Table 15.1 Patient-related outcome measures and quality of life

Measures	Definition and characteristics
Patient-reported outcome measures (PROMs)	• Evaluate experiential domains of health, including disease symptoms, treatment side effects, function and QOL [9–11]
	• Their use is increasing as performance indicators in chronic illness, and their reliability is similar to clinical measures such as blood glucose or blood pressure [12]
Quality of life (QOL)	• Defined as an overall sense of well-being, happiness, and satisfaction with life as a whole. The themes for QOL include physical functioning, social functioning, and mental well-being, which can produce a multidimensional QOL score that can be measured and followed
	• There is consensus that QOL measurements are most meaningful when addressing key concepts, logically and precisely [13]
	• Overall, QOL involves health, job, housing, school, neighborhood, culture, values, and spirituality
Health-related quality of life (HRQOL)	• Encompass aspects of overall quality of life that can affect physical or mental health [14] and which can guide the clinician to evaluate interventions and plan of care (Patrick 2000)
	• The five major domains of HRQOL (biological and physiological factors, symptoms status, functional status, general health perceptions, overall HRQOL) are impacted by characteristics pertinent to the individual (sociodemographic, age, gender, disease type) and the environment [15]
	• Effective self-management and quality of life are described as key outcomes of diabetes education and self-management and should be measured and monitored as part of the plan of care in patients with diabetes [16]

Table 15.2 Instruments to assess quality of life

Type	Concept	Contrast
Generic	• Contain items applicable to a wide variety of patients, healthy or with coexistent conditions or diseases. Examples:	• Clinically practical, widespread available
		• Limitations to assess a specific disease, i.e., diabetes, albeit they can be well validated
	The Medical Outcomes Study 36-item short form (SF-36) [17]	• Allow comparison with health controls
	The World Health Organization Quality of Life (WHOQOL) [18]	
Disease specific	• Contain details specific to a particular disease. Examples:	• May provide greater insight into specific issues impairing health status, pertinent to the specific disease
	The diabetes quality of life measure [19]	
	The problem areas in diabetes questionnaire [20]	• Validation may be limited due to smaller number of studies, a narrow focus, and inapplicability to compare with healthy controls
		• Ideal for monitoring patients in the clinical setting [21]

There is no agreement which is the best tool to assess QOL in patients with diabetes. Consequently, when reviewing studies assessing the impact of exercise in QOL in patients with diabetes, we find a variety of tools used

(HARD-D) was a 9-month exercise study comparing the effects of exercise (aerobic, resistance, or a combination) versus a non-exercise control group [25]. Their research team conducted an ancillary analysis to examine changes in QOL (using SF-36) [26]. In this study, the exercise prescription in the three exercise groups aimed to achieve 50–80% of maximal oxygen consumption. The resistance training was based on a circuit protocol, and aerobic exercise was performed using a treadmill. The intervention included a phase of stretching and relaxation focused on increasing flexibility and reducing stress. The researchers found that exercise training has a beneficial effect on QOL, in all exercise groups. Interestingly, bodily pain was higher after the exercise intervention (compared to pre-intervention) in all groups, including the control group. However, only resistance training appeared to mitigate the increase in pain observed in the participants of the study. On the other hand, only aerobic and combined training (thus including aerobic) had the most beneficial effect in physical functioning subscale, which addresses the ability to perform physical activities required for daily living. Furthermore, the combined exercise provided the most beneficial effects on mental QOL. Nevertheless, they also noted the difference with IDES, where most mental health domains improved, whereas HARD-D found benefits only in the vitality domain, similar to the findings from the Diabetes Prevention Program lifestyle arm (discussed below). Of note, the diabetes was fairly well controlled in the participants of this study. This does not undermine the efforts or results. However, we want to highlight again the impact of the disease (and its control and comorbidities) in the HRQOL, thus, as we will describe, the degree of diabetes control can impact the results from exercise interventions.

(C) The *Look AHEAD study* delivered an intensive lifestyle intervention: dietary (similar to the diabetes prevention program) and exercise (aerobic exercise more than 175 min/week) versus control (diabetes support and education) [27]. A major advantage of this study is the long follow-up (median of 9.6 years), longer than most studies. The researchers evaluated QOL with SF-36 (collected yearly) and depression with the Beck Depression Inventory. After 1 year, significant improvements in HRQOL were found in the participants, who had diabetes and overweight [28]. At the long-term follow-up, there were no changes in the mental components and "only" a mitigation of the

Table 15.3 Exercise training on QOL, depression, anxiety, and well-being

	Aerobic training (six studies)	Resistance training (four studies)	Combined aerobic and resistance training (ten studies)
QOL instrument			
SF-36	3	3	8
World Health Organization quality of life questionnaire	1		
Swedish HRQOL	1		
Quality of well-being scale	1		
SF-12		1	
European QOL			1
Combined[a]			1
Results			
On QOL	No effects	Mixed results	Mixed results
On depression	No effects	Reduced symptoms (one study)	No effects
On anxiety	Positive effect (one study)	–	–
On well-being	Mixed results	Mixed	No effects

Results from the first systematic review focused on the effects of exercise training on QOL, symptoms of depression, anxiety, and well-being in people with diabetes [22]

[a]Combined diabetes QOL (from the Diabetes Interventions and Complications Trial) and the modified QOL measure for youths

worsening in physical components only in the intervention group, yet with worse scores in the control group [29]. It has been described that chronicity of disease and aging worsen QOL scores. The Look AHEAD is considered a negative study for the primary cardiovascular outcomes. Notwithstanding, it shows the protective effects of lifestyle interventions and exercise against progressive symptoms of depression and reductions in HRQOL in patients with long-standing diabetes.

(D) *The Diabetes Prevention Program (DPP)* is a randomized clinical trial focused on patients at risk for diabetes. The intensive lifestyle program aimed for at least 7% weight loss and 150 min of physical activity per week. The study used SF-36 to evaluate the HRQOL. After a mean follow-up of 3.2 years, there were improvements in most of the physical components and in vitality scores [30]. The results of this study highlight the need to promote exercise in patients at risk for diabetes.

Exercise, Depression, and Quality of Life in Diabetes

Depression is a major factor impacting HRQOL and is more prevalent in diabetes. Furthermore, almost 20% of patients with diabetes have depression, and the incidence is 24% higher compared to the general population [31–34]. Depressive symptoms affect one third of people with diabetes, impairing their self-management and QOL [35]. The presence of depression can be a manifestation or a determinant of poor quality of life, and patients with diabetes already have greater risk for poor HRQOL [36]. Moreover, the physical and mental components of the SF-36 are poorer in the patients with both depression and diabetes versus those with depression alone [37]. A systematic review addressing depression and HRQOL in patients with type 2 diabetes found that self-reported depressive symptoms markedly impaired HRQOL on several domains, albeit not all [38], confirming that certain aspect or HRQOL varies between clinical and demographic subgroups, as mentioned above.

On the other hand, it is not only that diabetes is associated with an increased in depression, but depression is also associated with increased risk for diabetes [39]. Depression is associated with poor diabetes control. It is described that patients with coexistent diabetes and depression have poorer adherence to diet, exercise, and medications [40], thus leading to impaired self-management and greater complications and costs [41]. Thus, this association leads to *a vicious cycle*, in which impaired QOL is at the center of the storm. Concurrent depression is associated with impaired metabolic control, poor lifestyle and medication adherence, decreased quality of life, and increased health care expenditures. Furthermore, poor metabolic control may exacerbate depression and impair the response to pharmacologic antidepressant interventions [42]. Different studies have shown that *exercise can improve diabetes control, as well as depression and QOL* [43–47]. Thus, exercise could potentially contribute to breaking this vicious cycle and promote a healthier one, where better outcomes lead to greater motivation, weight loss, improvement of clinical values, and further motivation to continue the exercise. Furthermore, not only major clinical depression but the presence of depressive symptoms (subsyndromal depression) also present emotional problems related to diabetes, occurring in both type 2 and type 1 diabetes [48, 49].

The evidence suggests that fostering improvements in disease management and diabetes distress can be achieved through interventions that target both of these linked problems [50]. A small, randomized control study compared the impact from psychoeducation, physical exercise, and enhanced standard of care in patients with diabetes who screened positive for depression and expressed the need for professional help with mood-related issues [51]. The exercise intervention consisted of six weekly 90-min small group sessions aimed at educating participants on the interaction between physical activity, mood, diabetes, and recommendations, warm-up, flexibility, strengthening, and stretching exercises. The exercise intensity was of light to medium intensity. All groups presented benefits in depressive symptoms, diabetes self-management, HRQOL, and metabolic control. The improvement in emotional symptoms was more apparent in cases with higher depressive symptoms at baseline, as well as more serious emotional problems related to diabetes. These findings highlight the need to address subclinical depression with physical activity and exercise interventions, which are likely to benefit both conditions. Of note, as described above, the subjects did not receive an intensive exercise program; hence, milder exercise interventions could prove to be as effective in this subpopulation of patients.

Exercise Interventions for QOL in Older Adults

Older age can be associated with a longer duration of disease, greater prevalence of diabetes complications, and lower HRQOL [52]. Of note, older adults have an increased prevalence of multimorbidity and lower QOL [53]. Moreover, the prevalence, they also present greater coexistence of diabetes and depression [54], which as we discussed earlier, negatively impacts HRQOL. Thus, we considered necessary to focus this section on studies in older adults:

(A) A Canadian study evaluated the effects of aerobic physical exercise in older adults with type 2 diabetes [55]. To assess QOL, they used a tool combining the diabetes QOL, which was adapted from the Diabetes Interventions and Complications Trial (DCCT), and the modified QOL measure for youths. They also used a questionnaire to address positive attitudes. The exercise intervention consisted of 16 weeks of supervised exercise, three times per week, which included aerobic, resistance, and stretching exercises. The researchers found that the QOL did not change in any of their groups, but that the attitudes did improve in the exercise group.

(B) A Japanese study evaluated the impact from a 3-month exercise intervention in QOL (using SF-36) in patients older than 65 years

of age and tried to identify predictors of better outcomes [56]. The study had a few limitations (convenience sample, size), but it was a great attempt to identify predictors for good outcomes. The researchers adjusted for patient characteristics and changes from baseline to follow-up. They defined good or bad outcomes by the changes in the domains of the SF-36 (good respondent domains, e.g., bodily pain, vitality, social functioning, mental health; poor respondent domains e.g., physical functioning, physical role, general health, emotional role):

- Using a univariate model of screening for predictors, they found that absence of non-specific low back pain, diabetes, and hypertension, presence of osteoporosis, and more frequent habitual exercise at baseline were associated with good outcomes.
- Using a multivariate model, the raw analysis determined that the absence of diabetes was associated with good outcome, but this was no longer significant after adjusting for age, gender, body mass index, and multimorbidity. On the other hand, the presence of osteoarthritis, even after controlling for confounders, remained as the sole significant predictor for poor outcome.

  This study suggests that the presence of diabetes alone hinders the potential for improvements in QOL in older people, but most importantly, greater baseline exercise contributes to improved outcomes, even in the presence of multimorbidity.

(C) A 1-year, randomized clinical trial evaluated if exercise, alone or combined with weight loss, was more effective in older patients with obesity and mild-to-moderate frailty syndrome. The exercise intervention included flexibility, endurance, and strength training. After the intervention was completed, the physical components of the SF-36 increased in the combined intervention group, greater than the weight-loss alone group, and almost double the exercise alone group [57].

(D) We studied the impact from a supervised evidence-based group exercise program (Enhance Fitness [58]) in older veterans with overweight and obesity and with diabetes or at risk for it [59]. Using a quasi-experimental design, we analyzed HRQOL outcomes between participants with good adherence or poor adherence, based on attendance to the exercise classes (equal or more than 50%, or lower, respectively). Both groups received standard of care interventions for weight loss, including the training and interventions at the MOVE! Weight Management Program. The follow-up was completed at 4 months. As expected, we found much greater improvements in SF-36 domains for participants in the good adherence group. Most importantly, when addressing what may have been the factors associated with the improvement (there were positive changes in anthropometric parameters, physical function tests, and depression scores), we found there were additional factors that we had not initially considered. Among those, the development of strong friendships among the participants, the socialization, and their interaction and motivation among each other were witnessed by our research team. While this is difficult to quantify, there was no question that the positive results in HRQOL with supervised exercise were enhanced by the delivery in groups.

Special Considerations

(A) *Multimorbidity*: Patients with multiple coexistent chronic conditions experience variable health status, between individuals and over time [60]. Chronic medical conditions can impact daily functioning and perceived HRQOL [61]. The presence of diabetes complications and severity of diabetes symptoms negatively influence daily functioning and HRQOL in people living with diabetes [62–66]

(B) *Glycemic control and tools used to assess QOL*: The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial compared intensive versus standard glycemic control. They used SF-36 to evaluate HRQOL and found that intensive glycemic control did not lead to QOL benefits (no change) [67]. The Veterans Affairs Diabetes Trial (VADT) used an adapted version of the diabetes-specific QOL questionnaire used in the DCCT to evaluate QOL. We found negative QOL scores in the intensive treatment [68], which were elicited by using the proper patient-related outcome measure. Previous reports have suggested that adding diabetes-specific questions to generic instruments (such as SF-36 or other generic PROM) would enhance our understanding of diabetes interventions on health status and HRQOL [69, 70].

Thus, the degree of control and the intensity of the antihyperglycemic interventions need to be considered when assessing the impact of exercise interventions in the QOL of patients with diabetes.

(C) *Specific subpopulations*: Require special attention. In particular, those with diabetic peripheral neuropathy (DPN), where the presence of pain will be an additional factor that will negatively impact QOL. A small, randomized study addressed the role of moderate exercise training versus standard care in DPN [71]. The researchers used the neuropathy QOL (a 35-item questionnaire neuropathy-specific QOL tool) and found greater benefits in the intervention group, both physiological and psychological, independent of changes in anthropometric measures.

Limitations from Exercise Interventions

A number of potential pitfalls are found in this type of research, from adherence to the interventions, fidelity, and reproducibility. On the other hand, such studies usually benefit from enrolling a cohort of motivated subjects, who are obviously interested in their health, and will probably engage in follow-up. People with diabetes in the "real world" may suffer from lack of motivation, and if the intervention is interrupted, people may resume prior poor habits such as poor nutrition, regain weight, and lose the benefits that were gained from the initial bout of exercise. Furthermore, patients often report increasing appetite when exercising. Thus, a proper nutritional intervention must be paired to the exercise interventions. In addition, if the individual does not follow safety precautions and performs activities for which the body is not ready yet, there is risk of injury or just fatigue, leading to interruption of the intervention and possible weight gain. Hence, the risk for injury and further lost time and motivation are a constant risk, which can only be addressed by pertinent and timely, and likely repetitive, instructions that include the explanation and consideration for such potential scenario. Probably, for most exercise interventions, positive reinforcement and continuous monitoring are required to secure successful results, but this may increase the costs from the interventions. Technological progress offer a variety of tools that can deliver automated reminders, education, and counseling to patients which may increase cost effectiveness.

Future Directions

Assessing effectiveness of exercise interventions needs to be effectively incorporated into the usual care in people with diabetes. It is critical to account for depression and other factors that may hinder response to the intervention. These considerations need not delay the intervention, but concomitant intervention should be encouraged, explaining patients that exercise will provide benefits, as will the treatment of underlying mental problems. Given the known benefits from exercise, it might not be ethical to randomize patients to not receive this intervention. However, we still do not know what should be the duration, intensity, modality, and frequency. This needs to be acknowledged by providers which will encourage

them to gradually add exercise, in 10 min doses, and work with people on their individual goals. We do know it works, while it is implemented. Sustainability can only be expected when we help the individual come up with a plan that respects their individual needs (this is challenging for the provider and the individual with diabetes). Lifelong exercise is the real target, but while some commit to it, others do not. Thus, the true gap in knowledge is to properly understand how to implement lifelong interventions that will also be cost-effective.

Studies ought to incorporate markers such as mobility, physical activity, and costs of the interventions and compare between different approaches, ideally selected by the patient. Thus, study designs may require the use of a quasi-experimental design, where participants are allowed to choose the intervention. We still need to identify the best approaches to engage people to be adherent and consistent in exercise interventions, for long term.

Furthermore, we need a practical way to assess the exercise prescription for people with diabetes. Provided there are no absolute contraindications, all people with diabetes should exercise. In reality, the current data most strongly support a supervised exercise intervention, but there is only as much space to deliver supervised interventions to the nearly 30 million US adults with diabetes and 100 million with prediabetes.

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16 Guidelines for Medical Evaluation and Exercise Testing in Persons with Diabetes Starting an Exercise Program

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Exercise testing and training are vital components in the evaluation and medical treatment of patients with diabetes mellitus (DM). Nevertheless, there are associated risks of exercise training, specific exercise precautions, and contemporary guidelines for the medical evaluation and exercise testing of diabetics prior to initiating a moderate-to-vigorous intensity exercise program. This chapter addresses these issues, with specific reference to the medical evaluation and assessment and role of exercise testing in screening patients with known or suspected DM and potential underlying cardiovascular disease (CVD).

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Medical Evaluation of the Patient with Type 2 DM

DM has two major forms, types 1 and 2, with two very different etiologies and clinical courses. Type 1 DM accounts for 5–10% of individuals with DM and stems from an autoimmune destruction of the beta cells of the pancreas, resulting in its inability to secrete insulin. These individuals are totally dependent on supplemental insulin for survival. In contrast, type 2 diabetes accounts for 90–95% of DM. Accordingly, the following text pertains to the evaluation of the patient with type 2 DM initiating an exercise program.

Lifestyle therapy is recommended as first-line treatment for patients with type 2 DM [1]. Key components of lifestyle therapy include structured exercise, increased daily physical activity, or both, along with nutrition therapy, particularly weight loss if needed, adequate sleep, and avoidance of cigarette smoking and secondhand smoke. Both aerobic physical activity and strength training favorably modify insulin resistance, which is a major underlying pathophysiologic feature of type 2 DM. Exercise in patients with type 2 DM improves glycemic control, lipid levels, and blood pressure. Additionally, it may decrease the risk of falls, increase functional capacity, and improve quality of life. However, there are specific risks associated with exercise in patients with type 2 DM. Careful clinical evaluation is recommended to potentially mitigate the

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associated risks and tailor the exercise prescription accordingly [2].

Components of the initial clinical evaluation of DM include historical information such as the known duration of DM, current pharmacologic treatment (oral agents, subcutaneous insulin and/or insulin pump, and subcutaneous incretin mimetic agents), and glycemic and blood pressure control. Additionally, individuals should be assessed for common diabetic sequelae, which include both macrovascular and microvascular complications. Macrovascular complications include CVD, cerebrovascular disease, and peripheral arterial disease. Microvascular complications, which can be reduced or attenuated by optimizing glucose and blood pressure control, include diabetic nephropathy, retinopathy, and neuropathy. For macrovascular complications, CVD risk factor management including blood pressure and lipid control appears to play larger roles than glycemic control in decreasing risk and slowing disease progression [3].

Relative to the macrovascular complications of CVD, patients with DM are considered to have comparable risk for acute cardiac events as those with known coronary artery disease (CAD). However, preliminary exercise stress testing is not routinely recommended for previously sedentary type 2 DM individuals starting a low-intensity physical activity regimen, such as walking. Baseline exercise stress testing may be indicated if initially contemplating more vigorous exercise (which is *not* recommended) or if an individual has signs or symptoms suggestive of myocardial ischemia, such as exertional angina pectoris and/or ischemic ST-segment depression. Peripheral arterial disease (PAD) of the lower extremities, another macrovascular complication of DM, may be associated with intermittent claudication, which involves cramping of the legs during exercise that resolves with rest though many patients do not experience claudication but will have reduced exercise capacity. Although physical activity for this patient subset may be associated with leg pain and reduced exercise capacity, regular exercise can, over time, lead to a decrease in symptoms and improvements in function associated with PAD. A third macrovascular complication, cerebrovascular disease, can cause ischemic stroke(s) with resultant neurological deficits, such as hemiplegia or imbalance. Tailored exercise prescriptions that accommodate neurologic deficits and reduce the likelihood of falls are advised.

Diabetic nephropathy is a common microvascular complication of DM, occurring in approximately 20–40% of patients, and is the leading cause of end-stage renal disease [4]. The urine albumin to creatinine ratio, and serum creatinine with corresponding estimated glomerular filtration rate (eGFR), should be noted in the medical record. In general, if the spot urine albumin to creatinine ratio is >30 mg/g, the patient has albuminuria and diabetic nephropathy is likely present. Two of three urine specimens collected within a 3- to 6-month period should be abnormally elevated before considering a patient to have nephropathy. The eGFR defines the stage of chronic kidney diseases. An eGFR <60 ml/min/1.73 m^2 signifies stage 3 chronic kidney disease, which is considered moderate impairment of kidney filtration function, whereas an eGFR <15 indicates stage 5 chronic kidney disease, which corresponds to severe impairment requiring dialysis. A patient with diabetic nephropathy is more likely to die of CVD than progress to end-stage renal disease requiring dialysis. Over a 5-year period, 50% of patients with diabetic nephropathy will experience an acute cardiac event, which may include myocardial infarction and/or sudden cardiac death [5].

Another important microvascular end-organ complication is diabetic retinopathy, which is a leading cause of new cases of blindness among adults 20–74 years [4]. The prevalence of retinopathy is strongly correlated with the duration of diabetes. Individuals with type 2 DM should have a comprehensive exam by an ophthalmologist shortly after the diagnosis of DM and on an annual basis thereafter. The third type of diabetic microvascular complication, neuropathy, has two major forms: diabetic peripheral neuropathy and cardiovascular autonomic neuropathy. Peripheral neuropathy may initially present as pain, burning, tingling, and numbness, most commonly affecting the feet. Over time, this can progress to

greatly reduced sensation to pain, including no pain sensation with blisters, cuts, or burns on the feet. There is high risk of imperceptible injuries to the feet and lower extremities that can evolve rapidly to non-healing ulcers and secondary infections due to lack of pain sensation and compromised micro- and macrovascular circulation associated with DM. All type 2 DM patients should be screened for diabetic peripheral neuropathy at initial diagnosis and at least annually thereafter, using simple clinical tests, such as assessment of pinprick sensation or light touch perception via a 10-g monofilament. In contrast, signs and symptoms of cardiac autonomic neuropathy include orthostasis and resting tachycardia (>100 beats per minute). Orthostasis is heralded by a fall in systolic blood pressure >20 mmHg or diastolic blood pressure >10 mmHg upon standing without an appropriate compensatory increase in heart rate. This may be associated with lightheadedness and/or unsteadiness with standing from a sitting or lying position, which increases the risk of falls. Autonomic neuropathy is usually a complication of more advanced DM. Similar to nephropathy, autonomic neuropathy is an independent risk factor for cardiovascular mortality [6].

One of the most important aspects of the physical exam in a patient with DM is accurate, standardized assessment of the resting blood pressure in the brachial artery, obtaining the measurement after 5 min of rest, with feet flat on the floor, using the appropriate size cuff for the upper arm circumference, and support of the arm at heart level. Hypertension is a major determinant of end-organ complications. When blood pressure consistently exceeds >140/90 mmHg, hypertension is present [7]. Blood pressure goals should be individualized, but a target of <130/80 mmHg is appropriate for most patients with DM [1]. More aggressive goals, such as <120/80 mmHg, may be sought but should be carefully considered along with a heightened risk of hypotensive events from medications. More intensive medical therapy to a goal of <120/80 mmHg has been shown to significantly reduce stroke and albuminuria (nephropathy), but these reductions were associated with a greater number of serious complications. A careful general physical examination of the extremities should be made for evidence of decreased sensation, assessment of foot pulses, and examination of feet and lower extremities for blisters, cuts, skin breakdown, or discoloration. Reduced macro- and microvascular flow to the skin, as well as peripheral neuropathy, increases of the risk of minor cuts and abrasions developing into penetrating diabetic ulcers, which can lead to deep tissue infections including osteomyelitis (infection of the bone). Proper socks and athletic shoes should be recommended for a patient about to embark on an exercise program to reduce the likelihood of diabetic foot lesions [2].

A focused evaluation for the manifestations of underlying CVD and cerebrovascular diseases should be obtained. Any self-reported history of angina pectoris, myocardial infarction, stroke, or heart failure should be corroborated by medical records and additional diagnostic testing, if indicated. Anginal symptoms should be quantified according to the Canadian Cardiovascular Society (Classes 1–4) [8]. An electrocardiogram (ECG) is essential on the initial visit with attention to the presence of Q waves, left ventricular hypertrophy, and abnormalities of the conduction system. The physical examination should attempt to identify normal versus impaired systolic function. A normally placed point of maximal impulse, normal S1 and S2, and an unremarkable ECG in the same patient strongly suggest the left ventricular ejection fraction is preserved. Other findings, including soft heart tones, an S3, jugular venous distention, lower extremity edema, and ECG evidence of Q waves or bundle branch block, make it more likely that the ejection fraction is reduced. Echocardiographic studies may also reveal impaired left ventricular diastolic function, which is common in diabetes, and often precedes systolic dysfunction. Neurological examination should be used to assess focal deficits, such as weakness, decreased sensation, ataxia, and/or imbalance.

The physical examination should also attempt to identify the presence of PAD. A history of leg

claudication, or carotid or peripheral revascularization, suggests PAD. The presence of bruits in the neck, the abdomen, or over the femoral arteries may represent other signs of PAD. In addition, if the posterior tibial artery pulse is reduced, PAD at some level in the lower extremity circulation is likely present. The dorsalis pedis pulse is less reliable in its anatomic position in the dorsum of the foot; thus, its absence on examination is not especially helpful. The ankle/brachial systolic pressure index (or ABI) is another assessment for PAD. It is derived by measuring the brachial artery cuff systolic blood pressure and dividing it by the systolic pressure measured in the posterior tibial artery using a cuff and a continuous wave Doppler probe. Of note, the ABI should be measured in each leg by dividing the ankle blood pressure from each leg by the highest blood pressure from either arm. Because of peripheral amplification of the arterial pulse wave, the ABI should normally be ≥1.00. If this value is <0.90, PAD is present and a comprehensive lower extremity vascular exam may be considered, using a dedicated vascular laboratory with ultrasound and plethysmography. Discovering and documenting PAD, with or without intermittent claudication, is important since it is a common limiting factor in aerobic exercise and can be a treatment target. Moreover, as noted above, regular exercise therapy to the point of tolerable pain improves PAD symptoms and quality of life for the afflicted patient [9].

The laboratory evaluation for the diabetic patient should include a biochemistry profile with serum creatinine, glycosylated hemoglobin (hemoglobin A1c), urine albumin to creatinine ratio, and fasting lipid profile. The goal for hemoglobin A1c, which reflects the prior 90 days of glycemic control, should consider age, comorbidities, and hypoglycemia risk. For most patients, a hemoglobin A1c goal of ≤6.5% is recommended [1]. However, a goal of >6.5%, and up to 8%, is advised if the lower target cannot be achieved without adverse outcomes, such as episodes of significant hypoglycemia. As discussed above, the treatment goal for the urine albumin to creatinine ratio is <30 mg/g. This is usually accomplished with strict blood pressure control, including drugs that block the renin-angiotensin system. For patients with type 2 DM and ≥1 major CVD risk factor, or established CVD, the low-density-lipoprotein cholesterol goal is <70 mg/dL, which usually requires statin therapy [10] and, in some cases, treatment with the newer PCSK9 inhibitors [11]. Other CVD risk factors include cigarette smoking, obesity, hypertension, high-density-lipoprotein cholesterol <40 mg/dL, family history of coronary heart disease, and age ≥45 years for men or ≥50 years for women. For diabetic patients without major CVD risk factors and/or age <40 years, the low-density-lipoprotein target is <100 mg/dL.

In summary, the clinical evaluation of the patient with DM that is performed by primary care and specialty physicians is critically important in the ongoing medical management of this "high-risk" patient subset. Careful and thorough examination of the diabetic patient prior to exercise, with further evaluation and treatment of uncontrolled conditions if indicated, may decrease the risk of exercise-related complications. A careful history, physical exam, medical record review, ECG, laboratory evaluation, and exercise stress testing, if indicated, are important components of this evaluation. Assessment for medical conditions that may increase risk with certain types or intensities of exercise, or predispose patients to injury, should be performed. These conditions include uncontrolled hypertension, severe autonomic neuropathy, severe peripheral neuropathy, blisters, cuts or foot ulcers, unstable proliferative retinopathy, and angina or other signs and symptoms of myocardial ischemia, including threatening ventricular arrhythmias. Other considerations include the patient's age and current physical activity level. At-risk patients should be encouraged to start with short duration, low-to-moderate intensity exercise (i.e., level walking at a 1–2 mph pace) and gradually increase duration and/or intensity as tolerated over time, provided they remain asymptomatic [12].

Conducting and Interpreting the Exercise Stress Test

Exercise testing permits evaluation of the following variables: cardiorespiratory fitness or aerobic capacity (the estimated or actual peak or maximal oxygen consumption [VO_2 max]), hemodynamic responses including the heart rate and systolic/diastolic blood pressure responses during and after exercise, adverse clinical signs or symptoms (e.g., exertional angina and/or dyspnea), and associated changes in electrical functions of the heart, especially supraventricular and ventricular arrhythmias and ST-segment displacement. This section addresses the physiological basis and rationale for exercise testing in assessing asymptomatic and symptomatic patients with DM and known or suspected CAD, with specific reference to indications and contraindications, end points, test modalities/protocols, and test interpretation, including ECG, symptomatic and hemodynamic responses, exercise capacity, and treadmill scores.

Rationale for Stress Testing in Patients with DM: Contemporary Guidelines

CVD is the leading cause of morbidity and mortality in patients with DM [13]; an estimated 80% die from CVD, and 75% of these fatalities are attributed to CAD [14]. The Framingham Study [15] demonstrated that diabetics had a two- to fivefold risk of developing the manifestations of CAD (e.g., angina pectoris, acute myocardial infarction, congestive heart failure). When individuals <45 years of age are examined, the risk of CVD escalates to >11-fold that of the general population [16]. Although early detection of occult CAD in diabetics is important, the role of routine exercise testing in this patient population is controversial, since outcome data from randomized controlled trials are lacking [17].

In 1998, consensus guidelines issued by the American Diabetes Association (ADA) indicated that screening by stress testing was appropriate in diabetics with ≥2 additional risk factors [14]. Subsequently, the ADA expanded this recommendation by suggesting that an exercise stress test should be conducted in virtually all diabetic individuals who were beginning a moderate or vigorous exercise program [18]. However, the earlier recommendation has been challenged in other studies [19, 20] that have identified ischemic ST-segment depression and/or angiographically documented CAD in asymptomatic patients with type 2 diabetes, independent of the risk factor profile.

The American College of Cardiology/American Heart Association Guidelines on Exercise Testing [8] and the American College of Sports Medicine (ACSM) [21] have addressed the role of exercise testing before exercise training for patients with DM. The former group classified routine exercise testing in asymptomatic persons with DM who plan to start vigorous exercise (≥60% VO_2 reserve) as a class IIa recommendation (i.e., weight of evidence/opinion is in favor of usefulness/efficacy). Similarly, the ACSM recommended exercise testing for diabetics who plan to start a moderate (40–59% VO_2 reserve) to vigorous exercise program. In contrast, the US Preventive Services Task Force [22, 23] concluded that insufficient evidence exists to determine the benefits and limitations of exercise stress testing before exercise programs or, for that matter, in the routine screening of asymptomatic individuals at low CAD risk (<10% risk of a cardiac event over 10 years). In 2004, the latter recommendation was echoed by the ADA [24].

A major limitation of exercise testing is that a truly positive exercise test requires a hemodynamically significant coronary lesion (e.g., >75% stenosis; Fig. 16.1), whereas nearly 90% of acute myocardial infarctions occur at the site of previously nonobstructive atherosclerotic plaques [25]. These findings, coupled with the extremely low rate of cardiovascular complications in asymptomatic persons who exercise [26], suggest that it is impractical and cost prohibitive to use exercise testing to forestall serious cardiovascular events in all asymptomatic exercisers [27]. Recently, the ACSM published updated, research-based recommendations for

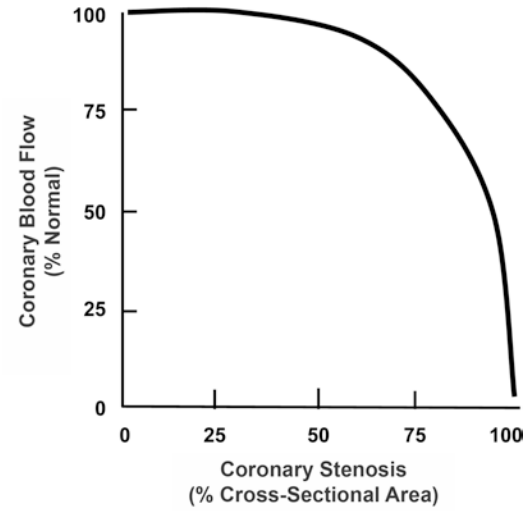

Fig. 16.1 Relation between coronary blood flow and coronary artery stenosis shows how perfusion is not significantly reduced until the obstruction exceeds 75% of the vessel's cross-sectional area

exercise preparticipation screening [12]. The need for "medical clearance," which replaced specific recommendations for a physical examination and/or exercise testing, focused on three major variables: the individual's current level of physical activity; known cardiovascular, metabolic (e.g., DM), or renal disease or signs/symptoms suggestive of disease; and the desired or anticipated exercise intensity. The potential hazards of unaccustomed, high-intensity physical activity, in persons with known or occult CAD, were also addressed.

Indications and Contraindications

Exercise testing is generally recommended for the following reasons: to aid in the diagnosis of occult or suspected CAD, especially in symptomatic individuals; to evaluate cardiorespiratory fitness; to assess the efficacy of interventions such as pacemaker implantation, coronary revascularization, anti-ischemic medications, or physical training; to establish the safety of vigorous physical exertion; to formulate a safe and effective exercise prescription; and to assess work-related capabilities after an acute coronary event or intervention.

Common absolute contraindications to peak or symptom-limited exercise testing include a recent significant change in the resting ECG suggesting cardiac ischemia (e.g., ST-T wave abnormalities), recent myocardial infarction (within 2 days), unstable angina, uncontrolled symptomatic heart failure and/or atrial or ventricular arrhythmias that may compromise cardiac function, severe aortic stenosis, acute infection, third-degree heart block (without pacemaker), and active myocarditis or pericarditis [28]. Patients with relative contraindications such as electrolyte abnormalities (e.g., hypokalemia, hypomagnesemia), severe arterial hypertension (i.e., resting systolic and/or diastolic blood pressure >200 mmHg or >110 mmHg, respectively), hypertrophic cardiomyopathy and other forms of outflow obstruction, ventricular aneurysm, or uncontrolled metabolic disease (e.g., DM) may be tested after careful medical evaluation of the risk/benefit ratio [28]. Oftentimes, individuals with relative contraindications can be exercised with caution using modified protocols and/or low-level end points, especially if they are asymptomatic at rest.

Test Modalities/Protocols

Both treadmill exercise and cycle ergometry have advantages and disadvantages in evaluating patients with and without documented CAD. Table 16.1 shows the approximate energy expenditure in mL/kg/min during progressive leg cycle ergometry, expressed as kilogram meters per minute (kg/m/min), which at a given power output or work rate is inversely related to body weight [21]. Treadmill testing provides a more common form of physiologic stress (i.e., walking) in which subjects are more likely to attain a slightly higher VO_2 max and peak heart rate. The test should generally last 8–12 min for patients limited by fatigue. Figure 16.2 shows three commonly used multistage treadmill exercise protocols. The conventional Bruce treadmill protocol offers a rapid and safe exercise progression for which aerobic capacity can be estimated from the treadmill time in men, women, and patients with

Table 16.1 Approximate energy expenditure (mL/kg/min)[a] during leg cycle ergometry

Body weight		Power output or work rate (kg/m/min)[b]						
kg	lbs	300	450	600	750	900	1050	1200
50	110	17.9	23.1	28.7	34.0	39.6	44.8	50.1
60	132	16.1	20.7	24.9	29.4	34.0	38.5	43.1
70	154	14.7	18.6	22.4	26.3	30.1	34.0	37.8
80	176	13.7	17.2	20.7	23.8	27.3	30.8	34.0
90	198	13.0	16.1	18.9	22.1	24.9	28.0	31.2
100	220	12.3	15.1	17.9	20.7	23.1	25.9	28.7

[a]Estimated values are based on completion of each 3-min stage. To convert to METs, divide the estimated value (mL/kg/min) by 3.5

[b]The work rate or power output is expressed as kilogram meters per minute (kg/m/min) and is determined by the designated internal resistance (kg), pedal speed (in revolutions per minute), and the distance in meters (m) the flywheel travels for one pedal revolution. This distance is 6 m for Monarch leg ergometers and 3 m for Tunturi and BodyGuard ergometers

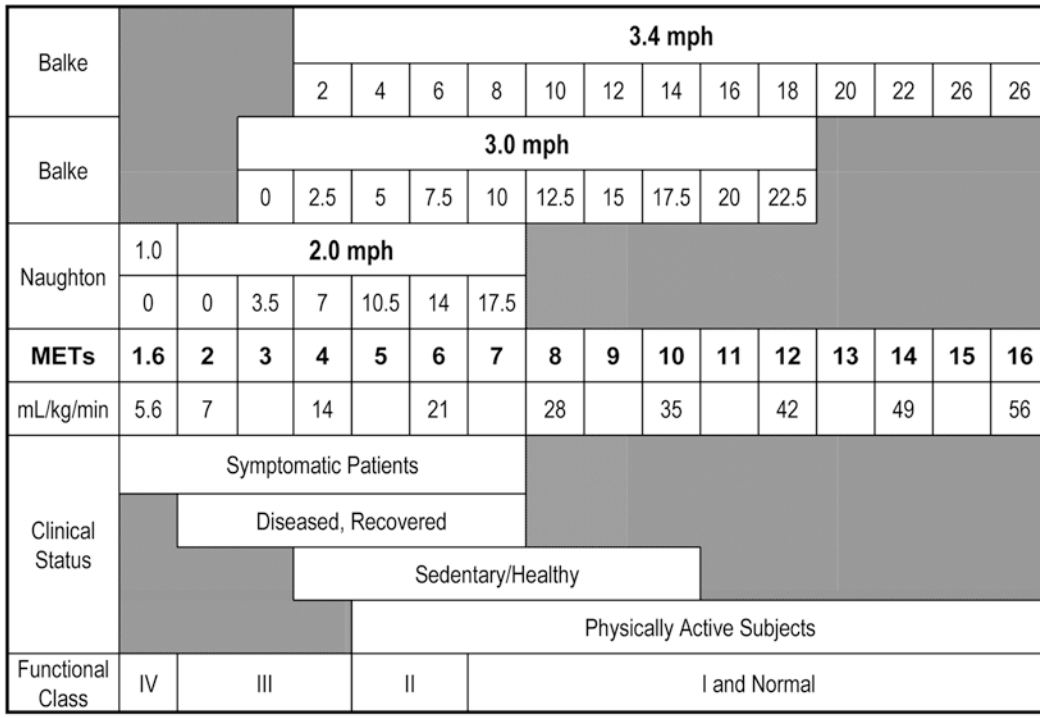

Fig. 16.2 Metabolic cost of three common treadmill protocols. One MET signifies resting energy expenditure, equivalent to approximately 3.5 mL/kg/min. Unlabeled numbers refer to the treadmill grade, expressed as percent. The patient's clinical status and functional class (I–IV) for the peak-attained workload are also shown

CAD (Table 16.2) [29]. Alternatively, ramp protocols provide a nearly continuous and uniform increase in aerobic requirements [30].

End Points for Testing

Commonly used criteria for discontinuing an exercise test are listed in Table 16.3 [28].

Responses to Exercise Testing and Their Diagnostic/Prognostic Significance

Risk stratification or prognostic evaluation is a critical strategy in contemporary medical practice on which many patient management decisions are based (e.g., prescription of cardioprotective medications, need for coronary revascularization and/or, an implantable cardioverter defibrillator). Data derived from a resting ECG (e.g., bundle branch block) [31] and from exercise testing are most helpful in this regard, especially when considered in the context of other clinical information. Informative diagnostic/prognostic variables that can be derived from the exercise test include chronotropic incompetence [32, 33], heart rate recovery [34–36], dyspnea [37], systolic hypotension [38], diastolic hypertension [39], exercise-induced premature contractions [40, 41], ST-segment displacement [42], angina symptoms [28, 43], as well as cardiorespiratory fitness or functional capacity, expressed as mL/kg/min or

Table 16.2 The conventional Bruce treadmill protocol with MET values for each minute interval completed

				MET requirement[a]		
Stage	MPH	Grade	Min	Men	Women	Cardiac
I	1.7	10%	1	3.2	3.1	3.6
			2	4.0	3.9	4.3
			3	4.9	4.7	4.9
II	2.5	12%	4	5.7	5.4	5.6
			5	6.6	6.2	6.2
			6	7.4	7.0	7.0
III	3.4	14%	7	8.3	8.0	7.6
			8	9.1	8.6	8.3
			9	10.0	9.4	9.0
IV	4.2	16%	10	10.7	10.1	9.7
			11	11.6	10.9	10.4
			12	12.5	11.7	11.0
V	5.0	18%	13	13.3	12.5	11.7
			14	14.1	13.5	12.3
			15	15.0	14.1	13.0

Modified from Lea and Febiger [29], with permission from ACSM and Wolters Kluwer

[a]MET values are for each minute *completed*. Note that women and cardiac patients achieve *lower* VO_2 for equivalent workload. Holding onto front rail will *increase* the apparent MET capacity

Table 16.3 Common end points for terminating exercise testing[a]

Absolute indications
• Exertional hypotension (drop in systolic blood pressure ≥10 mmHg from baseline blood pressure despite an increase in workload, when accompanied by signs and/or symptoms of myocardial ischemia)
• Moderate-to-severe angina pectoris (≥2/4 chest pain)
• Signs of poor perfusion or central nervous system dysfunction (ataxia, cyanosis or pallor, staggering, failure to respond to questions)
• Onset of ventricular tachycardia (≥3 consecutive premature ventricular contractions [PVCs])
• ST-segment elevation (≥1.0 mm) in ECG leads without diagnostic Q waves (other than V_1 or aVR)
• Technical difficulties monitoring the ECG or systolic blood pressure (i.e., equipment malfunction)
• Subject's desire to stop
Relative indications
• Excessive horizontal or downsloping ST-segment depression (≥2 mm)
• Selected supraventricular or ventricular arrhythmias (e.g., increasing multifocal PVCs and/or ventricular couplets, supraventricular tachycardia, bradyarrhythmias)
• Development of bundle branch block or intraventricular conduction delay that cannot be distinguished from ventricular tachycardia
• Exertional hypotension in the absence of other evidence of myocardial ischemia
• Hypertensive blood pressure response (systolic and/or diastolic pressure >250 mmHg or 115 mmHg, respectively)
• Marked fatigue, shortness of breath, or limiting claudication

Ratings of perceived exertion ≥17 (very hard) on the Borg category scale, signifying near-maximal to maximal exertion or a peak heart rate ~100% of the predicted maximal heart rate

[a]Adapted from JACC 1997;30(1):260–315, with permission of Elsevier

METs. In fact, by incorporating several of these measurements and/or related clinical data into a mathematical formula or Duke treadmill score [44–46], conventional exercise testing can often outperform the newer, more costly, noninvasive studies. Other reports have highlighted the diagnostic value of stress echocardiography and stress myocardial perfusion imaging with or without gated single-photon emission computed tomography in the diabetic population [17, 47–50].

Exercise Capacity and Related Responses

Large cohort and clinical studies have identified a low level of aerobic fitness as an independent risk factor for all-cause and cardiovascular mortality [51, 52], as well as varied comorbid conditions, including diabetes. Previously, researchers at the Cooper Institute/Clinic studied >8600 nondiabetic men who were followed for approximately 6 years [53]. After adjusting for confounding variables, men in the low-fitness group (the least 20% of the cohort) at baseline had a 1.9- and 3.7-fold risk of developing impaired fasting glucose and diabetes, respectively, as compared with those in the high-fitness group (the most fit 40% of the cohort). A more recent report by several of these investigators found that diabetic men in the lowest, second, and third quartiles of cardiorespiratory fitness had 4.5-, 2.8-, and 1.6-fold greater risk for overall mortality than men in the highest quartile of cardiorespiratory fitness, even after adjusting for age, risk factors, and other potential confounders [54].

Numerous studies in men and women with and without CAD now suggest that each 1-MET increase in exercise capacity appears to convey an ~15% reduction in mortality risk [55, 56]. The Aerobic Center Longitudinal Study represents a unique database regarding fitness and mortality. Tables 16.4 and 16.5 illustrate low-, moderate-, and high-fitness levels (in METs), expressed as a function of age and gender. The low-fitness groups are at increased mortality risk, whereas the high-fitness groups generally have an excellent prognosis, regardless of existing comorbidities or underlying CAD. These data should be helpful in counseling patients regarding their current exercise capacity and long-term fitness goals. For example, a 55-year-old man who achieves 7 min on the conventional Bruce treadmill protocol, corresponding to an estimated aerobic capacity of 8.3 METs (Table 16.2), would be classified in the low-fitness category (Table 16.4), which is associated with an increased mortality rate. An initial goal would be to increase his fitness to the moderate category (8.9–10.9 METs) and higher (>10.9 METs), if possible, in the future. Conversely, a 65-year-old woman who achieves 6 min on the conventional Bruce treadmill protocol would have an estimated aerobic capacity of 7.0 METs (Table 16.2), corresponding to the moderate or average fitness category (Table 16.5). A goal for her would be to achieve high fitness or >7.5 METs.

A summary of recent studies examining the relation of exercise test responses to mortality and incident coronary events in patients with diabetes is provided in Table 16.6 [57–61]. In general, cardiorespiratory fitness, expressed as peak

Table 16.4 Fitness and mortality in men, ACLS, fitness categories

Fitness			Age groups (years)	
Group	20–39	40–49	50–59	60+
Low	≤10.5	≤9.9	≤8.8	≤7.5
Moderate	10.6–12.7	10.0–12.1	8.9–10.9	7.6–9.7
High	>12.7	>12.1	>10.9	>9.7

Courtesy of the Cooper Institute for Aerobics Research, Dallas, Texas, with permission
Table values are maximal estimated METs attained during treadmill exercise testing

Table 16.5 Fitness and mortality in women, ACLS, fitness categories

Fitness			Age groups (years)	
Group	20–39	40–49	50–59	60+
Low	≤8.1	≤7.5	≤6.5	≤5.7
Moderate	8.2–10.5	7.6–9.5	6.6–8.3	5.7–7.5
High	>10.5	>9.5	>8.3	>7.5

Courtesy of the Cooper Institute for Aerobics Research, Dallas, Texas; with permission
Table values are maximal estimated METs attained during treadmill exercise testing

Table 16.6 Relation of exercise test responses to mortality or incident coronary events in diabetic patients

First author (reference #)	Population	Age (years)	Follow-up (years)	Exercise test variable	Mortality or CV events
Pierre-Louis [57]	490 nondiabetics, 404 diabetics	67 ± 10	4.4	Exercise capacity (peak METs)	↓ EC was an independent and significant risk factor for MACE among nondiabetics (HR, 3.3; $p < 0.0001$) and diabetics (HR, 2.7; $p < 0.0001$)
Nylen [58]	2,867 men with type 2 diabetes mellitus	50–87	7.8 ± 5.1	Exercise capacity (peak METs)	For each 1-MET increase in EC, the mortality risk was 23% lower in those aged 55–65 and 16% lower for those >65 years
Padala [59]	14,849 consecutive pts (3,654 diabetics and 11,195 nondiabetics)	62 ± 14	2.4 ± 1.6 (maximum of 6 years)	Exercise capacity (peak METs)	Diabetic pts who achieve ≥5 METs during stress SPECT MPI have significantly reduced risk for cardiac events. Diabetics who achieve ≥10 METs have a very low (0.9%) annualized event rate
Sudó [60]	21,396 pts (65% men), including 1,200 pts with diabetes (5.4%)	51 ± 11	11.9 ± 4.9	Heart rate responses to exercise testing	Pts with diabetes have a lower CRI and HRR than pts without diabetes, which are independently predictive of reduced long-term survival in the former
Cortigiani [61]	14,140 pts (2,835 diabetics and 11,305 nondiabetics)	66 ± 9 (diabetics) 63 ± 11 (nondiabetics)	2.5	Stress echocardiography	Ischemia at stress echocardiography is a strong and independent predictor of total mortality in diabetic (HR, 1.71; 95% CI, 1.34–2.18) as well as nondiabetic pts (HR 1.54; 95% CI, 1.32–1.80)

METs metabolic equivalents (1 MET = 3.5 mL O_2/kg/min), ↓ decreased, *EC* exercise capacity, *MACE* major adverse cardiovascular events, *HR* hazard ratio, *CI* confidence interval, *SPECT* single-photon emission computed tomography, *MPI* myocardial perfusion imaging, *CRI* chronotropic index, *HRR* heart rate recovery, *pts* patients

METs, was inversely related to mortality. Moreover, autonomic dysfunction, as reflected by chronotropic impairment and/or abnormal heart recovery, was associated with reduced long-term survival. In addition, ischemia at stress echocardiography provided a strong and independent predictor of total mortality in diabetic patients.

Role of Coronary Computed Tomography Angiography in Pre-exercise Evaluation of Patients with Diabetes

Whether there is a role for coronary computed tomography angiography (CTA) in the assessment of diabetic patients prior to starting an exercise program is not currently well established. Coronary CTA allows noninvasive visualization of the coronary lumen, wall, and degree of stenosis and can detect both calcified and non-calcified plaque. Of note, coronary artery calcium scanning, which is a separate noninvasive CAD screening test, only detects calcified plaque. Risks associated with coronary CTA include the requirement of an IV contrast agent, which can adversely impact renal function, and increase radiation exposure [62].

As stated earlier, routine use of cardiac stress testing in asymptomatic diabetic patients prior to starting a low-intensity exercise regimen is not advised, and this likely holds true for routine use of coronary CTA as well. However, coronary CTA may be useful to evaluate high-risk or symptomatic diabetic patients prior to exercise or may be considered prior to starting a high-intensity exercise program. However, risks of this test must be weighed against potential benefits. Identification of significant vascular lesions on coronary CTA may lead to intensification of medical therapy or coronary revascularization prior to starting an exercise program.

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Part IV

Special Considerations for Exercise in People with Diabetes

Conditions That May Interfere with Exercise

17

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Each year, 1.4 million Americans are diagnosed with diabetes. In 2012, 9.3% of the population, 29.1 million Americans, had this condition [1]. Diabetes is a chronic, often debilitating and disabling illness due to the complications that accompany the disease. These complications, including coronary artery disease, peripheral neuropathy, nephropathy, and retinopathy, can largely be prevented through proper medical therapy and lifestyle measures, such as eating a healthy diet, maintaining a normal weight, and participating in regular exercise. However, only a minority of people with diabetes achieves adequate glycemic control (A1C <7.0%), and even fewer also reach established targets for blood pressure and lipids [2]. Consequently, long-term complications of diabetes are still prevalent and may even be present at the time of diagnosis in people with type 2 diabetes. Careful evaluation of patients for complications that may present incremental risks or interfere with the capacity for exercise is an important first step in planning an appropriate exercise program.

Role of Exercise in Diabetes Management

Exercise often has many positive effects on diabetes management. These include improved glycemic control, assistance with weight maintenance, increase cardiorespiratory fitness, and general sense of well-being. In type 1 diabetes, the primary exercise-related goal is to make it possible for patients to participate in recreational exercise and sports and to capture the general health benefits afforded by exercise. In type 2 diabetes, a regular program of physical exercise should be an integral part of the treatment program. The American Diabetes Association recommends adults with diabetes perform 150 min per week of moderate-intensity aerobic physical activity (50–70% of maximum heart rate), spread over at least 3 days per week with no more than 2 consecutive days without exercise [3]. In the absence of contraindications, adults with type 2 diabetes should be encouraged to perform resistance training at least twice per week.

Certainly, imparting the above recommendations to patients is quite facile. “Advised exercise regimen? Check.” But diabetes complications

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plague many patients with diabetes before they undertake an exercise program and may affect their ability to safely exercise. What advice is appropriate for the 25-year-old woman with type 1 diabetes and diabetic retinopathy who wants to start horseback riding? Or the 50-year-old man with peripheral neuropathy who wants to start exercising on a treadmill? This chapter outlines an approach to exercise in patients with pre-existing complications of diabetes—neuropathy, nephropathy, and retinopathy. Patients with established coronary artery disease often require the monitored environment of cardiac rehabilitation, which is reviewed in the following chapter.

Glucose Control and Exercise

All people with diabetes, particularly those with type 1 diabetes or people with type 2 diabetes who require insulin therapy, may have problems with glucose control with exercise (see Table 17.1). There may be a decreased need for insulin during exercise, as well as increased risk of hypoglycemia. High-intensity, short-term exercise may also cause an acute rise in blood glucose in people, even with well-controlled diabetes [4]. Clearly glucose regulation, particularly in type 1 diabetes, is critical. Problems include hypoglycemia during and following exercise, as well as hyperglycemia and ketosis as a response to strenuous exercise. The details of glucose management and alterations in insulin and glucose physiology with exercise are covered elsewhere.

Table 17.1 Limiting factors and risks of exercise for patients with diabetic complications [9]

Precipitating or exacerbating cardiovascular disease:
– Angina pectoris
– Myocardial infarction
– Arrhythmia
– Sudden cardiac death
Proliferative retinopathy
– Vitreous hemorrhage
– Retinal detachment
– Retinal hemorrhage
Nephropathy
– Increased proteinuria
Peripheral neuropathy
– Soft-tissue and joint injury
Autonomic neuropathy
– Blunted cardiovascular response to exercise
– Decreased maximal aerobic capacity
– Impaired response to dehydration
– Postural hypotension

Cardiovascular Disease

Exercise has beneficial effects in patients with coronary artery disease. Exercise training as part of a cardiac rehabilitation program after myocardial infarction, for example, has been shown to decrease mortality [5]. Exercise also improves insulin sensitivity, lipid metabolism, and blood flow and increases energy expenditure, all of which may have a positive impact on the development of cardiovascular disease. As remarked elsewhere, however, patients with diabetes have high prevalence of cardiovascular disease—both overt and undiagnosed. Hypercholesterolemia, hypertension, and associated cardiac disease frequently accompany diabetes. Some consider the diagnosis of diabetes akin to a coronary heart disease equivalent [6]. For example, a population-based nationwide study found that diabetes is associated with a significant increase in the risk of ischemic stroke and systemic thromboembolism [7]. Complications of diabetes confer additional risks to patients. Autonomic neuropathy, for example, is associated with "silent" ischemia as well as increased risk of sudden death. In general, people with diabetes have a lower survival rate after myocardial infarction and a poorer prognosis after diagnosis of coronary artery disease [8]. Therefore appropriate screening is necessary before initiating an exercise program. Procedures and limits related to testing are covered in Chap. 10.

Retinopathy

The confluence of diabetes and retinopathy poses an additional layer of concern for risks of exercise to the patient. As covered in other chapters,

exercise may help to delay or prevent complications in diabetes. The concern is that exercise may also exacerbate several diabetes-related complications. One of the most potentially serious among those is proliferative retinopathy, which predisposes to vitreous hemorrhage and traction retinal detachment. Exercises that increase blood pressure, particularly high-intensity resistance exercise that involves Valsalva maneuvers, as well as jarring head motions, can precipitate these devastating complications. Patients with proliferative retinopathy have significant restrictions on the type and intensity of activity that they can safely engage in due to this risk of severe ocular damage.

The underlying mechanisms hypothesized to incite these devastating events include increasing systolic blood pressure causing vessel rupture and retinal hemorrhage, trauma causing retinal detachment, or hemorrhage. It was found that patients with diabetic retinopathy had a higher resting heart rate, while those without diabetic retinopathy showed a higher heart rate increase during exercise [9]. It was also observed that there were differences in the increase of heart rate during exercise and in the recovery phase after exercise [9]. Such increases in systolic BP could precipitate retinal or vitreous hemorrhage. Activities that include rapid head motion may also precipitate retinal detachment or vitreous hemorrhage, which helps to explain why moderate weight training may be a safer activity than most high-intensity aerobic exercise [10]. There is no such concern in nonproliferative retinal disease or macular edema.

Systolic blood pressure increases linearly with work, reaching peak values between 200 and 240 mmHg in normotensive persons in intense exercise, while diastolic pressure remains near-resting levels [9]. This phenomenon is present both in resistance and aerobic exercise [11]. In a study of healthy older men, blood pressure and heart rate were measured during a variety of activities. Peak systolic blood pressure occurred with aerobic exercise and the military press (271 and 261 mmHg respectively) [12]. Interestingly, in another study, exaggerated blood pressure increase with exercise (>60 mmHg) was associated with future development of hypertension—1,036 out of 7,082 (14.6%) subjects developed hypertension during a follow-up of 5±3 years [13]. Vigorous aerobic or resistance activity may be contraindicated in patients with proliferative retinopathy due to risk of inciting retinal detachment or retinal or vitreous hemorrhage due to blood pressure increases [14]. Healthcare providers should be mindful and use clinical judgment in deciding whether to recommend pre-exercise testing for patients who want to perform low-intensity activities like walking [15].

The general recommendation to patients with proliferative diabetic retinopathy is thus to avoid any activity that is jarring, is traumatic, or involves excessive strain. The latter includes maximal isometric contractions and Valsalva maneuvers such as weight training. Practical general advice to the patient with proliferative retinopathy may include avoidance of bending at the waist, lifting (particularly overhead), and near-maximal isometric contraction. This advice may be particularly useful for the patient who exercises in classes at gyms or with a personal trainer and may or may not plan their own routines. Low-impact exercises, such as stationary biking (not maximal efforts as in spinning), walking, and swimming, are recommended (see Table 17.2 for more detail).

Despite these recommendations—or perhaps because of them—most retinal and vitreous hemorrhages do not occur with activity. In one retrospective report of diabetic patients with episodes of vitreous hemorrhage, the most common antecedent activity was sleep (36%) followed closely by sitting or lying (26%) [16]. Only one of six hemorrhages was associated with strenuous activity in this report. Finally, physical activity does not appear to be associated with progression or development of proliferative retinopathy. In a population-based cross-sectional study, it was observed that higher levels of physical activity were associated with a lower prevalence of retinal microvascular abnormalities [17].

In the early stages of retinopathy, however, exercise may be beneficial. Because exercise can lower blood pressure and increase HDL, both of which are associated with retinopathy, it may

Table 17.2 Examples of recommended and contraindicated exercises in proliferative diabetic retinopathy

Exercise	Recommendation	Exercise	Recommendation
Walking	Recommended	Yoga	Use extreme caution; avoid bending as in downward facing dog and shoulder stands
Running	Not recommended due to jarring	Pilates	Avoid due to Valsalva with abdominal exercise
Aerobics	Not recommended due to jarring	Dance	Use caution with rapid spinning, bending
Rowing machine	Recommended at low intensity	Cycling/spinning	Avoid highest intensity Valsalva in spinning, avoid trauma in mountain biking
Soccer	Not recommended due to heading, contact	Tennis	Avoid *only if* significant Valsalva and active proliferative retinopathy and vitreous hemorrhage
Basketball	Use caution, avoid contact	Swimming	Use caution with kick turns
Weightlifting	Not recommended due to Valsalva; 5–10 lb free weights okay	Downhill skiing	Avoid jumps and falls
Horseback riding	Avoid due to risk of trauma	Snowboarding	Not recommended
Contact sports	Avoid due to rapid eye-head movement	Alpine skiing	Use caution

reduce risk of developing proliferative diabetic retinopathy and diabetic macular edema. When exercise plan is recommended, regular ophthalmology follow-up for patients with or without diabetic retinopathy is essential. With proliferative diabetic retinopathy, follow-up should be every 1–2 months and, without evidence of eye complications, a minimum of annually [13].

Nephropathy

There are no explicit limitations to exercise in patients with diabetic nephropathy. The pathophysiology underlying development of microalbuminuria has not been determined but is generally considered to be associated with endothelial dysfunction and changes in renal blood flow. Increased blood pressure is related to albuminuria progression, and therefore hemodynamic factors play a role. Numerous studies have noted that in patients with diabetes-related nephropathy, exercise can acutely increase urinary protein excretion. For example, one study examined children and adolescents with and without type 1 diabetes. While baseline albumin excretion rates were similar between groups, albumin excretion rates after exercise were significantly higher in the subjects with type 1 diabetes [18].

In another study of children and adolescents with type 1 diabetes, post-exercise albuminuria was not correlated with the development of microalbuminuria at 6-year follow-up [19]. In contrast, a study of adults with type 1 diabetes who were initially normoalbuminuric for 10 years found that the post-exercise urine albumin-to-creatinine ratio at baseline was predictive of rest microalbuminuria in 80% of affected subjects at 10-year follow-up [20]. Another study examined post-exercise albuminuria in children with differing durations of diabetes. While children who had diabetes for less than 5 years did not have significant albuminuria with exercise, those with the disease for longer than 5 years did have significant albuminuria with exercise, and 43% had accompanying IgG and transferrin, indicating glomerular damage [21]. In a similar study, where participants exercised at a fixed workload, exercise-induced increase in systolic blood pressure was exaggerated in subjects with

diabetes-related microalbuminuria as compared to patients with uncomplicated diabetes and control subjects [22].

ACE inhibitors may decrease the amount of exercise-induced albumin excretion in type 1 diabetes [23, 24], perhaps through reduction in renal intracapillary pressure by inhibiting angiotensin-induced vasoconstriction on the efferent glomerular artery [21]. ACE inhibitors are currently standard of care for rest microalbuminuria.

Efforts to link exercise-induced proteinuria to a precursor stage of microalbuminuria have been inconclusive [21]. One study of fixed workload demonstrated that exercise-induced albuminuria was not a useful predictor of microalbuminuria at 6 years of follow-up [19]. Alternatively, another fixed-workload study found that exercise-induced albuminuria improved with lowering hemoglobin A1C and that a "window" exists during which an elevated exercise-related albumin excretion may be reversed by improved glucose control [25]. Regardless of whether post-exercise microalbuminuria is a harbinger of overt nephropathy, there is no evidence that exercise accelerates the course of diabetic nephropathy.

In chronic kidney disease, the rationale for including exercise as a part of therapy is so that patients can maintain their well-being and functional capacity. Healthcare providers should direct their attention in creating treatment plans that focus on preserving patients' strength and increase aerobic fitness so as to avoid loss of muscle mass that could further complicate clinical syndromes and interfere with quality of life [26]. There are few rigorous trials looking at the effect of exercise in chronic kidney disease. One small study of ten elderly patients showed that inactive patients on hemodialysis can be considered to have low exercise tolerance. In order to combat this, it is imperative that they reduce their time being inactive and instead should receive comprehensive care that addresses psychosocial aspects so they can improve their attitudes toward exercise [27]. Resistance exercise has evidently been associated with increased muscle mass, strength, and appetite and a reduction in muscle weakness and frailty in the elderly. This type of training can be seen as a way to combat some of the challenges associated with a low-protein diet plan that is common for renal disease [28].

There is no evidence that exercise improves or decreases glomerular filtration rate over time, but limited randomized-controlled trials have been performed [29]. There is, however, evidence that the presence of diabetic nephropathy is associated with diminished exercise capacity (peak VO2 max) [30]. Anemia contributes to this relationship. In addition, exercise capacity may be used as a predictor of risk for cardiovascular events, and the presence of nephropathy may also be associated with increased risk of cardiovascular disease. The risk factors for nephropathy are similar to those for coronary artery disease, so appropriate pre-exercise screening should be performed as covered in Chap. X.

In summary, as there is no evidence that exercise accelerates the course of diabetic nephropathy, there are no recommended limits on participation in exercise in those patients. However fatigue and anemia that often accompany chronic kidney disease may hamper patients' desire and ability to exercise.

Neuropathy

Peripheral neuropathy, along with peripheral arterial disease, is a main underlying cause of foot pathology in patients with diabetes. Neuropathy can predispose to muscular atrophy resulting in clawing of the toes, and collagen glycation can lead to limited joint mobility, changing foot pressures and leading to ulceration [31]. Peripheral neuropathy results in decreased pain sensation in extremities, which can lead to injury unawareness and, ultimately, Charcot joint morphology [32].

Because peripheral neuropathy results in impaired proprioception, patient with neuropathy needs to rely on vision. Mirrors can help patients orient without having to look at their feet. Equilibrium training and use of external supports may also be helpful. Range-of-motion exercises are also important for preventing and minimizing contractures [30].

Some clinicians recommend complete avoidance of weight-bearing exercise for those patients, although education and proper footwear may help to prevent these complications. Certainly, limiting weight-bearing exercise and focusing instead on bicycling, swimming, and arm exercises are prudent. Daily inspection of the feet and limiting wearing shoes to 5-h at a time are essential for patients with peripheral neuropathy and/or Charcot feet. Corrective footwear can also redistribute pressures to limit pressure on deformities.

Autonomic neuropathy presents both metabolic and hormonal derangements, both of which alter normal response to exercise. The adrenergic response of norepinephrine, epinephrine, growth hormone, cortisol, and pancreatic polypeptide is impaired in autonomic neuropathy [33], although plasma metabolite concentration does not differ between diabetes patients with and without neuropathy [34]. Hypoglycemia is more common during exercise in patients with autonomic neuropathy as the blunted adrenergic response to hypoglycemia limits counter-regulatory activity on the liver. Neuropathic patients may also be more apt to be unaware of this hypoglycemia due to blunted autonomic activity. Diminished catecholamine-derived symptoms (including classic symptoms of tremor, sweating, and anxiety) may then result in progression to neuroglycopenia without antecedent warning [9]. Gastroparesis—concomitant with autonomic neuropathy—may also result in variable delivery of calories, contributing to both hyper- and hypoglycemia.

Autonomic neuropathy may also increase risk of injury due to decreased cardiac response to exercise, postural hypotension, impaired thermoregulation, impaired thirst sensation, and gastroparesis [35]. Most inhibiting to exercise is perhaps the impairments of heart rate and blood pressure adaptations to exercise. In terms of heart rate, autonomic neuropathy is associated with changes in resting work and impaired work capacity during exercise [36]. Patients with autonomic neuropathy often have an increased resting heart rate, likely secondary to a cardiac vagal defect. The increase in heart rate during exercise at low intensity is in part mediated by reduction in vagal tone, and increased heart rate in more intense exercise is related to sympathetic outflow. Patients with autonomic neuropathy do not exhibit the same increases in heart rate that unaffected people do, as autonomic neuropathy impairs both vagal tone and sympathetic outflow. In addition, maximal aerobic capacity is impaired in autonomic neuropathy, which may be related to the above detailed blunting of heart rate increase and cardiac output. For example, one study of young patients with type 1 diabetes found that exercise capacity of active subjects with both peripheral and autonomic neuropathy was reduced compared to active controls and diabetic patients without neuropathy [37]. Exercise capacity of physically active patients with diabetic neuropathy was similar to that of sedentary individuals without diabetes and patients with diabetes without neuropathy [38]. Impaired lung function as well as reduction in oxidative capacity of muscle fibers may also contribute [30].

Patients with autonomic neuropathy also have lower resting blood pressure and blunted blood pressure response to exercise compared to individuals without diabetes and patients with diabetes without neuropathy [39–41]. The autonomic nervous system normally regulates increases in blood pressure with exercise. In autonomic neuropathy, blood pressure falls with exercise, due to decreased stimulations of the heart and vasculature from epinephrine and norepinephrine. Impaired exercise-induced increase in norepinephrine is associated with a fall in systemic vascular resistance [42], which reduces systemic blood pressure.

Because patients with autonomic neuropathy may not experience the same responses to vigorous exercise—such as increased heart rate and blood pressure—alternative measures of exertion need to be employed. A commonly used scale is the Borg Scale of Perceived Exertion. Sitting or recumbent exercise is beneficial for maintaining blood pressure during exercise; water therapy may also help in maintaining blood pressure during exercise [30]. Autonomic neuropathy is also strongly associated with CVD, and affected patients should undergo a cardiac work-up before initiating exercise.

Summary

- Diabetes is an increasingly prevalent and debilitating disease. Exercise is an important part of general health for patients with type 1 diabetes and essential to care for patients with type 2 diabetes.
- Complications of diabetes—particularly coronary artery disease, retinopathy, nephropathy, and both peripheral and autonomic neuropathy—increase risks associated with exercise and can limit types of exercise.
- Exercise can precipitate cardiac ischemia in patients with coronary artery disease, both known and unknown. Pre-exercise evaluation, including a graded exercise stress test, is advised.
- Patients with proliferative retinopathy need guidelines for activity; jarring and strenuous activities can predispose to traction retinal detachment and vitreous hemorrhage and should be avoided.
- After an acute retinal detachment or hemorrhage, exercise is limited, and patient must be cleared to exercise by an ophthalmologist.
- Exercise may cause exercise-related microalbuminuria due to increase in systolic blood pressure, but there is no evidence that exercise leads to progression of renal disease.
- Peripheral neuropathy can predispose to ulcers and Charcot foot morphology with exercise due to lack of sensation. Non-weight-bearing exercise is recommended for those patients.
- Autonomic neuropathy impairs cardiac reactivity to exercise and can lead to orthostasis. Gastroparesis and impaired sweating can further interfere with ability to exercise. Relative perceived level of exertion may be needed as a proxy for heart rate with exercise. Pre-exercise cardiac evaluation is essential (Fig. 1).

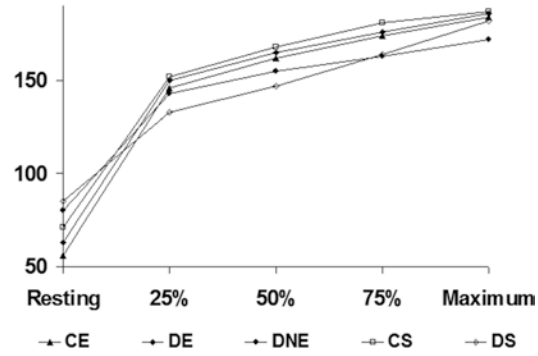

Fig. 1 The mean heart rate in healthy, nondiabetic subjects who exercised regularly (*CE*), diabetic patients regular exercisers (*DE*), diabetic neuropathic regular exercisers (*DNE*), healthy nondiabetic subjects who did not exercise regularly (*CS*), and diabetic patients who did not exercise regularly (*DS*). All exercisers exercised regularly primarily in the form of endurance training (running) more than three times per week and at least 45 min per session. At resting conditions, heart rate was lowest in CE and highest in DS ($p < 0.0001$). No difference existed at the 25% and 50% of the total exercise time, but at the 75% and maximal effort points, the heart rate was lower in DNE compared to all other groups ($p < 0.05$) [37]

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18 Diabetes Mellitus and Exercise Physiology in the Presence of Diabetic Comorbidities

Irene E. Schauer, Amy G. Huebschmann, and Judith G. Regensteiner

Introduction

People with type 2 diabetes mellitus (T2DM), even when uncomplicated, have been shown to have decreased exercise capacity as compared with age- and weight-matched nondiabetic subjects as detailed in Chap. 1 of this book. Since the prevalence of comorbidities is relatively high in the diabetic population (Table 18.1), the impact of comorbidities on exercise performance is of major concern. Since exercise has a central therapeutic role in diabetes, it is important to recognize how differences in exercise physiology in the presence of diabetic comorbidities may impact upon exercise recommendations to this population. This chapter will describe the exercise abnormalities correlated with the common diabetic comorbidities of hypertension, arterial stiffness, congestive heart failure (CHF, including systolic and diastolic dysfunction), as well as macrovascular and microvascular disease. Certainly, many people with diabetes with complications will have more than one of these entities simultaneously, but the changes in exercise physiology attendant to these comorbidities will be addressed individually where possible. This chapter will also discuss the available data on the particular benefits of exercise training with each comorbidity when those data are available. The focus will be on exercise pathophysiology in subjects with T2DM with type 1 diabetes mellitus (T1DM) included as well, although the data in T1DM are more limited.

As context for this chapter's discussion of diabetic comorbidities impact upon exercise impairment, it is useful to quickly review the exercise abnormalities in uncomplicated diabetes. Subjects with T1DM have been shown in two small studies to have no exercise impairment (as assessed by maximal exercise capacity) in comparison with similarly active nondiabetic controls matched for age, sex, and body weight [1, 2]. However, more recently, Nadeau et al. did find impaired functional exercise capacity in T1DM compared to similarly matched controls [3].

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Table 18.1 Prevalence of selected comorbidities in people with type 2 diabetes mellitus (T2DM)

Comorbidity	HTN (%)	CHF (%)	CAD (%)	PAD (%)	Nephropathy (%)	Retinopathy (%)
T2DM	39–71[1,2,3]	11.8[4]	27–55[5]	1.2–12.5[6]	7–30[7]	3–27[8]

References = [[1], [239] = Albright et al. 1995], [[2], [14] = Geiss et al. 2002], [[3], [12] = HDS I 1993], [[4], [100] = Nichols et al. 2001], [[5], [240] = Anand et al.], [[6], [133] = Adler et al. 2002], [[7], [167] = Adler et al. 2003], [[8], [168] = Brown et al. 2003]
KEY: *HTN* hypertension, *CHF* congestive heart failure, *CAD* coronary artery disease, *PAD* peripheral arterial disease

Exercise impairment has incontrovertibly been shown in subjects with uncomplicated T2DM and will be discussed briefly.

Despite a lack of apparent microvascular or macrovascular complications, subjects with T2DM have approximately 20% worse maximal exercise capacity as compared with control subjects [4–8]. This impairment appears to be caused by slowed oxygen delivery to working muscles of both "central" (cardiac) and "peripheral" (exercising muscle) origins. The peripheral causes of decreased exercise capacity may include endothelial dysfunction (precluding appropriate vasodilation to increase perfusion of exercising muscle), impaired microvascular distribution of flow, decreased oxygen diffusion, and/or decreased oxygen extraction [9]. The central causes may include endothelial dysfunction (precluding appropriate vasodilation of coronary arteries in response to increased myocardial workload [9], decreased cardiac output during exercise [9], and exercise-associated impaired left ventricular function [10, 11]). Exercise-associated impaired left ventricular function (also termed "diabetic cardiomyopathy") is not present in all subjects with T2DM but is relatively common and will be discussed separately in the "Congestive Heart Failure" section of this chapter.

Hypertension and Arterial Stiffness

Hypertension and arterial stiffness both reflect similar vascular pathophysiology relating to increased peripheral vascular resistance and/or cardiac output. Both may play important roles in altering usual exercise physiology. It is important to consider how these pathophysiologic factors may impact on exercise, since the prevalence of hypertension in subjects with T2DM ranges from 39% to 71% [12–14] and arterial stiffness has been shown to be 13% higher in subjects with T2DM than in those without [15]. This section will review how hypertension and arterial stiffness impair exercise performance in diabetes, the methods by which routine exercise training can remediate these deficits, and the attendant benefits to exercise in diabetics beyond improving exercise performance.

Effects of Hypertension on Exercise Performance in T2DM

The addition of hypertension to diabetes has been shown to decrease exercise capacity. One small Austrian study showed a significantly decreased maximal oxygen consumption (VO_2max) in eight subjects with T2DM and hypertension as compared with six normotensive T2DM subjects, eight nondiabetic hypertensive subjects, and eight age-, sex-, and BMI-matched controls ($p < 0.01$ vs. normotensive T2DM, nondiabetic hypertensives, and controls) [16]. Babalola et al. showed a tendency toward a lower exercise time in diabetic hypertensives (289 ± 110 s) as compared to diabetic subjects without hypertension (321 ± 119 s), hypertensives who did not have diabetes (309 ± 73 s), and healthy controls (490 ± 156 s) using a modified Bruce protocol treadmill test [17]. This study lacked sample size to differentiate between the diabetic normotensive and diabetic hypertensive groups. However, there was a statistically significant difference in exercise duration between the four groups ($p < 0.05$), and a rank-order trend suggested the worst exercise capacity (as measured by maximal exercise time) was in the diabetic hypertensive group.

Effects of Hypertension on Exaggerated Sympathetic Nervous System Response to Exercise in T2DM

The greater response of the sympathetic nervous system to exercise in people with diabetes and comorbid hypertension is of interest for three reasons. Firstly, it is known that the sympathetic nervous system is already more active in resting subjects with diabetes or hypertension than in nondiabetic or non-hypertensive subjects [18–21]. This raises the question as to how that elevated baseline activity will impact sympathetic activity with exercise. Secondly, it is known that exercise induces an increase in sympathetic nervous system activity and catecholamine release in all subjects but that during exercise there are feedback mechanisms which further mediate sympathoadrenal activity levels [22]. Since catecholamines induce lipolysis, the insulin resistance-induced impairment of lipolysis in adipocytes is one such diabetic maladaptation which may result in positive feedback to the sympathoadrenal axis during exercise [23]. The existence of greater sympathetic activation with exercise in subjects with both diabetes and hypertension encourages the investigation of other possible contributors to this positive feedback. Thirdly, it is of clinical interest to know that catecholamine levels become higher with exercise in diabetic hypertensive than in diabetic normotensive individuals due to a more robust sympathoadrenal response. Future research may explore to what degree the exaggerated sympathoadrenal response to exercise in diabetes is a beneficial compensatory adaptation or a maladaptive response due to abnormal metabolic and circulatory factors.

Sympathoadrenal overactivity has been demonstrated in subjects with T2DM and comorbid hypertension as expressed by the increased release of catecholamines with exercise. One study looked at differences in exercise-induced catecholamine response between four groups: T2DM with hypertension, T2DM without hypertension, hypertension without T2DM, and control subjects [16]. Each subject performed a stationary cycling exercise for 15 min with 5-min incremental workload steps of 25%, 50%, and 75% of individually measured VO_2max. Blood pressure and plasma catecholamine measurements were obtained 10 min prior to exercise and then at each 5-min workload and at timed intervals during recovery. This study showed greater exercise-induced unconjugated normetanephrine levels in the hypertensive T2DM subjects as compared with their age-, sex-, and BMI-matched controls (2156 ± 373 pg/ml/min vs. 1133 ± 180 pg/ml/min, $p = 0.04$) with no change in the normotensive T2DM or nondiabetic hypertensive subjects as compared with controls. At baseline, unconjugated metanephrines were lower in hypertensive T2DM and normotensive T2DM subjects ($p = 0.03$ and 0.04, respectively) than in their respective controls. Although there was a lower VO_2max in the T2DM hypertensives than in the other groups ($p < 0.01$ vs. normotensive T2DM, nondiabetic hypertensives, and controls), no tests of correlation were performed between the unconjugated metanephrine levels and exercise capacity. The authors of this study concluded that the excessive response of plasma unconjugated normetanephrines may serve as a marker of exaggerated sympathoadrenal function in hypertensive T2DM [16]. Previous studies have found that subjects with excessive sympathoadrenal activity had elevated noradrenaline levels during exercise testing but not at baseline [24, 25]. It is not yet certain if the elevated catecholamine response to exercise is due to sympathoadrenal overactivity or to a greater catecholamine response requirement to maintain cardiac output and glucose homeostasis with exercise. Again, this suggests further research is warranted into the mechanisms of exaggerated exercise-induced sympathetic outflow as well as whether this greater sympathetic activity is beneficial or only maladaptive.

Arterial Stiffness in the Presence of Hypertension and T2DM

Increased arterial stiffness (also termed "decreased elasticity" or "decreased vascular compliance") is a ubiquitous endpoint of many disease processes. Not only diabetes but also arterial hypertension, hyperlipidemia, congestive heart failure, and chronic uremia have all been

shown to lead to decreased elasticity in large arteries [26]. However, arterial stiffness may be particularly pronounced in T2DM. Given that arterial stiffness is a newer physiologic measure as yet without well-defined reference normal levels, the prevalence of arterial stiffness in T2DM is uncertain. However, one epidemiologic study showed a 13% increase in arterial stiffness (as measured by pulse pressure/stroke volume) in T2DM subjects as compared with controls [15]. In addition, measures of arterial stiffness have been shown to correlate with CVD risk and death, supporting arterial stiffness as a clinically important complication/comorbidity of diabetes [27].

Increased arterial stiffness results from three general types of changes to arterial structure and function [26]. Structural arterial changes include smooth muscle cell hypertrophy, increased collagen matrix deposits, and abnormal proteoglycan metabolism [26]. Functional abnormalities such as endothelial dysfunction, vascular insulin resistance, and abnormal vasa vasorum microcirculation also increase arterial wall stiffness [26, 28]. Finally, increased permeability of vessel walls leads to disruption of the interstitial matrix [26]. Thus, arterial stiffness results from a combination of structural and functional processes.

The degree of arterial stiffness observed is determined by the timing and magnitude of reflected waves from the peripheral vasculature as well as the cardiac output and central arterial vascular resistance [29, 30]. Noninvasive measurements of arterial stiffness include pulse pressure, pulse pressure/stroke volume, augmentation index (AI), pulse wave velocity (PWV), and ultrasound stiffness index β. For each of these metrics, higher measurements indicate greater stiffness. Like hypertension, increased arterial stiffness is related to increased vascular resistance but is felt to reflect central aortic blood pressure as opposed to the peripheral blood pressure measured with a sphygmomanometer [31]. Though a paucity of data exist to compare the utility of lowering arterial stiffness vs. treating blood pressure with regard to morbidity, the large ASCOT-CAFÉ randomized controlled trial illustrated that improved arterial stiffness between groups correlated with better cardiovascular outcomes (decreased cardiovascular events/procedures and/or decreased renal impairment) despite equivalent blood pressures between the amlodipine and atenolol-based regimens [32]. This illustrates that although arterial stiffness is related to hypertension, vascular compliance may have additional physiologic relevance beyond hypertension. The next section will review the implications of arterial stiffness upon exercise performance in subjects with T2DM.

Effects of Arterial Stiffness on Exercise Performance in T2DM

Arterial stiffness has been shown to be associated with low physical activity and reduced exercise capacity in adults with and without T2DM. In a study of 65 subjects with early uncomplicated T2DM and 65 controls, arterial stiffness, measured as carotid femoral PWV, correlated more tightly with low physical activity than with presence or absence of T2DM [33]. The negative correlation between several measures of arterial stiffness and exercise capacity has been reported in several studies (reviewed in [34]). The cause and effect relationship between exercise capacity/physical activity and arterial stiffness remains unclear, but some studies have found arterial stiffness-related defects that could worsen exercise capacity and tolerance. Increased arterial stiffness in diabetes is associated with abnormalities in the vascular circulation with exercise in subjects with T1DM and T2DM. Arterial stiffness (as measured by ultrasound with stiffness "β") independently predicted decreased peripheral circulation to the foot during exercise (as measured by the well-validated transcutaneous oxygen tension index (TcPO2 index, [35–37]) in Japanese subjects with T2DM and normal peripheral circulation (ABI >0.9) [38]. In another study, arterial stiffness (measured as radial artery AI) correlated with echocardiographic measures of diastolic dysfunction in 213 high-risk individuals without CVD [39]. Consistent with this was the increased risk of incident congestive heart failure in individuals with higher carotid femoral PWV in 2539 participants in the Framingham study [40]. Furthermore, subjects with T1DM maintained a higher peripheral vascular resistance during cycle ergometry as compared with control

subjects ($p < 0.01$) with an associated greater rise in diastolic blood pressure ($p < 0.01$, T1DM vs. controls) [41]. Other studies have also confirmed an exaggerated diastolic blood pressure rise with exercise in T1DM subjects vs. controls [42, 43]. In T1DM adolescents with increased arterial stiffness, elevated diastolic blood pressure with exercise and endothelial dysfunction (as measured by impaired forearm vasodilator response to brachial ischemia) were present and correlated with diabetes duration and glycemic control [42]. Overall, these studies support, but do not prove, the hypothesis that increased central arterial stiffness in T2DM, with resulting higher exercise afterload and a mechanistically related ventricular stiffness and diastolic dysfunction, leads to impaired cardiac output during exercise, thus directly contributing to reduced maximum exercise capacity in T2DM.

Benefits of Exercise Training in Persons with Diabetes Mellitus and Hypertension or Arterial Stiffness

Aerobic exercise has repeatedly been shown to lower blood pressure in nondiabetic hypertensive individuals by an average of 5–6 (systolic) and/or 4–5 (diastolic) mm Hg [44, 45]. Even lower-intensity exercise such as regular walking has been shown to lower blood pressure by 3 (systolic) and/or 2 (diastolic) mm Hg [46]. Less information is present on benefits in subjects with diabetes and comorbid hypertension (reviewed in [47]), but the available data will be reviewed briefly.

Several randomized control trials of exercise training in human subjects with both diabetes mellitus and hypertension have now been performed. Of note, some are confounded by concomitant weight loss. The trial with the highest percent of comorbid hypertension compared an "intensively treated" group with uncontrolled T2DM ($n = 36$, HbA1c >8%) vs. a comparable T2DM control group ($n = 36$) receiving "usual care" [48]. Over 85% of both study groups had comorbid hypertension with a similar degree of hypertensive control at baseline. The exercise intervention consisted of a recommended aerobic exercise bicycling regimen as well as resistance exercises with elastic exercise bands, three to five times per week for 45–55 min at 50–80% of maximal heart rate with adjustments over the course of the study to maintain this intensity level. Over 12 months in subjects with T2DM, weekly exercise levels increased 2.5-fold in the intervention group (from 7.5 to 19.7 METs) with no significant change in the control group. There was no increase in the use of antihypertensive agents from baseline in either the intervention or control groups, but there was a significant 12-month improvement in the intervention group's mean blood pressure from 144/85 to 130/76 ($p < 0.005$). Interestingly, although this intervention also included diet, the intervention group did not significantly lose weight. In addition, over the 6 months following this intervention, the exercise level worsened significantly in the intervention group (from 19.7 to 9.1 METs), and the accompanying increased systolic blood pressure and weight in that group correlated negatively to amount of time spent on exercise ($r = 0.43$ for systolic blood pressure, $r = 0.363$ for weight, both $p < 0.05$) confirming the relationship between increased exercise and improved blood pressure. The largest randomized controlled studies that looked at effect of lifestyle (diet plus exercise) interventions on blood pressure in T2DM were the Look AHEAD [49] and the Italian Diabetes and Exercise Study (IDES) [50]. In Look AHEAD 5145 individuals with T2DM (75% on antihypertensive medications) were randomized to an intensive lifestyle intervention (ILI) group versus a diabetes support and education (DSE) group. The ILI included calorie restriction and increased physical activity with a goal of 175 min per week of moderate-intensity physical activity. After 1 year of follow-up, blood pressure was significantly improved in the ILI compared to the DSE group (−6.8/−3.0 vs. −2.8/−1.8, $p < 0.001$). However, confounding this result is the fact that this group also lost 8.6% of their body weight compared to 0.7% in the DSE group. In contrast, the IDES emphasized exercise alone. Six hundred six subjects with T2DM and metabolic syndrome were randomized to twice-weekly supervised aerobic plus resistance training plus counseling ver-

sus counseling alone. At baseline, BP was ~140/85 in both groups, and >60% of the cohort was on antihypertensive medication. At 1 year, the exercise group had significantly greater improvement in BP than the control group (difference in delta BP −4.2/−1.7; $p = 0.002$ for SBP, 0.03 for DBP). BMI also decreased in the intervention group, but the decline, though significant, was small (2.9%). Three smaller RTCs similarly found improved BP in individuals with T2DM (68%, 50%, and 52% with apparent comorbid HTN, respectively) in the exercise group compared to a control group [51–53]. Weight decreased significantly in one [52] but not in the other two. In contrast, three other small RTCs did not find a benefit of an exercise intervention on blood pressure in T2DM individuals [54–56]. One study [56] compared calorie restriction with or without aerobic exercise in 29 individuals with T2DM and was likely simply underpowered in that a similar decrease in SBP was noted in the diet plus exercise group ($n = 13$) but did not reach statistical significance ($p = 0.09$). Another implemented a 2-year supervised endurance plus resistance training intervention in 50 men with T2DM and found no change in either weight or SBP [54]. Finally, Sigal et al. compared 22 weeks of aerobic, resistance, combined, and no-exercise control groups (~60 per group) and found no change in BP in any of the groups despite a significant weight loss in only the aerobic exercise group [55]. In summary, there is evidence that exercise can improve blood pressure in T2DM, but this conclusion is [1] not universally supported by the literature and [2] confounded by the concomitant weight loss in some of the studies.

The impact of training exercise on arterial stiffness has also been examined (reviewed in [57]). Several studies in adults without T2DM but with metabolic syndrome [58, 59] or end-stage renal disease [60] have demonstrated reduced arterial stiffness after an exercise intervention. In metabolic syndrome both aerobic [59] and resistance [58] training have been found to improve arterial stiffness. In a cohort of 23 human subjects with T2DM, 3 weeks of moderate exercise training for all subjects resulted in lessened arterial stiffness (as measured by ultrasound stiffness index β) at the carotid ($p = 0.020$) and femoral ($p < 0.001$) arteries [61]. In this study, improved insulin resistance resulting from exercise training correlated with decreased arterial stiffness at the carotid ($p = 0.040$) and femoral artery ($p = 0.016$). Another study randomized 35 women with T2DM to an aerobic exercise group (AEG) or a control group [62]. The AEG completed a 12 week intervention of accelerometer-confirmed 60 min of aerobic exercise three times a week. Arterial stiffness (AI) improved significantly in the AEG, and the percent change in AI correlated with the increase in physical activity energy expenditure, but interestingly not with insulin sensitivity. In contrast, despite increasing VO_2max, another small crossover human study did not show an improvement in arterial stiffness or blood pressure after 8 weeks of bicycle exercise training (thrice-weekly at 60% maximum heart rate) in five men and women with T2DM and isolated systolic hypertension [63].

In summary, hypertension and arterial stiffness are related abnormal pathophysiological processes which are prevalent in diabetes. Arterial stiffness is a much newer physiologic measurement than hypertension, and so the clinical consequences of its presence and treatment are generally less well known than that of hypertension. Comorbid hypertension has been shown to impair exercise capacity and increase catecholamine release with exercise in subjects with T2DM. Arterial stiffness has been correlated with impaired diastolic function and decreased peripheral muscle perfusion during exercise in T2DM persons with normal peripheral circulation as well as increased peripheral vascular resistance with exercise in T1DM. In the majority of studies done to date, both hypertension and arterial stiffness are at least partially remediable with exercise training. The benefits of lowering blood pressure and arterial stiffness in diabetic hypertensive subjects and lack of harmful side effects with appropriate prescreening of subjects are encouraging enough to recommend exercise routinely to patients with diabetes mellitus and comorbid hypertension.

Congestive Heart Failure (CHF)

It is well established that cardiac function is impaired even early in diabetes with a predominance of diastolic dysfunction that may play a role in exercise impairment in diabetes [64]. This section is divided into two parts focused on the roles in exercise impairment and response to exercise of diastolic and systolic dysfunction, respectively.

Effects of Impaired Diastolic Dysfunction on Exercise Performance in T2DM

In 1972, Rubler et al. described four diabetic subjects with congestive heart failure (CHF) despite normal coronary arteries and no convincing etiology for their cardiomyopathy [65]. Further recognition of "diabetic cardiomyopathy" followed, with prevalence rate estimates of diastolic dysfunction in diabetic subjects ranging from 30% in studies using conventional echocardiography [66–68] to 52–70% with more detailed Doppler echocardiograms using Valsalva maneuvers and pulmonary venous recordings [69, 70]. Since then many studies have confirmed this high prevalence of diastolic dysfunction even in early uncomplicated, asymptomatic well-controlled T2DM without hypertension or evidence of coronary artery disease [71–78]. Since its discovery four decades ago, greater understanding has developed as to the characteristics and causes of diabetic cardiomyopathy, though it is still incompletely understood. Current theory holds that diabetic cardiomyopathy is caused by multiple factors including hyperglycemia-induced myocardial fibrosis, metabolic disturbances related to insulin resistance, chronically increased oxidative stress, endothelial dysfunction, coronary microvascular dysfunction, cardiac autonomic dysfunction, advanced glycation end products, activated protein kinase C-β, microRNAs, mitochondrial dysfunction, and possibly more (reviewed in [77, 79–83]). Physiologically, diastolic dysfunction is a cardinal feature of the diabetic cardiomyopathy [84, 85].

Diastolic dysfunction is usually asymptomatic unless accompanied by other comorbidities [84]. In the presence of comorbid hypertension or myocardial ischemia, clinical features of CHF may develop from diastolic dysfunction despite the maintenance of a normal ejection fraction [85]. Several studies have shown that asymptomatic subjects with T2DM and diastolic dysfunction still remain at higher risk to develop CHF [84, 85] and also appear to have lower exercise capacity than diabetic subjects without diastolic dysfunction [73, 75, 76].

Considerable evidence links diastolic dysfunction to impaired exercise capacity in populations without diabetes (reviewed in [86, 87]). Four studies to date have correlated diastolic dysfunction with exercise impairment specifically in diabetes, while one did not. Poirier et al. showed worse maximal exercise treadmill performance in men with well-controlled uncomplicated T2DM and diastolic dysfunction ($n = 10$) as compared with age, weight, and clinically matched T2DM controls without diastolic dysfunction ($n = 9$) [10]. In this study, the diabetic subjects with resting diastolic dysfunction had a decreased duration of exercise time on a modified Bruce protocol (662 vs. 803 s, $p < 0.02$) and decreased metabolic equivalents ("METs") of 9.5 vs. 11.4 METs ($p < 0.02$). A correlation was also seen between the E_m/A_m ratio (echocardiographic marker of diastolic dysfunction as defined by the ratio of early to late mitral valve filling velocities) and exercise duration ($r = 0.64$, $p = 0.004$) and METs ($r = 0.66$, $p = 0.003$). In another study, a group of both T1DM and T2DM subjects (69.6% T2DM) performed symptom-limited Bruce protocol exercise tests. In this study exercise performance in METs was lower in the diabetic subjects with diastolic dysfunction vs. those without diastolic dysfunction (8.56 vs. 10.32 METs, $p < 0.05$) [76]. Irace et al. performed ergometer exercise stress tests in 38 subjects with T2DM and compared the presence of diastolic dysfunction in the subjects with a symptom-limited stress test (prior to reaching maximal predicted heart rate) vs. the subjects who completed ergometer tests to maximal predicted heart rate [73]. The 24 T2DM subjects with symptom-limited ergometer

exercise stress tests had a correlation between decreased diastolic function and exercise duration. However, no significant correlation between diastolic dysfunction and exercise duration was found in the 14 subjects with T2DM who were able to complete ergometer exercise stress tests to maximal predicted heart rate. In comparing subjects with T2DM and normal exercise capacity (n = 52) or abnormal exercise capacity (n = 118), Fang et al. showed that preserved diastolic function (as defined by maximal early mitral valve filling velocity = E_m) was correlated with better maximal exercise treadmill capacity (r = 0.43, $p < 0.001$) and remained an independent predictor of exercise capacity after multivariate analysis ($p < 0.05$) [88]. Finally and in contrast, Gurdal et al. studied 43 individuals with T2DM and 20 healthy controls. They found that the significantly reduced exercise capacity in T2DM was independent of diastolic function [89]. In summary, most studies do find a correlation between diastolic dysfunction and decreased exercise capacity in T2DM.

Though diastolic dysfunction is certainly a cardinal feature of "diabetic cardiomyopathy", some evidence is mounting that a subclinical depression of systolic function may also be present in some diabetic individuals. Despite maintaining categorically "normal" systolic function, subjects with T2DM have been shown to have significantly lower cardiac ejection fractions as compared to nondiabetic subjects. Sasso et al. found subjects with well-controlled, recent onset T2DM (3.9-year mean duration of diabetes) have lower ejection fractions both at rest (57% vs. 67%, $p < 0.001$) and during exercise (64% vs. 72%, $P < 0.001$) than age-, gender-, and body mass index-matched control subjects [90]. Among the T2DM subjects, greater insulin sensitivity was correlated with higher rest and exercise ejection fractions ($r = 0.59$, $p < 0.004$ for rest, $r = 0.58$, $p < 0.005$ for exercise). Conversely, a study by Willemson et al. in subjects with overt congestive heart failure with or without diabetes found that despite similar systolic function, the subjects with diabetes had worse exercise capacity. They proposed that the differential impairment in exercise capacity in diabetes was a result of diastolic dysfunction which in turn correlated with levels of advanced glycation end products [91].

Although exercise training is generally accepted to improve diastolic function in populations without T2DM (reviewed in [86]), the literature is more conflicted in diabetic cardiomyopathy (reviewed in [92]). Several studies have now examined the impact of exercise training in diabetes upon diastolic dysfunction with mixed results. In addition, comparison of these studies is difficult in light of the considerable methodological differences between them in exercise intervention, assessment of diastolic function, and statistical analysis.

Two small studies found completely negative results for exercise benefits on diastolic function. Sacre et al. studied a 6-month exercise intervention (combined aerobic and resistance training for ≥150 min moderate or ≥90 min vigorous intensity per week) versus standard care in 49 individuals with T2DM and diastolic dysfunction. They found improvement in exercise capacity but not in diastolic function [93]. Similarly, another randomized controlled trial of 42 men with T2DM in which the intervention group underwent supervised training four times a week for 12 months found no change in diastolic function (myocardial diastolic tissue velocity) despite improved BP, VO_2max, HbA1c, and strength [53]. Another very small study found no improvement at rest, but improved cardiac output response to exercise suggesting that exercise may improve diastolic function response to stress, but not resting diastolic function [94].

In apparent contrast, Brassard et al. demonstrated normalization of diastolic dysfunction (E/A ratio) in 5 of 11 subjects with well-controlled T2DM and varying degrees of diastolic dysfunction after a 3-month aerobic exercise intervention [95]. A control group did not improve. Of note, the five subjects in whom diastolic function normalized were five of the six subjects with the mildest impairment in diastolic function. The authors also do not present a comparison of pre- and post-intervention averages for the exercise group raising the question of whether this difference reached statistical significance. In the largest study, 223 patients with T2DM were randomized to a usual care group versus a 3-year intervention group that started with supervised exercise

and lifestyle and diet advice and then progressed to telephone-guided supervision [96]. Diastolic function was assessed at baseline and at 3 years, and diastolic dysfunction was defined based on E/Em ratio and/or deceleration time. In the intention to treat analysis, the between-group difference in prevalence of diastolic dysfunction at the 3 years did not achieve statistical significance (60% for usual care vs. 48% in the intervention group, $p = 0.10$). However, in a subgroup analysis of only those subjects who completed the full 3-year study, a significantly increased OR for diastolic dysfunction was found only in the usual care group (OR 2.46, $p = 0.034$). Interestingly diastolic function did not correlate with exercise capacity. Similarly the ABCD study randomized 100 patients with T2DM to a multi-intervention arm versus standard care and reported a neutral effect of the intervention on cardiac function, including diastolic function [97]. Again, though there was no statistically significant difference, the data showed a trend to increased E/A ratio at 2 years in the intervention group ($p = 0.082$). Finally, a recent study investigated high-intensity intermittent training (HIIT) in T2DM [98]. Twenty-eight subjects were randomized to 12 weeks of HIIT vs. standard care. This study found increased early diastolic filling (E) with stable late diastolic filling (A) suggesting improved E/A ratio though this data analysis is not provided. Another large RCT is currently underway in Australia that may shed more light on the controversial effect of exercise training on diabetic diastolic dysfunction [99]. However, results to date suggest that exercise may improve diastolic function in T2DM, particularly in those with mild impairment, and that this benefit may be dependent on duration and intensity of exercise.

Impairment of Exercise Performance in Diabetes Mellitus with Comorbid CHF Due to Systolic Cardiomyopathy

Congestive heart failure due to systolic cardiomyopathy has an estimated prevalence of 11.8% in T2DM [100]. Several studies have shown that diabetes in conjunction with systolic cardiomyopathy (T2DM-CHF) leads to worse exercise performance even when compared to subjects with CHF due to systolic cardiomyopathy alone. In 20 subjects with tightly controlled T2DM (HbA1c <7%) and moderate CHF symptoms, peak exercise performance yielded a VO_2max nearly 20% less than nondiabetic age- and gender-matched subjects with moderate CHF (LVEF <40%) [101]. Multivariate linear regression further determined that the strongest predictor of VO_2max in the DM-CHF subjects was alveolar-capillary membrane conductance (which determines the diffusing capacity of the lung (DLCO) along with pulmonary capillary blood volume). The authors suggested that the T2DM-CHF subjects may have a pulmonary angiopathy which allows leakage across the alveolar-capillary membrane as exercise raises the capillary pulmonary pressure. More on the pulmonary complications of diabetes is included in a later section of this chapter. Tibb et al. found a 30% reduction in VO_2max in 78 subjects with systolic cardiomyopathy (defined by LVEF <40%) and comorbid T2DM as compared with 78 similarly sedentary age- and gender-matched controls (Fig. 18.1) [102]. Ingle et al. showed that 6-min walking distances are impaired in subjects with T2DM-CHF as compared with age- and gender-matched nondiabetic CHF patients (238 vs. 296 m, $p = 0.005$) [103]. In both the Tibb and Ingle studies, there was a higher prevalence of cardiovascular disease (CVD) in the T2DM subjects, but the Ingle study performed a sub-analysis matching only subjects with CVD, and the walking distance remained statistically impaired (231 vs. 283 m, $p = 0.001$). Prevalence of angiotensin-converting enzyme inhibitor, angiotensin-II receptor blocker, and beta-blocker usage between groups was analyzed in all three studies, and no differences were observed. In summary, subjects with T2DM and CHF from systolic cardiomyopathy have a greater exercise impairment than nondiabetic subjects with systolic cardiomyopathy alone; however, the reasons for this difference are not fully understood.

Theoretically, insulin may improve exercise tolerance in DM-CHF subjects by increasing the ejection fraction. Insulin has been shown to have a direct inotropic effect on the myocardium in animals [104] and to increase resting left ventricular ejection fraction in nondiabetic human subjects (54% vs. 47%, $p < 0.01$) [105].

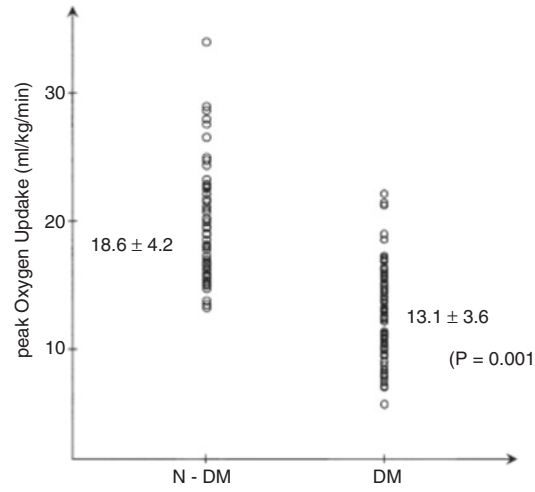

Fig. 18.1 Individual peak oxygen uptake (VO_2peak) in diabetic (DM) and nondiabetic (N-DM) patients with chronic heart failure due to left ventricular systolic dysfunction. Mean VO_2peak is significantly lower in DM than in N-DM patients (Reprinted from Tibb et al. [102], with permission from American College of Cardiology Foundation)

When an insulin-dextrose infusion was administered to T2DM and nondiabetic subjects (both groups with preserved systolic function), the left ventricular ejection fraction rose both at baseline and with exercise in T2DM [90]. In the nondiabetic subjects given insulin-dextrose, the LVEF rose with exercise but not at baseline. The exact physiologic mechanisms whereby insulin is able to increase LVEF without provoking hypoglycemia are still uncertain.

One study has shown that insulin administration may improve maximal exercise capacity in T2DM-CHF subjects by mechanisms other than increased LVEF. Guazzi postulated that insulin administration may improve exercise capacity in T2DM-CHF subjects in part by ameliorating pulmonary angiopathy and therefore looked at the impact of insulin therapy on VO_2max and alveolar-capillary membrane diffusing capacity (DL_{CO}) in T2DM-CHF subjects [106]. Using a parallel crossover design with subjects acting as their own controls, they found administration of insulin improved VO_2max by 13.5% ($p < 0.01$) and improved ventilatory efficiency (slope of ventilation/carbon dioxide production decreased by 18%, $p < 0.01$). Changes in both VO_2max and ventilatory efficiency after insulin administration correlated strongly with a better alveolar-capillary membrane diffusing capacity ($r = 0.67$, $p = 0.002$ for VO_2max and DL_{CO}, $r = -0.73$, $p < 0.001$ for ventilatory efficiency and DL_{CO}). These changes were present both 1 h and 6 h after a 60-min insulin infusion but had resolved within 24 h after the insulin. The changes from insulin were not due to glycemic changes (dextrose counter-infusions maintained glucose homeostasis) or from a change in ejection fraction in these subjects. In summary, insulin therapy has been shown to improve exercise capacity in subjects with T2DM and CHF from systolic cardiomyopathy, at least in part by improving pulmonary angiopathy and seemingly without any changes in glycemic control or ejection fraction. However, it is unlikely that insulin would be utilized clinically to increase exercise capacity alone, as the risk of hypoglycemia creates an unfavorable risk-benefit ratio.

Several of the studies discussed above regarding effects of exercise on diastolic dysfunction also addressed systolic function and found no benefit of exercise for systolic dysfunction [93, 94, 96, 97]. However, in the HIIT intervention study, both stroke volume and EF improved significantly, suggesting that high-intensity exercise may also have the potential to improve systolic function [98].

Macrovascular Disease

The incidence of CVD in subjects with diabetes mellitus (both type 1 and type 2) is two to three times increased over that of the general population [107, 108], and mortality following acute myocardial infarction (MI) in individuals with diabetes is double than that of nondiabetic controls similar in age [109, 110]. Importantly, it has been shown that post-MI subjects with greater peak VO_2max levels achieved through cardiac rehabilitation have lower cardiovascular mortality and morbidity [111, 112]. In addition, inadequate physical activity has been linked to increased mortality, largely through T2DM and CVD, in many epidemiological studies [113–116]. However, it has become clear that the development of macrovascular disease in T2DM is a nearly lifelong process, beginning well before the development of overt diabetes [117]. Furthermore, large-scale studies of interventions in diabetes have all been multitargeted, including combinations of diet, weight loss, glycemic control, and exercise. Thus, the exploration of specific effects of macrovascular disease on exercise performance and of exercise interventions on macrovascular disease has been challenging. This section will first present a selection of specific studies and otherwise summarize the current view of the interaction between exercise physiology and active macrovascular disease in the context of diabetes. More detailed information in this area is available in several recent systematic reviews [108, 117, 118]. The section will conclude with a discussion of two recent large RCTs of lifestyle intervention and their implications for the role of exercise in prevention of macrovascular disease. Current recommendations for exercise in macrovascular disease are summarized in Table 18.2.

Impairment of Exercise Performance and Response to Exercise in Diabetes Mellitus with Comorbid CVD

In general studies of exercise capacity post MI, with or without cardiac rehabilitation (CR), have continued the trend of lower exercise capacity in diabetes compared to the population without diabetes although the results are somewhat mixed. In post-MI populations without cardiac rehabilitation Izawa et al. found that the maximal exercise capacity was impaired in 30 post-MI T2DM subjects as opposed to 41 nondiabetic controls (22.6 mL/min/kg vs. 26.1 mL/min/kg, $p < 0.01$) despite similar resting ejection fractions between groups [119]. However, another study found no difference in exercise capacity without CR between 59 post-MI subjects with T2DM and 36 post-MI nondiabetic controls (20.2 mL/min/kg vs. 22.4 mL/min/kg, p = NS) [120]. Results in the first study implicated an impaired chronotropic response to exercise, possibly due to beta-adrenergic desensitization [121] which correlated with impaired VO_2max in post-MI subjects with diabetes as compared with the nondiabetic post-MI controls. This chronotropic response to exercise has also been shown by Colucci et al. to inversely correspond to impaired VO_2max in nondiabetic subjects with systolic cardiomyopathy [121]. Apart from lowering VO_2max, an inhibited chronotropic response has been shown elsewhere to predict cardiovascular events within a T2DM cohort [122]. In contrast, a study of 225 patients, most without diabetes, found the most significant predictor of impaired exercise capacity 1 month after MI was impaired diastolic function, suggesting that mediators of impaired exercise function after MI may differ between diabetic and nondiabetic populations [123].

Recent studies have also explored the ability of exercise to improve exercise capacity in CVD. Kim et al. found lower VO_2peak in 12 patients with T2DM than in 25 without both pre- and post-cardiac rehabilitation, with neither group showing a significant improvement with CR [124]. A cohort of 59 T2DM subjects and 36 well-matched (including for baseline exercise capacity) nondiabetic subjects were followed after a CR program performed for indications of acute MI or unstable angina in the month prior to enrollment [120]. Both groups compliantly participated in a 2-month CR program consisting of three 1-h moderate exercise training sessions per week. The T2DM group did show improvement with the CR program, including an increased VO_2max of 13% from study entry, but their improvement was drastically attenuated as compared with the nondiabetic subjects. Despite

Table 18.2 Considerations for activity limitation in diabetes with complications [47]

Nature of complication	Level of complication	Recommendations
CVD	Asymptomatic	Stress test not required
		Start with low intensity and low volume and increase slowly
	Angina/active ischemia	Initiate through cardiac rehab program only after cardiac evaluation
PAD	All levels	Physical activity as tolerated is the primary nonsurgical treatment for PAD
Peripheral neuropathy	No active lesions	Moderate weight-bearing allowed
		Recommend daily foot inspection
	With active lesions	Avoid weight-bearing activity
CAN		High risk for cardiac dysfunction/CVD
		If CAN suspected, recommendations are as above for CVD
DR	No DR, mild-moderate nonproliferative diabetic retinopathy (NPDR) Severe NPDR or Proliferative diabetic retinopathy	Activity dictated by other medical status Recommend low-impact, cardiovascular conditioning (swimming, walking, low-impact aerobics, stationary cycling, other low-intensity endurance exercises). Avoid activities that substantially increase systolic blood pressure or intraocular pressure or involve active jarring, including Valsalva maneuvers and related activities (e.g., trumpet playing), boxing, heavy competitive sports, significant weight lifting, and pounding or jarring activities such as jogging, high-impact aerobics, racquet sports
Nephropathy	Early (stage 1,2)	No limitations. Exercise may delay progression
	Overt to end stage	Because of high risk of CVD, recommend physician exam and approval with consideration of stress test if concern for active disease or CAN
		Once approved, start low volume and intensity and increase slowly

no difference between groups VO_2max at study entry, at completion of the study the nondiabetic subjects had a higher VO_2max (28.8 vs. 22.6, $P < 0.001$), peak workload (139 W vs. 120 W, $p = 0.009$), and longer duration of exercise (13.7 vs. 11.8 min, $p - 0.017$) than the subjects with T2DM. Linear regression was performed to determine predictors of change in VO_2max in the T2DM group and showed the change in VO_2max was independently associated with fasting blood glucose ($p = 0.001$) These results have been supported by two other larger studies. One study of 370 subjects with T2DM compared to 942 without who completed a 36 session CR. Both groups improved there exercise capacity, but the group with T2DM had lower exercise capacity at baseline and significantly less improvement with CR [125]. A study of >7000 T2DM and >1500 non DM subjects found lower adherence to CR in the T2DM group, as well as a smaller increase in exercise capacity at 1-year post-CR [126]. The DARE study found that glycemic control was an important predictor of improvement in peak VO_2 after CR [127]. In another study of exercise training in subjects with T2DM and known CVD with or without prior MI, an exercise intervention improved peak VO_2 only in the subgroup of patients without a prior MI suggesting that the extent of macrovascular disease may impact the ability of exercise to improve functional capacity [128]. Exercise rehabilitation has also been shown to improve mortality in post-MI patients by 20%, but benefits may be attenuated in T2DM subjects whose exercise training response appears inhibited [129, 130]. To our knowledge, no studies to date have compared mortality after CR in post-MI nondiabetic subjects vs. those with T2DM.

In summary, data now strongly suggest that diabetic subjects post-MI have an impaired maximal exercise capacity prior to CR as compared to similar nondiabetic post-MI individuals. Differences may be mediated by an impaired chronotropic response to exercise. Patients with T2DM appear to be less likely to participate in CR, but even in those who do, post-MI subjects with T2DM show less improvement in exercise capacity as compared to those without T2DM. Fasting glucose levels and overall glycemic control were the best predictors of improved exercise capacity after CR in T2DM post-MI subjects. In general, response to exercise interventions may have greater benefit in patients with earlier, milder macrovascular disease, i.e., before an actual ischemic event. More study is warranted to determine the impact of exercise training on outcomes such as mortality and cardiovascular morbidity in subjects with T2DM and comorbid CVD.

Impairment of Exercise Performance in Diabetes Mellitus with Comorbid Peripheral Arterial Disease (PAD)

T2DM is a strong risk factor for the development of PAD. Prevalence of PAD based on ankle-brachial index in T2DM ranges from 15% to 30% [131, 132]. The cumulative incidence of PAD was 11% over 18 years following T2DM diagnosis in the UK Prospective Diabetes Study (UKPDS) cohort [133]. In the UKPDS study, a multivariate model examined the relative contributions of different risks for PAD in this diabetic cohort, and the strongest predictors were cardiovascular disease and current smoking which both ascribed threefold odds of PAD. Lesser but distinct risk was ascribed to worse glycemic control, higher systolic blood pressure, and lower high-density lipoprotein levels.

There are conflicting results in the small studies to date comparing exercise capacity in subjects with PAD and comorbid T2DM to nondiabetic PAD subjects [134–137]. Oka et al. found a decreased maximal walking distance (279 m vs. 461 m, $p = 0.01$) and decreased distance to onset of claudication (127 m vs. 187 m, $p = 0.01$) in patients with T2DM and PAD as compared with PAD alone [137]. Both groups were well matched for ankle brachial index (ABI), cholesterol, and systolic blood pressure levels and had similar prevalence of known CVD. Similarly, Dolan et al. showed T2DM subjects with PAD had a shorter 6-min walking distance (1040 vs. 1168 ft, $p < 0.001$) and slower walking velocity 0.83 vs. 0.90 m/s, $p < 0.001$) despite age adjustment between groups and similar baseline ABI and physical activity levels [134]. Unfortunately, there was a greater BMI in the subjects with

T2DM as compared to the subjects without in this study. A multivariate linear regression model in this study found DM-associated neuropathy, greater exertional leg symptomatology, and greater comorbid CVD to be predictive of the worsened exercise capacity in the T2DM group. However, in subjects with a comparable BMI, ABI, and blood pressure levels, Katzel et al. found no difference in either age-adjusted VO_2max or onset of claudication time between 47 diabetic and 72 nondiabetic subjects with PAD (1.16 in diabetics vs. 1.12 L/min in nondiabetics) [136]. Green et al. furthered the concept of BMI as an explanatory variable of exercise performance [135]. In their study, there was a significant difference in maximal exercise time between 12 T2DM PAD subjects and 12 age- and gender-matched leaner nondiabetic PAD subjects, but no difference between maximal walking time between the 12 T2DM PAD subjects and 7 nondiabetic subjects matched for BMI (median 845 s T2DM, 915 s "heavy" nondiabetics, 1448 s "leaner" nondiabetics). No difference was found between the three groups for pain-free exercise time, maximum cycling time, or VO_2max, although trends toward significance were seen in the latter two parameters for "leaner" nondiabetics vs. both T2DM and "heavy" nondiabetics. Maximal walking time was significantly negatively correlated with BMI ($r = -0.38$, $p < 0.05$) as well as with the VO_2 time constant, tau ($r = -0.49$, $p > 0.05$). The time constant, tau, reflects the rapidity with which VO_2 responds to exercise and was significantly worse in T2DM subjects as compared to both the "heavy" and "lean" nondiabetic groups ($p < 0.05$, 71 s (T2DM) vs. 38 s ("heavy") vs. 37 s ("lean"), respectively). The longer tau in T2DM and its inverse correlation with maximal walking time suggest the greater time for working muscles to receive steady-state oxygen distribution may decrease walking time in T2DM separately from BMI. A significant limitation of this study is the greater female distribution in the "heavy" control group as compared to both the T2DM and "lean" control groups, which may have lowered the exercise capacity in the "heavy" control group. Thus, current limited evidence suggests a greater BMI and longer VO_2 time constant, tau, may play a role in the impaired maximal exercise times for T2DM subjects with PAD found in some studies.

The optimal form of exercise for subjects with T2DM and symptomatic PAD is a supervised exercise rehabilitation program with therapeutic modality of walking to near-maximal claudication pain over 6 months [138, 139]. It has been recommended that subjects with PAD and comorbid conditions that limit weight-bearing exercise consider low-impact activities such as stationary bicycling or aquatic exercise, although improvements in walking may be less [13, 140].

Data are lacking on the impact of exercise training on exercise capacity in subjects with diabetes and comorbid PAD; only limited subgroup analyses have been made to date. A systematic review and meta-analysis of exercise intervention studies in PAD identified 18 studies, 12 of which were confirmed to include subjects with diabetes (19–43%). Comparison of studies that included at least 25 % of subjects with diabetes to those that did not found greater improvements in maximum walking distance in the studies that did not, suggesting that subjects with PAD and diabetes benefited less than those without diabetes. Pain-free walking distance and 6-min walking distance were equally improved in both subsets of studies [141]. Sanderson et al. studied 42 subjects with PAD, 33% of whom had diabetes, and randomized the subjects (stratified for age, gender, and diabetes) to 6 weeks of treadmill exercise training at 80% of subject's VO_2max (n = 13), 6 weeks of bicycle exercise training at 80% of subject's VO_2max (n = 15), or no-exercise therapy [140]. Both the treadmill exercise training and cycling training regimens improved VO_2max in this study. A subgroup analysis showed more severe pain in the symptomatic limb was the only baseline characteristic to differentiate "exercise responders" who increased their mean cycling or walking times from the entire sample; therefore, diabetes did not appear to play a role in the likelihood of a subject to respond. Ekroth et al. showed a mean 234% improved walking distance after 4–6 months of training in PAD subjects that was independent of the presence of diabetes [142]. Gardner et al. performed two studies with subjects with intermittent claudication. In one with 43% of subjects with

T2DM, maximum walking time and VO_2peak were improved with either a supervised intervention or a home-based exercise program compared to usual care [143]. A later larger study from the same group (23% T2DM) compared usual care with a supervised exercise program and again found improved maximum walking time and VO_2peak within 2 months of intervention [144]. McDermott et al. similarly performed two studies. In the first, 156 subjects with PAD (~43% T2DM) were randomized to usual care versus supervised treadmill exercise versus lower extremity resistance training. VO_2peak was not reported, but maximum walking time improved with both interventions (more with the treadmill intervention), and 6-min walking distance improved with the treadmill intervention, but not with the resistance training [145]. In the second study from this group, 194 PAD patients (32% T2DM) were randomized to a home-based behavioral walking intervention versus an attention control condition. VO_2peak was again not reported, but the walking intervention significantly improved 6-min walking time and maximum walking distance, including in the subgroup with T2DM [146].

Beyond these subgroup analyses, we are not aware of any studies designed to differentiate the response to exercise training in subjects with PAD and comorbid DM as compared to nondiabetic PAD controls. In summary it appears that exercise does improve PAD in T2DM, but definitive studies in T2DM alone are lacking.

The Role of Exercise in Prevention of Cardiovascular Outcomes

Many observational studies have linked increased habitual physical activity with improved cardiovascular outcomes in diabetes. Because of the extensive confounding of these observational studies by other uncontrolled variables, they will not be discussed here. This section will focus on the few interventional studies that have explored the effect of exercise-inclusive lifestyle interventions on hard clinical CVD outcomes.

Two large long-term multicenter randomized controlled trials have explored the utility of a lifestyle intervention that includes exercise in the prevention of CVD, the Chinese Da Qing study and Look AHEAD and found interestingly contrasting results. Da Qing enrolled 577 adults with impaired fasting glucose, but not diabetes, and randomized them to a control group versus one of three 6-year intervention groups: diet, exercise, or both. After 23 years of follow-up, the intervention groups combined had reduced CVD mortality (HR 0.59, 95%CI 0.36–0.96, $p - 0.033$), as well as decreased incident diabetes (HR 0.55, 95%CI 0.40–0.76, $p = 0.001$) [147]. A subgroup analysis demonstrated that the majority of the deaths that occurred were in individuals who subsequently developed diabetes [148]. Unfortunately the study was not large enough to allow separate analyses of the three intervention groups, and it remains impossible to say whether exercise was a key intervention component in the CVD mortality reduction.

In contrast the Look AHEAD study recruited over 5000 overweight or obese patients with T2DM to a participate in a randomized controlled study of an intervention with the primary goal of weight loss [149]. The primary outcome was a composite cardiovascular outcome including death from cardiovascular cause, nonfatal MI or stroke, and angina-related hospitalization. The intervention included caloric restriction and nonsupervised increased physical activity compared to a control group that received diabetes support and education. The study was intended to continue for 13.5 years but was stopped early at 9.6 years for futility as the event rate in the control group was much lower than anticipated and there was virtually no signal for a difference in the intervention group. It is, however, a gross overinterpretation of the study to say that exercise does not provide CVD benefit in T2DM for several reasons: (1) It does not appear that physical activity was monitored in the intervention group; (2) in fact, exercise capacity was measured only in the first 4 years. Exercise capacity increased markedly over the first year but then declined to nearly the level of the control group by year 4 raising the likelihood that compliance with the increased physical activity advice was poor; (3) weight, waist circumference, and

HbA1c all rebounded dramatically after the first year again suggesting poor compliance with the overall intervention; and (4) despite this there is a strong trend to benefit in the subgroup of individuals who did not have CVD at baseline (HR 0.86, 95% CI 0.72–1.02) [150].

In addition one smaller study combined an observational component with an exercise intervention in a subgroup of the observational cohort [151]. The study recruited 539 CVD patients with T2DM and 507 without T2DM. All completed a validated questionnaire to measure leisure-time physical activity (LTPA). Of these 143 and 148, respectively, were willing and appropriate for inclusion in a 2-year exercise intervention. The observational analysis confirmed the benefits of higher LTPA in decreasing CVD events with and without T2DM, with the groups that reported <thrice-weekly LTPA having at least a twofold increase in CVD events over the 2-year follow-up compared to the group that reported LTPA at least three times a week. This difference persisted after adjusting for participation in the exercise intervention. In contrast the 2-year exercise intervention had no effect on CVD event rates over the 2 years.

In summary these two large studies, as well several smaller studies described above, suggest that failure of exercise to provide CVD benefit may be a case of "too little, too late" in diabetes where macrovascular damage may already be quite advanced by the time of diagnosis. Studies and subgroup analyses in earlier prediabetes, those with T2DM but no evidence of CVD, and those that explore longer-term physical activity habits do show, or at least hint at, reduction in macrovascular disease with exercise.

Cardiac Autonomic Dysfunction

Cardiac autonomic neuropathy (CAN) may be a specific neuropathy and therefore could be considered together with microvascular neuropathies. However, in light of evidence for a significant role of CAN in exercise intolerance, diabetic cardiomyopathy, and CVD risk, it is briefly discussed separately in this section. Two separate aspects of CAN may have significant roles in T2DM: (1) impaired resting cardiac sympathetic/parasympathetic balance and (2) impaired chronotropic response to exercise. Both appear to be associated with CVD risk, have been linked to cardiac maladaptation to exercise, and are improved with exercise.

Reduced heart rate variability (HRV), the simplest and most commonly used measure of CAN, has repeatedly been shown to correlate with CVD risk in T2DM [152–156]. In addition, the DIAD study found that CAN was one of the independent predictors of silent ischemia in T2DM [157]. More detailed analysis of HRV includes the isolation of high-frequency (HF) variation reflective of parasympathetic/vagal input. Decline in parasympathetic/vagal input and/or increase in sympathetic input at rest is thought to contribute to the increased CVD risk associated with CAN. The other significant measure of CAN is the response of cardiac autonomic modulation or chronotropic response to stress, usually exercise. This is typically measured as the increase in heart rate with exercise [158] and reflects the desirable increase in sympathetic and decrease in parasympathetic stimulation with stress, usually exercise. Impairment in this response, known as chronotropic incompetence (CI), is another measure of CAN that has also been associated with poor CVD prognosis [158].

No studies have directly addressed the relationship between CAN and reduced exercise capacity in diabetes. However, a few studies have linked CAN to other measures that may impact exercise tolerance and exercise capacity. A recent study recruited 83 patients with T2DM without CVD and performed sophisticated "state-of-the-art" measures of autonomic function, as well as ^{82}Rb-PET/CT and ^{123}I-MIBG measurement of cardiac perfusion and sympathetic responsiveness thereof [159]. Eleven percent met ADA criteria for CAN, but nearly half of the patients had at least one measure consistent with some degree of CAN. In the full cohort, multiple measures of CAN correlated significantly with impaired cardiac flow reserve. Although exercise tolerance was not tested in this study, it is likely that this impairment in increased blood flow with sympa-

thetic activation, as well as the CI described above would contribute to increased perceived exertion and hence exercise intolerance in T2DM. CAN has also been correlated with diastolic dysfunction [160]. As described above, diastolic dysfunction may also contribute to decreased exercise capacity in T2DM. In fact, Baldi argues that CAN is a major contributor to the diabetic cardiac dysfunction described earlier and implicated in impaired exercise capacity in diabetes [64].

The literature on response of CAN to exercise in T2DM is limited, complicated by the multiple measures used to assess CAN, and mixed in results. Multiple studies (reviewed in [161]) have found improved cardiac autonomic function with exercise in individuals without CAN at baseline. However, few studies have looked at effects in individuals with CAN at baseline. One small study in T1DM demonstrated improved HRV after a 12-week supervised intervention in early CAN but no change in severe CAN [162]. A similar study in T2DM of a 6-month supervised exercise intervention found improved HRV with increased HF variation indicating increased parasympathetic tone [163]. In contrast, Sacre et al. randomized 49 subjects with T2DM to a 6-month exercise intervention versus usual care and found no changes in CAN despite improved VO_2peak and lowered resting heart rate [93].

The response of CI to exercise has been demonstrated in CHF and CVD but has not been studied directly in diabetes. One study found an increase in peak HR with a walking intervention in T2DM suggesting that exercise may improve CI in T2DM as well [164]. Another study used glucose ingestion as a metabolic stress that also stimulates cardiac sympathetic tone in a manner similar to exercise [165]. Fifty-nine obese subjects (23 with T2DM, 36 without) were recruited to this observational study of a 16-week moderate-intensity aerobic exercise program. Multiple measures of cardiac autonomic modulation including HRV, blood pressure variability, and baroreflex sensitivity were performed before and after glucose ingestion and before and after the intervention. These demonstrated increased sympathetic cardiac modulation and decreased vagal modulation with glucose ingestion after the intervention, indirectly suggesting that the exercise intervention improved CI.

A recent study explored the impact of an exercise intervention on a new index of CAN, heart rate recovery [166]. In this study 42 subjects with T2DM and abnormal heart rate recovery (about a third of the screened subjects with T2DM) were randomized to usual care versus an intervention that combined resistance and moderate-intensity aerobic training for 12 weeks. The intervention group was found to have significantly lower resting heart rate and greater improvement in heart rate recovery than the control group.

In summary, CAN likely plays a significant role in the cardiac dysfunction in diabetes and hence in the decreased exercise capacity in diabetes. A beneficial role of exercise is supported by limited studies, but more studies are needed addressing direct effects of exercise on CAN.

Microvascular Disease

Impaired Exercise Capacity from Microvascular Complications in Diabetes Mellitus

Microvascular complications of T2DM include nephropathy, neuropathy, and retinopathy, and all of these have an increasing incidence with greater duration of T2DM. The prevalence of nephropathy and retinopathy in T2DM have been reported to range from 7% to 30% [167] and from 3% to 27% [168], respectively. Given their occurrence later in the course of diabetes, microvascular complications are present at a more advanced stage of diabetic pathophysiology. As such, it is reasonable to consider they may be explicitly associated with increased exercise impairment but also present simultaneously with other abnormalities that impair exercise capacity (e.g., nephropathy in the form of microalbuminuria has been linked with the presence of diastolic dysfunction [169]). This section will review the evidence in the literature that microvascular complications are correlated with exercise impairment and that exercise can improve or

slow progression of many of these complications and review current guidelines for exercising with complications (Table 18.2).

Diabetic Nephropathy Decreases Exercise Capacity

Diabetic nephropathy has been shown to adversely affect exercise capacity in both T1DM and T2DM subjects. Jensen et al. found a 25–30% reduction in maximal exercise capacity when comparing normoalbuminuric T1DM subjects and T1DM subjects with either microalbuminuria (30–300 mg/day) or macroalbuminuria (>300 mg/day) [170]. In an earlier non-exercise-related study by this group, resting left ventricular function was also found to be impaired in T1DM subjects with microalbuminuria and macroalbuminuria as evidenced by greater left ventricular end-diastolic volume ($p < 0.05$), lower stroke volumes ($p < 0.05$), and a trend toward decreased cardiac output ($p = 0.10$ for macroalbuminuric subjects and $p < 0.05$ for microalbuminuric subjects) [171]. More recently, Bjornstad et al. demonstrated decreased VO_2peak in adolescents with T1DM relative to controls [172]. These adolescents exhibited only the presumed earliest sign of renal disease, hyperfiltration, with an elevated eGFR relative to controls. Peak VO_2 was strongly inversely correlated with eGFR (the degree of hyperfiltration), but not with HbA1c, LDL, insulin resistance, or blood pressure.

In T2DM, the Strong Heart Study showed a correlation between the severity of microalbuminuria and the degree of diastolic dysfunction [169]. Lau et al. also showed a decrement in maximal exercise capacity in T2DM subjects with microalbuminuria (30–300 mg/day of microalbumin) as compared with normoalbuminuric T2DM subjects ($p = 0.015$) and nondiabetic control subjects ($p < 0.001$) [173]. The authors hypothesized pulmonary microangiopathy and diastolic dysfunction may partially explain this exercise decrement, as their subjects had worsened gas exchange with exercise ($p = 0.019$ for group trend between control, T2DM, and T2DM with nephropathy for minute ventilation/carbon dioxide production) and a greater frequency of diastolic dysfunction that normoalbuminuric T2DM subjects ($p = 0.013$). Thus, diabetic nephropathy was clearly correlated with exercise impairment [170], and comorbid diastolic dysfunction [169, 171, 173] as well as pulmonary angiopathy [173] may partially explain this impairment.

Other studies that were not limited to subjects with diabetes have further strengthened the association of chronic kidney disease with impaired exercise performance, including in diabetes. One study of 136 patients with moderate chronic kidney disease (eGFR 40 ± 9, 38% with diabetes) found markedly impaired peak VO_2 and heart rate response that were more prevalent in the diabetes subgroup and were independently associated with aortic stiffness, impaired left ventricular function, and increased left ventricular afterload [174]. Another study of 39 CKD patients (11 with diabetes) found a nonsignificant ($p = 0.099$) reduction in VO_2max in the group with diabetes compared to those without [175]. They also demonstrated that VO_2max was independently inversely related to hsCRP levels independent of diabetes status, implicating inflammation as a contributory mechanism in CKD-associated exercise impairment.

Effects of End-Stage Renal Disease on Exercise Performance in T2DM

End-stage renal disease (ESRD) from T2DM has been shown to occur in only 0.8% of a cohort of T2DM patients followed for 10 years; however, incidence does continue to increase with time. Accordingly, diabetic nephropathy was the single most common cause of new-onset ESRD in the United States in 2002 (45% of incident dialysis patients). Given the multiple comorbidities associated with ESRD [176], it is understandable that it would correspond to even greater decreased exercise capacity than non-ESRD nephropathy. In both diabetic and nondiabetic subjects with ESRD on dialysis, maximal exercise capacity has been shown to be about 60% that of age-matched control subjects [177, 178]. Moderate anemia (hema-

tocrit <30%) has been shown to lower VO_2max, and is improved with erythropoietin administration [179]. However, other factors which depress exercise capacity are felt to be numerous and have not yet been specified [178, 180]. More intensive hemodialysis sessions (five to six nocturnal sessions/week lasting 6–8 h per session) led to significant improvements in VO_2max 3–6 months after the transition from thrice-weekly conventional hemodialysis [181]. Also, 1 month after renal transplant, VO_2max showed improvement to nearly that expected for sedentary age-matched subjects [180, 182]. These improvements in VO_2max either from more intensive hemodialysis or after renal transplant occurred despite the absence of any exercise training or significant improvements in anemia in these studies [180–182]. Such findings further suggest that as yet undefined factors related to ESRD significantly depress exercise capacity in both diabetic and nondiabetic subjects with ESRD.

Benefits of Exercise Training in Chronic Renal Disease

Exercise training-specific studies have not been done in the population with diabetes and comorbid renal failure. However, extensive literature exists on the benefits and safety of exercise training in the renal failure population independent of diabetes status. Since diabetes is well represented in this population, these studies are likely to be relevant to diabetes-related renal disease, and a few will be briefly discussed here. Watson et al. implemented a progressive resistance training program in CKD stage 3b/4 patients [183]. The intervention was safe and well tolerated and resulted in improved strength and endurance walking time. However, they note that this outpatient program was offered to over 400 patients and accepted by only 38 (15% with diabetes vs. 27% in the age- and BMI-matched control group), suggesting that this type of outpatient supervised strategy, while beneficial, is impractical, perhaps especially in the diabetes population. In a randomized, controlled trial of 16 weeks of aerobic exercise training in 25 patients with stage 3 CKD (40% diabetes), aerobic capacity, endothelin 1 levels, and QOL measures, but not aortic stiffness, were significantly improved [184]. No diabetes subgroup analyses were reported. Another small study randomized 20 stage 3/4 CKD patients to standard care versus 12 months of supervised resistance and aerobic training [185]. Unfortunately none of the intervention group had diabetic nephropathy, and the small study was confounded by significant between-group differences. However, the intervention group showed promising results with improved eGFR, PWV, VO_2peak, and waist circumference (versus worsening in the control group). The Look AHEAD study in T2DM had weight loss as its primary goal, but the intervention did include exercise. The rate of incident CKD in this large study population was significantly decreased in the intervention group (by 31%), and multivariate analysis implicated reductions in weight, A1c, and BP as significant mediators [149]. More studies in the diabetic CKD population are clearly needed given the debilitating effects of renal disease on functional capacity and the encouraging results from small intervention studies in the nondiabetic CKD population.

Limited Data on Exercise Capacity Association with Retinopathy or Neuropathy

Diabetic retinopathy has also been associated with reductions in exercise capacity in T2DM subjects. Despite adjusting for known predictors of exercise capacity such as age and duration of diabetes in a regression analysis, the VO_2max in ABCD trial subjects with T2DM was independently reduced by the presence of diabetic nephropathy ($p = 0.04$) and retinopathy ($p = 0.026$) [186]. Other studies have not explicitly looked at the relationship between diabetic retinopathy and exercise capacity or the causes of this abnormality. To our knowledge, no studies have explored any potential associations between diabetic neuropathy and exercise capacity.

Hazards of Exercise Training with Diabetic Microvascular Complications

Although exercise training is highly beneficial to most participants, the presence of microvascular complications raises some safety considerations. Diabetic retinopathy may lead to adverse outcomes with vigorous exercise. Diabetic subjects with active proliferative diabetic retinopathy (PDR) are at higher risk for vitreous hemorrhage or retinal detachment [187]. Subjects with PDR or moderate to severe nonproliferative retinopathy are recommended to avoid strenuous exercise, Valsalva maneuvers, and jarring activities per the most recent ADA position statements (Table 18.2) [188, 189]. No studies have looked specifically at the impact of exercise training on the remediation of retinopathy in humans.

Recent ADA position statements on diabetes and exercise have relaxed the recommended limitations on exercise for peripheral neuropathy. Current recommendations refer to the increased risk of skin breakdown and infection with peripheral neuropathy and recommend proper footwear and daily examination of the feet for lesions with weight-bearing exercise. However, the recommendation to avoid weight-bearing exercise has now been limited to individuals with foot injuries or open sores [188, 189]. The ADA suggests nonweight-bearing exercises such as swimming, bicycling, or rowing for these patients. This relaxation of exercise limitation for peripheral neuropathy was driven by recent studies demonstrating tolerance and safety of exercise interventions in peripheral neuropathy. In some cases, these studies also found improvement in neuropathy or in side effects of neuropathy (e.g., balance and gait issues) with the exercise interventions (reviewed in [190–192]). Streckman et al. performed a systemic review and identified 11 studies of exercise interventions in diabetic neuropathy [192]. Of these nine demonstrated improvement in side effects of neuropathy or neuropathy itself, while one did not (one did not report on intergroup differences). One study compared a weight-bearing intervention to a nonweight-bearing intervention and found no difference in the number of foot lesions occurring during the intervention [193]. A larger Italian study [194] randomized 78 diabetic participants without peripheral neuropathy to usual care versus 4 h/week of observed treadmill walking addressing a role in prevention of neuropathy. Treadmill walkers improved vibration detection and nerve conduction indices and were significantly less likely to develop neuropathy over the 4 years of the study. Most significantly, a 2012 study using a 10-week aerobic exercise plus strength training intervention in individuals with T2DM and peripheral neuropathy demonstrated improvement in maximum pain, overall symptom score, and intraepidermal nerve fiber branching [195]. No foot ulcerations, delayed healing of biopsy sites, or infections were noted during the study.

ADA guidelines for exercise with autonomic neuropathy note that autonomic neuropathy can increase the risk for exercise-induced injury and recommend that all individuals with autonomic neuropathy undergo cardiac investigation before beginning more-intense-than-usual physical activity [188, 189].

Some experts have discouraged strenuous physical activity in subjects with diabetic nephropathy given the propensity for exaggerated blood pressure elevations with high-intensity exercise and proteinuria [196–200] associated with acute exercise-induced blood pressure excursions [187]. Results have been mixed on whether microalbuminuria increases to a significant degree in subjects without baseline nephropathy [200–202]. However, the most recent ADA guidelines state that there is no evidence that vigorous intensity exercise increases the rate of progression of diabetic kidney disease and place no specific exercise restrictions on this population. In fact, a prior recommendation of exercise stress testing prior to an aerobic exercise program in previously sedentary individuals with diabetic kidney disease given their significant prevalence of CVD has been removed. The recommendations now simply state that high-risk (including individuals with significant nephropathy), previously sedentary individuals should be encouraged to start with short periods

of low-intensity exercise and slowly increase frequency and intensity [47, 188, 189].

Separate from safety considerations, high-intensity exercise may be precluded by pain or early fatigue from comorbid diabetic neuropathy [203, 204], musculoskeletal pain/osteoarthritis [205–207], renal osteodystrophy [208], or myopathy [208] and generally in subjects with end-stage renal disease [208, 209].

Pulmonary Function

Considerable evidence now exists that T2DM is also accompanied by impaired pulmonary function which may also play a role in exercise impairment. Similar evidence exists in T1DM, but this discussion will focus on T2DM. While past studies measuring pulmonary function tests in diabetes had yielded somewhat mixed results (reviewed in [210]), more recent studies have consistently demonstrated restrictive lung disease in diabetes relative to controls, while others have suggested additional obstructive and alveolar defects. In one cross-sectional study of pulmonary center patients with pulmonary function tests (PFTs) and no specific pulmonary diagnosis, patients with T2DM ($n = 560$) had decreased FVC, FEV1, and DLCO ($p < 0.0001$) compared to those without diabetes ($n = 3604$) after adjustment for age, sex, race, height, BMI, smoking, and heart failure [211, 212]. Similarly, a retrospective analysis of 62 diabetic and 27 obese nondiabetic patients admitted to an endocrinology service who also underwent pulmonary function testing found that FVC, FEV1, DLCO, and multiple other measures of pulmonary volume and function were significantly lower in the patients with T2DM compared to the obese nondiabetic group [213]. Furthermore, Kinney et al. studied a population of smokers with or without COPD and with and without T2DM. They found that across COPD stages, those with T2D had reduced FEV1 and FVC, as well as reduced 6 min walk and quality of life [214].

While these studies were admittedly confounded by apparent existing pulmonary issues (known smoking and/or COPD or some clinical indication for PFTs), other studies have measured PFTs either prospectively or as routine health care and found similar results. For instance, in a large Korean study after exclusion of all individuals with known pulmonary or neuromuscular disease or heart failure, over 35,000 adults who had PFTs as part of their routine health care were studied [215]. The prevalence of restrictive lung disease was more than doubled in those with T2DM compared to those with normal fasting glucose (18% vs. 8%). Obstructive ventilatory dysfunction was less prevalent overall but was also increased in T2DM. Multivariate analyses implicated insulin resistance (HOMA-IR, fasting insulin, and triglycerides) in the increased restrictive lung disease, while the obstructive lung disease appeared to be largely related to age blood pressure, and to glycemic control in the T2DM population. Similarly, the Berlin Aging Study II (BASE II) of about 700 individuals with adequately performed PFTs found the FEV1 and FVC were decreased in the T2DM population [216]. However, in contrast to the Korean study, restrictive lung disease in this study was largely related to central adiposity and muscle mass. Finally, several smaller but controlled and population-matched studies have found similar results linking T2DM to restrictive lung pathology, apparently independent of obesity. For instance, Aparna (2013) compared 40 subjects with T2DM to 40 age-, sex-, and BMI-matched controls and found that FVC, FEV1, and peak expiratory flow rate were significantly decreased in the subjects with T2DM [217]. FEV1/FVC% was significantly increased, again consistent with a primarily restrictive defect in T2DM. Shah et al. similarly studied 60 adult males with T2DM versus 60 obese adult males without T2DM and found decreased FEV1 and FVC, but no difference in FEV1/FVC [218]. In this study, the pulmonary measures showed no correlation with HbA1c or duration of T2DM.

Several studies demonstrating pulmonary defects in T2DM have further explored associations to shed light on causation. Overall these studies have suggested that the restrictive pulmonary disease component is independent of glycemic control, consistent with the Shah study above

[219, 220]. In addition, a review of pulmonary disease in metabolic syndrome [219] presents data from several studies demonstrating restrictive lung disease associated with all components of met abolic syndrome and concluding that insulin resistance, and not hyperglycemia, is the underlying mechanism. A 2013 study in India supported and added to this conclusion [220]. In this cross-sectional study of 30 T2DM patients and 30 age-, weight-, and sex-matched nondiabetic subjects, FVC, FEV1, PEFR, PIF, FIVC, TLC, DLCO, and DLCO/VA were significantly reduced in patients with T2DM. Within the T2DM population, DLCO and DLCO/VA (but not FVC and FEV1) were reduced in the subpopulation with HbA1c >7. They conclude that T2DM, independent of glycemic control, is associated with a restrictive pulmonary abnormality, while poor glycemic control then contributes an additional alveolar diffusion defect. This is consistent with other studies implicating microvascular disease in the alveolar diffusion defects in T2DM [213, 221]. However, other studies have also shown a correlation of the restrictive lung disease with other complications of diabetes typically associated with poor glycemic control, including nephropathy [222] and CAN [223]. Shafiee et al. demonstrated a worsening of restrictive pulmonary disease across three subgroups of T2DM patient with increasing evidence of nephropathy (no nephropathy vs. microalbuminuria vs. macroalbuminuria) [222]. Similarly in a study in adolescents with T1DM, restrictive pulmonary disease was found only in those with CAN [223]. In contrast, Kaminski et al. studied pulmonary disease in T2DM adults with and without CAN and found that PFTs and max expiratory pressure were similar, but inspiratory pressure (reflecting respiratory muscle strength) was decreased in subjects with CAN and correlated negatively with resting HR as a measure of sympathetic/parasympathetic ratio in CAN [224].

Overall, these studies suggest that several forms of pulmonary disease are prevalent in T2DM as complications/comorbidities of T2DM. These include (1) a prominent restrictive component that is likely at least in part related to insulin resistance and independent of glycemic control, (2) an alveolar diffusion defect that is likely an example of diabetic microvascular disease with a large contribution from hyperglycemia, and (3) lesser contributions from inspiratory muscle weakness and possibly obstructive pulmonary disease that are less well studied in T2DM.

Effects of Pulmonary Disease on Exercise Performance in T2DM

The effects of T2DM pulmonary disease on exercise performance and of exercise training on T2DM pulmonary disease have not been well studied. However, limited studies suggest that restrictive pulmonary disease does contribute to decreased exercise capacity in T2DM and that some forms of exercise training may improve restrictive pulmonary disease. Kitahara et al. measured exercise capacity and pulmonary function in 31 male patients with uncomplicated T2DM and no evidence of cardiopulmonary disease (including no frankly abnormal PFTs). They found that the percentage of predicted maximal oxygen uptake (%VO_2max) correlated significantly with percentage of predicted FEV1 (%FEV1) and that a mild reduction in %FEV1 was associated with measurably impaired exercise capacity [225]. Conversely, very limited studies have suggested that exercise training may improve pulmonary function. Inspiratory muscle training has been shown to dramatically improve (>2×) max inspiratory pressure [226]. However, this training failed to have any effect on PFTs or on functional exercise capacity (peak VO_2).

In contrast, arm swing exercise in T2DM did improve FVC, FEV1, and maximal voluntary ventilation, as well as HbA1c, a low-density lipoprotein, malondialdehyde, oxidized glutathione, and the percent body fat [227]. However, overall exercise capacity was not tested in this study.

In summary, there is strong evidence for multiple forms of pulmonary disease in both T1DM and T2DM, complications that are not widely recognized in diabetes. Relatively limited evidence suggests that pulmonary complications may contribute to the exercise defects in diabetes. Very limited

evidence exists to support benefits of exercise in specifically treating pulmonary complications of diabetes. Further studies are needed to explore methods and benefits of specifically targeting treatment of pulmonary disease in diabetes.

Special Cases

Exercise Impairment with Diabetes Mellitus and Atrial Fibrillation

Subjects with T2DM have been shown to develop atrial fibrillation more often than nondiabetics [228, 229]. The prevalence of comorbid diabetes was recently found to be 23% in a trial of elderly subjects with atrial fibrillation [230]. Physiologically, these two diseases may be linked as cardiovascular abnormalities predict the development of atrial fibrillation [228] and diabetes confers a significant risk of cardiovascular morbidity [231–233].

One small trial compared the VO_2max before and after direct current cardioversion to establish sinus rhythm in subjects with atrial fibrillation without comorbidity ("lone atrial fibrillation"), atrial fibrillation and hypertension, or atrial fibrillation and diabetes [234]. This study found no improvement in VO_2max or subject-measured effort of exercise (Borg scale) in subjects with diabetes and atrial fibrillation after cardioversion, despite an improvement in VO_2max and subject-measured effort of exercise in lone atrial fibrillation and, to a lesser degree, in subjects with hypertension and atrial fibrillation. The authors theorized the lack of improvement in diabetes and atrial fibrillation corresponded to the lack of improved endothelial function, as this had improved in both the hypertensive and lone atrial fibrillation groups.

Exercise and Fatty Liver in Type 2 Diabetes

A recent analysis was performed of >200,000 Korean subjects with T2DM who were part of an occupational health screening program that included ultrasound assessment for fatty liver and completion of a validated physical activity form [235]. The results demonstrated that exercise ≥5 times a week was associated with an OR of 0.86 for incident fatty liver and 1.4 for resolution of preexisting fatty liver ($p < 0.001$ for both). Although more was better, a significant improvement in both outcomes was also noted with any increase in physical activity and with one to two bouts of exercise per week. These results support the findings of other recent smaller studies demonstrating benefits of exercise for fatty liver [98, 236, 237]. Though the associated exercise interventions also improved exercise capacity, no studies have specifically linked fatty liver with reduced exercise capacity.

Exercise and Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) is a common comorbidity in T2DM that is also improved by exercise interventions. A recent systematic review and meta-analysis of eight articles demonstrated that exercise as a sole intervention decreased the apnea hypopnea index, BMI, and Epworth sleepiness scale [238]. Again, no studies have demonstrated that OSA itself independently contributes to exercise impairment in diabetes.

Summary

There is a high prevalence of hypertension, arterial stiffness, vascular disease, and diastolic and systolic dysfunction which deleteriously impact exercise capacity in diabetes. Hypertension and arterial stiffness may both be improved in diabetes by exercise training programs and exercise should be recommended. Subjects who have suffered an MI and have T2DM have been shown to rehabilitate to a lesser degree than nondiabetic post-MI subjects. Data on the impact of exercise training for diabetic individuals with diastolic dysfunction, systolic cardiomyopathy, and PAD are only available from subgroup analyses or nondiabetic populations. Since it is recognized that mortality is generally lower in the diabetic

population with better exercise capacity, exercise training to raise the exercise capacity is worthwhile, at least in theory, in diabetic individuals with all comorbid conditions. However, more studies are needed to explicitly clarify the benefits of exercise training in the diabetic with diastolic or systolic dysfunction, CVD (without recent MI), or PAD.

The presence of diabetic nephropathy has been consistently associated with decreased exercise capacity, while possible associations between exercise capacity and either diabetic retinopathy or diabetic neuropathy are understudied. Existing diabetic retinopathy, nephropathy, or neuropathy may pose safety concerns to the diabetic individual planning to institute a new exercise regimen more intense than brisk walking. Given the lack of randomized trial data, the recommendations given in the ADA position statement should be followed with regard to exercise precautions in the diabetic person with microvascular disease. More study in the area of safety and efficacy of exercise training in the diabetic person with microvascular disease is also warranted.

In summary, exercise training is important to treat the metabolic and cardiovascular abnormalities associated with T2DM. Clinicians should work to insure their diabetic patients may exercise safely to achieve these goals.

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Type 1 Diabetes Mellitus and Exercise

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Alissa J. Roberts, Gregory P. Forlenza, David Maahs, and Craig E. Taplin

Introduction

Exercise, in addition to diet and insulin, is a cornerstone of management of diabetes. However, the specific pathophysiology of type 1 diabetes mellitus (T1DM) as a fundamental disorder of insulin deficiency requiring treatment with exogenous insulin changes the dynamics of glucose homeostasis during exercise. This presents the patient with T1DM and his/her health-care provider with many challenges.

T1DM is characterized by autoimmune destruction of beta cells in the pancreas leading to absolute, or near-absolute, insulin deficiency and the need for daily insulin administration to control blood glucose concentrations [1]. A number of advances have been made in the past few decades in the care of individuals with T1DM, which include home glucose monitoring [2], development of more physiologic insulin analogues [3], demonstration of the benefit of intensive diabetes management on the prevention of microvascular [4] and macrovascular disease [5], insulin pump therapy [6], continuous glucose monitoring [7], and the impending implementation of "closed-loop" systems and artificial pancreas technology [8–11]. These advances have provided improved tools for daily management for persons with T1DM but are labor intensive and require a sophisticated understanding of diet, exercise, and insulin action. Despite these therapeutic advances, exercise for persons with T1DM requires thoughtful adaptations of daily dietary and insulin management and continues to be a challenge for patients and their health-care providers. In this chapter we will review general guidelines around exercise for those with T1DM, the risks and benefits of exercise for those with T1DM, the pathophysiology of T1DM related to exercise, glycemic excursions around exercise in T1DM, guidelines on management of diabetes around exercise, and a discussion of new technologies and their implications for exercise in T1DM.

General Guidelines

The American Diabetes Association (ADA) and International Society for Pediatric and Adolescent Diabetes (ISPAD) recognize both the importance and challenge of exercise in

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T1DM and specifically address these issues in their recent guidelines of care [12, 13]. The ADA identifies that exercise is a key part of a diabetes management plan. Evaluation of the patient with T1DM prior to initiating exercise is recommended with attention to any conditions that may limit exercise type and intensity such as hypertension, autonomic or peripheral neuropathy, or retinopathy [12]. Certain activities are discouraged in the presence of diabetic complications (e.g., micro- or macrovascular disease) such as activities that increase blood pressure (e.g., weight lifting) and may cause eye injuries (e.g., boxing) and foot injuries (e.g., in persons with Charcot joint), and special attention should be paid to precautions around risk of severe hypoglycemia, especially in those patients with decreased hypoglycemic awareness.

General guidelines by the ADA include targeting adequate glycemic control prior to physical activity: avoiding exercise if ketones are present; ingesting carbohydrates if glucose is <100 mg/dl; monitoring blood glucose before, during, and after physical activity; and consuming food and/or decreasing insulin before, during, and after extensive exercise to avoid hypoglycemia [12]. However, guidelines are not differentiated by exercise type or duration and are not age-specific.

The ISPAD guidelines on exercise state that children and adolescents with diabetes "should be allowed to participate [in physical activities] with equal opportunities and with equal safety." The most recent 2014 guidelines suggest tailoring insulin regimens (reduced pre-exercise meal bolus, reduced or suspended basal insulin on pump), adjusting carbohydrate intake, integrating sprint activity, and/or consuming a high-carbohydrate postexercise meal to avoid hypoglycemia during and following exercise, including avoidance of nocturnal hypoglycemia following exercise [13].

It has been shown, at least in some cohorts, that individuals with T1DM exercise at frequencies at least comparable to those without diabetes. Importantly, this may be true both in adults [14] and youth [15]. However, despite the traditional description of the T1DM phenotype as that of a lean individual, the multicenter SEARCH for Diabetes in Youth study in the United States showed that those with type 1 diabetes had high prevalence of both overweight (22.1%) and obesity (12.6%), rates that are overall similar to youth without diabetes [16]. Similarly, recent data from the T1D Exchange (T1DX) registry in the United States and the Diabetes Prospective Follow-up (DPV) registry from Germany and Austria both showed mean BMI in youth with T1DM above general population normative values [17]. Specifically, in the T1DX, of over 11,000 youth with T1DM, 24% were overweight and 15% obese, using WHO reference ranges. In more than 21,000 youth with T1DM represented in the DPV, 23% were overweight and 10% obese. These data support the importance of encouraging physical activity in this population. Additionally, fear of hypoglycemia has been cited as the greatest barrier to physical activity in adults [18]. Reviewing interventions to mitigate the risk of severe glycemic excursions, especially hypoglycemia, can improve exercise safety and compliance.

Benefits of Exercise in Type 1 Diabetes

While exercise is encouraged for all people, including those with T1DM, variable results have been reported regarding the role of exercise as an intervention to specifically improve glycemic control (as measured by HbA1c levels) [14]. A recent large cross-sectional analysis of nearly 5000 youth with T1DM in Sweden [19] demonstrated a significant association between self-reported physical activity and HbA1c. Specifically, HbA1c in the most sedentary group was 1.1% higher (8.8%) than in the group who exercised every day (7.7%). Results were highly statistically significant and were found in essentially all age and sex subgroups, with the exception of young girls. Interestingly, physical activity decreased as age increased in these youth, suggesting a component of "exercise attrition" as patients with T1DM move into later adolescence and young adulthood. These Swedish findings mirror similar cross-sectional data from Germany and Austria in youth and young adults

with T1DM which showed a strong association between regular exercise and glycemic control [20]. However in other cross-sectional studies, such as that published by the Hvidoere Study Group, an association between exercise and HbA1c was not found [21]. Important clarifying data has been provided in recent meta-analyses of prospective studies of exercise as an intervention in T1DM. One of these, which included 11 trials in youth with type 1 diabetes, showed an overall beneficial effect of exercise in improving HbA1c by 0.52% [22]. Table 19.1 reviews major studies in adults and youth examining exercise as an intervention in T1DM. In adults, benefits specifically for glycemic control are less clear, but a recent systematic review published in 2014 by Yardley et al. suggested an overall improvement in HbA1c of approximately 0.78%; however, overall they suggested that there is a lack of high-quality studies assessing impact of physical activity on glycemic control [23]. In another systematic review of exercise in adults with T1DM by Chimen et al., overall benefits were seen with regard to insulin sensitivity, lipid profile, and cardiovascular fitness, but mixed results were seen for impact on HbA1c [24].

It is clear that multiple other benefits exist for exercise including improved lipoprotein profile [25], cardiovascular fitness [26, 27], quality of life [28], reduced daily insulin requirement [29], and body weight [30]. Long-term follow-up of patients with T1DM in Pittsburgh suggested a beneficial association between physical activity and cardiovascular disease and mortality [31].

Cardiovascular Fitness and Exercise Performance in Type 1 Diabetes

T1DM may be associated with reduced cardiovascular fitness in youth. In one UK study of 60 youth with a mean age of 12.5 years and mean HbA1c of 8.4%, no difference in physical fitness was found compared with sibling controls, and no difference in baseline physical activity was found [32]. However, another study of European youth and young adults with T1DM showed that despite similar levels of self-reported baseline activity, decreased VO_2 max was seen in females of all ages and in older males, with T1DM [33]. Poorer glycemic control was independently associated with decreased physical fitness as measured by VO_2 max, in addition to female sex, lower baseline activity level, higher skinfold thickness, and age. Thus, youth with target glycemic control display substantially better aerobic capacity compared with those in poor control. Finally, these authors found that in a multiple regression analysis, including age, BMI, duration of diabetes, and all subtests of physical fitness, VO_2 max was the single best predictor of variance in HbA1c levels [33]. Maintenance of a regular physical activity regimen is of particular importance as it has been observed that short-term improvements in glycemic control after a physical activity intervention may not be sustained if the activity is not continued [34].

In adults, data supports that minimal differences are seen in VO_2 max in those with well-controlled T1DM compared to controls without diabetes, but, as in youth, VO_2 max is reduced in those with poor glycemic control [35]. There also is evidence of impaired muscle oxygen delivery in poorly controlled T1DM subjects compared to well-controlled participants with T1DM or controls without T1DM [35]. In adult trained triathletes, overall those with T1DM had lower VO_2 peak but similar maximum workload compared with controls. However, those with HbA1c< 7% were as fit as those without T1DM, while those with HbA1c above this range displayed poorer peak oxygen uptake and decreased maximum workload [36].

Peak minute ventilation volumes and markers of respiratory exchange do not appear to differ in those with type 1 diabetes [37]. However it has been reported that during exercise pulmonary diffusion is lower [38], as is arterial blood oxygen saturation, and that diffusion kinetics correlate with arterial oxygen saturation [36]. However, the role of glycemic control in these variables remains uncertain.

Importantly, changes in cardiac and hemodynamic adaptations to exercise may be seen in those with T1DM, especially in those with less than optimal glycemic control. Both reducedw-

Table 19.1 Key intervention trials assessing the impact of physical activity in type 1 diabetes

Authors	Country	Year	Study type	*n*	Age (years)	Exercise intervention	HbA1C	BMI	Fitness	Lipids	CV health
Seeger et al. [26]	Netherlands	2011	Intervention	7	8–12	Aerobic, 1 day supervised + 1 day unsupervised 2 days/week			+V02 max		+brachial artery FMD
Wong et al. [102]	Taiwan	2010	RCT	28	9.5–16.4	Aerobic, unsupervised guided/phone contact 3 days/week	+ at 9 months		No effect on peak oxygen uptake		
Aouadi et al. [103]	Tunisia	2011	RCT	33	12–14	Aerobic, supervised 2 days/week, 4 days/week	+ at 6 months in 4 days/week group			+TG, LDL, HDL	
Tunar et al. [104]	Turkey	2012	RCT	31	12–17	Resistance, supervised (Pilates) 3 days/week	NS		+strength/flexibility		
Salem et al. [25]	Egypt	2010	RCT	196	12–18	Mixed aerobic and resistance, supervised 1 day/week, 3 days/week	+ in both PA groups	+weight loss, BMI, waist circ in both PA groups		+chol, TG, HDL in both PA groups	+diastolic BP in 3 days/week PA group
Heyman et al. [105]	France	2007	RCT	16	13–18.5	Aerobic, 1d supervised +1 day unsupervised 2 days/week		+fat free mass	+PWC170	+apoB/apoA-1	
Laaksonen et al. [27]	Finland	2000	RCT	42	20–40	Aerobic, unsupervised guided/phone contact 3–5 days/week	No change		+VO2 max	+chol, LDL, apoB, HDL/apoA-1	

Authors	Country	Year	Study type	*n*	Age (years)	Exercise intervention	HbA1C	BMI	Fitness	Lipids	CV health
Perry et al. [106]	New Zealand	1997	RCT	61	20–69	Mixed aerobic and resistance, unsupervised guided 3 days/ week	No change		+V02 max	+HDL	
Durak et al. [107]	United States	1990	RCT	8	31 ± 3.5	Resistance, supervised 3 days/week	+		+strength	+chol	
Fuchsjager-Mayel et al. [108]	Austria	2002	Open-parallel study	26	42 ± 10	Aerobic, supervised (cycling) 3 days/ week	No change		+V02 max, change did not persist once intervention stopped		+brachial artery FMD, change did not persist once intervention stopped

Key: + indicates a beneficial effect of exercise

stroke volume and reduced maximal heart rate are seen in adults with T1DM during exercise [39], findings that have also been shown in youth with T1DM [40]. However, these findings seem to be attenuated in those with tight glycemic control; maximal cardiac index was reduced by 31% in a study of poorly controlled adults with T1DM, but by only 16% in those with target glycemic control, compared to controls [39]. Diastolic dysfunction, more than systolic dysfunction, appears to drive the reductions in stroke volume seen in both the baseline and exercise states in those with T1DM. Reduced diastolic relaxation, reduced ventricular compliance, and reduced preload all likely contribute to reduced end-diastolic volume (EDV). EDV is reduced in youth with T1DM (mean HbA1c 8.7%) under both rest and exercise conditions compared with nondiabetic controls [40], though a clear association with HbA1c has not yet been shown to our knowledge.

Finally, tissue level characteristics affected by acute and chronic glycemia may impair tissue oxygenation and vascular adaptations to exercise. In a recent report of 21 normal weight youth with T1DM (mean HbA1c 8.2%) and 17 control youth, those with T1DM displayed calf muscle mitochondrial dysfunction compared with control youth of similar age, pubertal stage, BMI, and baseline physical activity [41]. Importantly, this abnormal mitochondrial function occurred at both moderate and submaximal exercise loads. Increased reliance on anaerobic glycolysis and reduced oxidative phosphorylation were seen, and while insulin resistance was independently related to muscle mitochondrial dysfunction, HbA1c was not.

Peripheral oxygenation may be lower in those with very high glycated hemoglobin levels due to greater oxygen affinity, potentially lowering oxygen extraction in muscle especially [42]; however, overall the effect this has on exercise adaptations during exercise is likely minimal, as most data suggests cardiac dynamics such as stroke volume and cardiac output play the most important role in determining maximal oxygen uptake. It has been shown that peripheral vascular function is compromised with flow-mediated dilatation in active youth with T1DM lower than their active nondiabetic peers [43]. This effect is seen in the most sedentary who have lower flow-mediated dilatation compared to more active youth with T1DM, who in turn have similar vascular characteristics to sedentary nondiabetic youth. Importantly, vascular function appears to improve in diabetic youth after an exercise program [26]. Finally, it has been recently reported that in youth with T1DM cardiovascular fitness is related to renal dysfunction, as defined by estimated glomerular filtration rate (GFR) [44]. Estimated GFR was independently and negatively associated with fitness, as measured by VO_2 peak, controlling for lean mass, and independent of insulin sensitivity.

Increased insulin resistance has long been known to occur in persons with T1DM as compared to nondiabetic controls with studies using the euglycemic clamp technique [45, 46]. Recent data has demonstrated that adult patients with T1DM show decreased insulin-mediated suppression of free fatty acid levels compared to controls [47]. Insulin sensitivity has also been shown to be decreased in T1DM youth, when compared to lean controls [48]. Importantly, Nadeau and colleagues showed that a reduction in exercise function (VO_2 max) is found early in the pathophysiology of diabetes, regardless of diabetes type, and is directly related to insulin resistance [48]. Insulin-mediated glucose metabolism correlated directly with VO_2 max in subjects with T1DM, controlling for baseline activity, BMI, and pubertal stage, while HbA1c and diabetes duration did not [49]. Therefore, increasing exercise to reduce insulin resistance in persons with T1DM could have numerous health benefits that are self-potentiating, including reduction of cardiovascular disease risk which is the leading cause of mortality in T1DM [50, 51].

Physiology of Exercise in Type 1 Diabetes: Glucose Uptake, Insulin and Counterregulatory Hormones

Following is a brief review of metabolic adaptations to exercise in nondiabetic individuals, for comparison with the physiologic changes that occur in T1DM. Early glucose uptake during exercise occurs mostly through insulin-independent

mechanisms via GLUT4 translocation stimulated by muscle contraction, lowering the blood glucose. In response, complex neurohormonal regulation occurs to maintain euglycemia, including less insulin-driven glucose uptake and increased gluconeogenesis and glycogenolysis mediated by glucagon, cortisol, growth hormone, and catecholamines. With exercise, muscles utilize circulating free fatty acids, muscle triglycerides and glycogen, liver glycogen, and plasma glucose, with the proportion of fuel derived from plasma glucose, muscle and liver glycogen increasing as the intensity of exercise increases. Concomitantly, insulin secretion is automatically regulated, while the counterregulatory hormones adjust to maintain euglycemia as exercise continues [14, 52]. Indeed, and importantly, some forms of intense exercise are associated with an increase in these counterregulatory responses independent of hypoglycemia. This surge may result in hyperglycemia, at least transiently.

In T1DM, however, the inability of the pancreas to produce and tightly regulate insulin concentration impairs these normal metabolic adaptations to exercise. Compared to the normal physiologic response to decrease insulin concentrations with exercise, exogenous insulin delivery lacks the dynamic adaptability and precise control found in nondiabetics and can result in excess, or too little, insulin for the given exercise state. However, insulin-independent glucose uptake continues with muscle contraction, resulting in additive mechanisms driving glucose uptake via GLUT4 transporters. In the presence of excessive exogenous insulin during exercise, hypoglycemia may ensue. Mechanistic explanations for this include inappropriate inhibition of hepatic glucose production and lipolysis, impaired counterregulatory glucagon secretion with hypoglycemia, and decreased growth hormone and cortisol release [53].

Catecholamine responses in T1DM have been demonstrated to be impaired in youth during exercise [54], and this may be accentuated by tight glycemic control [55], while a lower glucose threshold in those with T1DM may be required to trigger catecholamine release. Exercise itself also reduces subsequent counterregulatory responses to hypoglycemia – glucagon, catecholamines, and growth hormone have all been shown to be blunted after exercise [56]. Furthermore, hypoglycemia in 24–48 h prior to exercise in young athletes has been shown to blunt counterregulatory responses during exercise [57]. Gender differences in the responses to hypoglycemia after exercise [58] or to exercise after hypoglycemia [59] have been investigated with better counterregulatory responses described in women as compared to men. Obese youth may also display blunted responses to exercise as circulating lipid levels impact growth hormone responses to exercise [60]. Fat ingestion before exercise in youth has also been shown to reduce growth hormone responses to exercise [61].

Finally, local factors that impact glycemia during exercise in those with T1DM include the dose of previous rapid-acting insulin with a later peak and longer duration of rapid-acting analogue insulin seen when higher doses are given [62]. Furthermore, a possible increase in subcutaneous insulin absorption secondary to increased blood flow to the area of the insulin injection may occur. For example, injection into subcutaneous tissue in the leg prior to running leads to higher insulin concentrations in the blood with exercise and consequent hypoglycemia [63].

In contrast, insufficient insulin during exercise can lead to hyperglycemia secondary to excessive hepatic glucose output as well as impaired muscle utilization of glucose. Insulin insufficiency can also lead to lipolysis with increased free fatty acid release and thus appearance of or increase in ketonemia. Dehydration resulting from hyperglycemia and resultant osmotic diuresis may further exacerbate the severity of ketonemia. High-intensity exercise can accentuate these pathophysiologic changes as counterregulatory hormones may surge [64] which is explored in more detail below.

Exercise Type, Glycemic Excursions, and Hypoglycemia

Exercise type, intensity, and duration all play a role in blood glucose patterns during and following exercise [65–68]. Table 19.2 lists some of the

Table 19.2 Factors that impact blood glucose during exercise

↓Blood glucose	↑Blood glucose
Aerobic exercise	Resistance/interval exercise
Prolonged exercise	Sprint/short burst activity
Active insulin	Insulinopenia
Prior hypoglycemia	Excess carbohydrates
Insulin sensitivity	Excitement/adrenaline

important contributing factors to observed blood glucose excursions around exercise. Resistance and high-intensity/interval training is associated with less hypoglycemic effect during and immediately after exercise when compared with aerobic exercise. In youth with T1DM, the DirecNet group found that most participants (83%) had a drop in blood glucose by at least 25% during 60 min of aerobic exercise on a treadmill [54].

High-intensity exercise provokes a surge in counterregulatory hormones, leading to higher risk of hyperglycemia during the exercise and potentially blunting the risk of hypoglycemia during and after exercise [64]. Studies of sprint intervals incorporated into exercise found a reduction in early hypoglycemia [69]. A short maximal sprint of 10-s duration was explored as a possible counter to exercise-induced decreases in blood glucose levels; in comparison to control subjects, a sprint was associated with stabilization of glycemia and increased levels of catecholamines, growth hormone, and cortisol and reduction of hypoglycemia in the acute recovery period [70]. The decline in glucose with intermittent high-intensity exercise is less than that of moderate-intensity exercise, and blood glucose seems to remain more stable postexercise [65]. This may have implications for planning exercise in T1DM – for example, Yardley et al. found that resistance exercise performed before aerobic exercise, rather than after, resulted in less hypoglycemia during exercise. When hypoglycemia did occur following exercise, it was shorter and less severe [68]. Thus, those who perform moderate-intensity exercise without higher-intensity bursts are likely at increased risk for hypoglycemia during exercise without interventions in place to mitigate this risk. Additionally, intense exercise that significantly depletes glycogen stores increases the risk of delayed hypoglycemia following exercise [67], possibly due to the need to replenish muscle glycogen stores that are more deplete than is the case with lower exercise intensity that relies more on fat for fueling performance.

Longer duration of exercise (endurance type) requires more intervention to maintain euglycemia during exercise as energy stores are depleted and in the postexercise period as glycogen stores are replaced in the presence of increased insulin sensitivity. Those with T1DM must account for the activity length when determining carbohydrate and/or insulin adjustments. A review by Riddell and colleagues [53] provides very useful information for patients and providers, detailing the duration of common types of exercise equivalent to one carbohydrate exchange (15 g). For example, for a child with body weight of 40 kg, for every 15 min of soccer or 25 min of tennis, an extra 15 g of carbohydrate is required to maintain blood glucose levels, assuming no reduction in insulin is made. Tables and charts such as these may be extremely useful to help patients plan for known activities. Furthermore, recent ISPAD guidelines outline specific interventions that can improve glycemic excursions around exercise as mentioned above and include a table of recommended carbohydrate ingestion for various activities in the absence of insulin adjustments [13].

Delayed hypoglycemia postexercise is a well-described complication occurring most frequently 7–11 h after strenuous exercise or play [71]. When exercise takes place in the afternoon or early evening, as is often the case for school-aged children, this window of susceptibility to delayed hypoglycemia corresponds to the middle of the night. In fact, up to 75% of severe hypoglycemic events in children are nocturnal [72]. It has been shown that the glucose infusion rate (GIR) required to maintain euglycemia increases between 7 and 11 h after 45 min of bicycle exercise at 55% of VO2 max [71]. In these youth, who exercised in the after-school period, this corresponded to a higher GIR between 11 pm and 3 am when compared to that required after a sedentary day. This, of course,

is a time when it might be expected that a patient with T1DM or their parents/caregivers are asleep and not monitoring blood sugars as intensively as during the waking hours.

Furthermore, in an experiment utilizing hyperinsulinemic stepped hypoglycemic clamps, subjects with T1DM had reduced awakening from sleep during hypoglycemia as compared to subjects without diabetes, likely due to impaired sympathoadrenal responses resulting in some degree of hypoglycemia unawareness [73]. Thus, impaired sleep-related autonomic responses to low blood glucose levels coupled with imperfect insulin replacement explain the high frequency of nocturnal hypoglycemia after exercise. Hypoglycemia-associated autonomic failure in diabetes has been extensively reviewed, including syndromes of defective glucose counterregulation and hypoglycemic unawareness (and that antecedent hypoglycemia – described as a unifying concept of hypoglycemia-associated autonomic failure – can cause both) [74, 75]. These mechanisms delineate the potential value for the active individual with T1DM of real-time glucose monitoring and automated systems to reduce risk of delayed nocturnal hypoglycemia, further explored later in this chapter.

A series of experiments to further investigate the effects of exercise on youth with T1DM has been undertaken by the Diabetes Research in Children Network (DirecNet) Study Group. Youth ages 11–17 years were more likely to experience nocturnal hypoglycemia (<60 mg/dl) after an afternoon aerobic exercise session than on a sedentary day (48% vs. 28%) when insulin doses and bedtime snacks were not adjusted [76]. The authors identified that hypoglycemia was unusual on the sedentary night if the pre-bedtime glucose level was ≥130 mg/dl. Furthermore, hypoglycemia was frequent (86% of subjects) during or within 45 min postexercise when pre-exercise glucose was <120 mg/dl as compared to 120–180 mg/dl (13%) or >180 mg/dl (6%). Importantly, the study reported that 15 g of oral glucose only increased glucose concentrations by approximately 20 mg/dl and suggested that 30–45 g of carbohydrate may be a more appropriate amount for treatment of exercise-induced hypoglycemia [54]. Of note, the levels of counterregulatory hormones epinephrine and growth hormone (but not cortisol or glucagon) were marginally higher in subjects whose glucose dropped below 70 mg/dl but were clearly insufficient to prevent hypoglycemia. Further investigation of counterregulatory hormone responses to hypoglycemia found no difference in norepinephrine, cortisol, or glucagon responses to nocturnal hypoglycemia with only small increases in epinephrine and growth hormone [54].

Practical Considerations for Insulin Adjustments Around Exercise in T1DM

Several clinical trials over the past decade have provided the evidence base for a series of practical strategies to prevent hypo- and hyperglycemia during exercise with data available in both adults and youth. Figure 19.1, adapted with permission from Pivovarov et al. [77], demonstrates one potential decision tree for exercise adjustment in type 1 diabetes. Self-monitoring of glucose concentrations prior to, during, and after exercise is of the utmost importance, and all approaches must be individualized and tailored based on personal experience as there is considerable variability in exercise responses between individuals. Individual patient goals and objectives should also be considered at the beginning of a program. For example, an insulin strategy to promote an exercise goal of weight loss may be quite different (emphasizing lower insulin doses and lower carbohydrate requirements) from that of an athlete who seeks to maximize performance with maximal substrate availability and higher tissue insulin levels.

The most recent ADA guidelines recommend ingestion of extra carbohydrate if pre-exercise glucose levels are <90 mg/dL. This may depend on flexibility to lower exposure to effective "insulin-on-board" during exercise, such as may be possible when using an insulin pump, or where pre-exercise insulin doses have been appropriately reduced. Other factors that the athlete may consider if pre-exercise BGL is <90 mg/dL

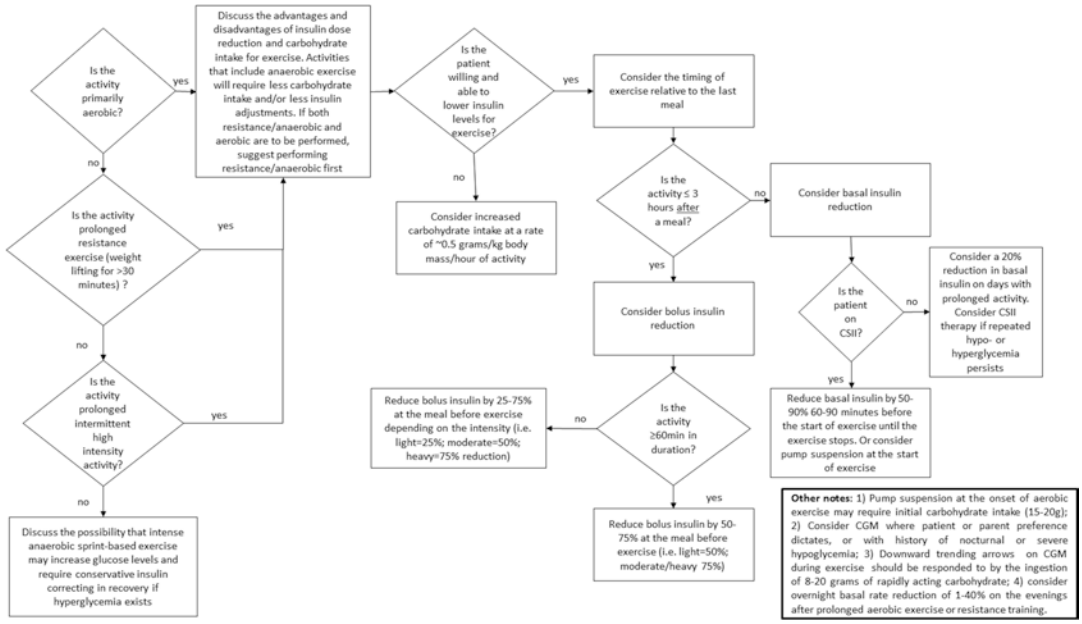

Fig. 19.1 One potential decision tree for exercise adjustment in type 1 diabetes (Adapted from Pivovarov et al. [77], with permission from John Wiley and Sons)

include the time of day exercise is done, the intensity and type of exercise (e.g., aerobic versus high-intensity intervals), and the duration of the activity. When in doubt, it is also reasonable to delay exercise until additional carbohydrate can be ingested to raise blood glucose [78], though this may be unnecessary if appropriate precautions as above are adhered to, and the ability to closely monitor peri-exercise glycemia exists. The DirecNet data suggests that a pre-exercise blood glucose of at least 120 mg/dl may be ideal [54], at least for aerobic exercise, but this may be inappropriate for high-intensity, interval, or resistance training. Prolonged aerobic exercise can lower blood glucose substantially and requires additional monitoring and ingestion of carbohydrates after each additional 30–60 min of continued exercise, perhaps in addition to considerable reductions in basal insulin. Delayed hypoglycemia can occur for up to 16 h after exercise and additional glucose monitoring during this time period is essential. Frequent glucose monitoring, or continuous real-time monitoring of interstitial glucose levels, along with each individual's past experience with exercise and ability to recognize hypoglycemia is extremely important. Snacks prior to and during exercise are often necessary to maintain euglycemia with rapidly absorbed carbohydrates required for treating hypoglycemia, whereas combining fat and protein with carbohydrate will have a more prolonged and blunted effect on glycemia. Reductions of pre-exercise insulin doses are often needed, and reductions of pre-exercise meal insulin of 50–75% have been found to reduce rates of hypoglycemia during exercise by 75% [79]. Conversely, hyperglycemia can occur with underinsulinization – sometimes related to prolonged pump suspension, excessive snacking, high-intensity exercise, or excitement (e.g., during a match vs. practice) causing increased catecholamine release.

Somewhat counterintuitively, when assessing those at highest risk of developing hypoglycemia during exercise, it appears that those who are most fit may be at the highest risk. A recent study looked at adolescents and adults with T1DM on insulin pump therapy and compared hypoglycemia rates during an exercise session in those with good fitness levels (assessed by VO_2 max) with

those with poor fitness levels [80] and found that the group with higher fitness levels had higher rates of hypoglycemia and a greater fall in glucose during exercise.

Exercise, especially in children, is often spontaneous. This can pose a challenge as reductions in insulin doses are often not possible if they are not on pump therapy and additional glucose monitoring and snacks to maintain euglycemia and safety are required. Insulin pump therapy provides the flexibility to either disconnect from the insulin infusion for up to 2 h or to set a reduced temporary basal rate of 50–75% of the usual basal rate for 30–60 min prior to and during exercise. This temporary reduction in basal rate can be continued postexercise if delayed hypoglycemia is a concern [81]. The DirecNet Study Group performed an experiment in which pump basal insulin was suspended for 2 h during a 75-min exercise session. Suspension of pump basal insulin compared to continued basal insulin resulted in significantly reduced hypoglycemia during the exercise (16% vs. 43%; $p = 0.003$). After the exercise session, however, hyperglycemia (≥20% rise in blood glucose to ≥200 mg/dl) was more frequent in the group with suspended basal insulin (27% vs. 4%; $p = 0.002$), although there was no detection of elevated blood ketones [82]. This finding points out a potential benefit of insulin pump therapy in being able to make real-time changes in insulin treatment to adjust for exercise.

An additional issue, as discussed earlier in this chapter, is to avoid injecting insulin into a part of the body that will be heavily used as exercise increases blood flow into the parts of the body that are moving, thus potentially increasing insulin uptake. A final practical consideration is to make coaches, teammates, and exercise partners aware of diabetes and provide hypoglycemia education as appropriate with easy availability of snacks, insulin, and glucose monitoring equipment. When hypoglycemia does occur, it is important to make certain that blood glucose levels rise prior to resuming the exercise.

In both children and adults, the few studies that have been performed support a reduction of 20% of basal insulin for the overnight period to prevent exercise-induced nocturnal hypoglycemia. In youth on insulin pump therapy, a 20% reduction of basal insulin for 6 h between bedtime (9 pm) and 3 am was very effective in reducing nocturnal hypoglycemia without adverse hyperglycemia. This study also found that basal insulin suspension during exercise alone reduced rates of hypoglycemia later in the night. This suggests that avoiding hypoglycemia during exercise may be beneficial in reducing risks for later hypoglycemia, consistent with the concept that "hypoglycemia begets hypoglycemia," likely due to exhaustion of counterregulatory responses [81].

Due to the mechanisms outlined above, and because of reports of ketosis [83], potentially related to excessive insulin reduction, with exercise, recommendations published by the ADA in 2015 are to avoid physical activity if ketones are present [12]. Guidelines published in 2014 by ISPAD recommend avoidance of strenuous exercise if pre-exercise glucose levels are >250 mg/dl with ketones present [13].

Of note, however, despite the practical daily challenges presented by T1DM, many examples of past and present male and female professional and/or elite athletes exist; multiple Olympic medals have been won by competitors with T1DM including in swimming and rowing. Professional leagues such as baseball, football (including the National Football League in the United States and the Australian Football League in Australia), soccer, golf, and cricket have all had athletes with T1DM among their highest-level players. Although T1DM has presented an additional challenge to these highly performing athletes, they have succeeded in managing their diabetes care regimen and training to achieve outstanding accomplishments in their sports.

Exercise, Type 1 Diabetes, and New Technologies

Advances in type 1 diabetes technology, both pharmacological and mechanical, hold substantial promise to improve both glycemic control and safety around exercise for persons with T1DM in the near-term. Insulin analogues, both

rapid acting and long acting, have enabled patients using multiple daily injection (MDI) therapy to better match their diabetes control to their lifestyle and carbohydrate intake. A new category of insulin analogues, so-called ultrarapid-acting insulins, is under development and beginning pivotal trials in the United States and Europe as of 2016. These ultrarapid-acting insulin analogues utilize additives to accelerate insulin absorption in the subcutaneous tissue helping to better match the pharmacokinetic profile of endogenous insulin [84–90]. Stable aqueous glucagon formulations are also under development for use in dual-pump systems which may aid in helping provide counterregulation [91]. These new pharmaceutical agents show early promise to more closely match nondiabetic glycemic regulation while minimizing hypoglycemia. In the context of exercise, ultrarapid insulins may have the benefit of reduced insulin-on-board time thereby reducing the burden of patients having to account for insulin taken several hours before an activity session.

Mechanical artificial pancreas (AP) devices are systems combining subcutaneous insulin infusion (CSII) pumps, continuous glucose monitors (CGM), and a closed-loop control tool which automatically adjusts the rate of insulin delivery in real-time. AP systems are based on design ideas arising from chemical engineering, mechanical engineering, aerospace engineering, and computer science [92]. As of early 2016, pivotal trials are underway or beginning for several different first-generation AP systems [93]. Most of these proposed systems are single hormone (insulin only), while others are bihormonal, combining insulin and a second counterregulatory agent (e.g., glucagon), with development of both proceeding on parallel pathways [94]. This may be especially beneficial in the exercise state given the well-described lack of counterregulatory hormone responses to hypoglycemia in T1DM during exercise [54]. First-generation AP systems will be "hybrid closed-loop" devices meaning that patients must input carbohydrate intake for meal boluses, while basal insulin delivery will be adjusted in the background by the closed-loop algorithm. Pre-pivotal studies on these systems have generally shown significantly increased percent time in target range during the day and night with decreased average daily blood glucose while at the same time decreasing hypoglycemia [94–96]. While first-generation systems do not yet capture exercise data directly, automated insulin delivery adjustment from these devices has been shown to decrease hypoglycemia after exercise [8].

Automated incorporation of exercise data into AP systems is believed to be both feasible and beneficial. Research is underway to develop exercise modules for future generations of this technology [97]. Proposed methods for capturing exercise data vary in terms of both burden and robustness of the data captured. These include real-time heart rate monitors, step counters, accelerometers, and bio-harnesses [98, 99]. Breton and colleagues have shown that adding a heart rate monitor to an AP system can significantly reduce blood glucose decline during exercise, reduce hypoglycemic events during exercise, and increase time in target range [100]. Dual-hormone systems are also being investigated for their role in exercise and to improve time in range during exercise while decreasing hypoglycemic events when compared to both CSII pump alone and single-hormone AP technology [101]. Over the next decade, it is likely that a wide variety of options will exist to assist people with T1D with all levels of exercise skill and intensity. The ultimate goal of this research is to allow these patients to fully engage in exercise with minimal burden and significantly reduced risk of hypoglycemia during and after exercise. However, exercise remains an important challenge to closed-loop devices.

Conclusions

Exercise for people with T1DM will continue to require close attention to glucose monitoring with adjustment of insulin doses and food prior to, during, and after exercise. The benefits of exercise for people with T1DM include improved cardiovascular disease risk profile, body composition, insulin sensitivity, and quality of life. There may also be an associated improvement in glycemic control, particularly in youth, while overall fitness

and even elite level performance are possible in people with T1DM, especially in the setting of target or near-normal glycemia. In those with poor glycemic control exercise capacity is impaired. Numerous clinical and research challenges remain in managing exercise safely in people with T1DM, including data to direct clinical care to maintain euglycemia (and prevent hypoglycemia) during, and after, exercise as well as technologic advances that will better adapt insulin and counterregulatory hormone responses during and after exercise to more closely mimic the normal neuroendocrine milieu. With the proper precautions, including consultation with a qualified health-care professional, exercise should be an important part of the daily life of people with T1DM; the number of highly accomplished athletes and millions of people worldwide with T1DM who exercise routinely attest to this.

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20 Exercise Programs to Improve Quality of Life and Reduce Fall Risk in Diabetic Patients with Lower Extremity Disease

Bijan Najafi, Naren Patel, and David G. Armstrong

Introduction

Diabetes is a global epidemic, and it is one of the most significant public health challenges of our day. It is estimated that 642 million people worldwide will have diabetes by 2040 [1] with 90% of them having type 2 diabetes [2, 3]. Diabetic peripheral neuropathy (DPN), a common complication of type 2 diabetes mellitus, affects up to 50% of people with diabetes [4] and increases risk for diabetic foot ulceration (DFU) and amputation [5, 6]. Deficits in sensory and motor skills lead to inadequate proprioceptive feedback, impaired postural balance, and high fall risk [7–10]. Fall-related injury risk is 15 times greater in this population compared to age-matched healthy adults [11]. Interestingly, most individuals suffering from distal sensorimotor polyneuropathy may not be aware of it [12]; and therefore, living with such conditions can significantly increase fall risk in this population. Furthermore, fall-related injuries in diabetes often trigger a vicious circle as they have potentially detrimental influence on the physical activity levels. This vicious circle of low physical activity, functional deficits, and high fall risk further increases healthcare and economic costs. The importance of decreasing sedentary time, as well as increasing time spent in physical activity, for metabolic health has also been identified [13]. If the health continues to deteriorate, foot ulcers can develop or worsen which can lead to hospitalization and ultimately lead to loss of limb [14–17]. Improved postural balance, gait, increased level of activity, and compliance to exercise recommendations can reduce risk of diabetes-related complications including lower extremity disease. Additionally, impairments in balance are key contributors to loss of physical independence and have a major impact on quality of life. This problem is magnified in DPN patients with active foot ulcers.

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Balance training is considered to be an important aspect of a fall prevention program. Several studies have demonstrated that exercise training is beneficial in improving postural balance and gait in diabetes, thereby reducing fall risk in populations [18–20]. Recent evidence also suggests that exercise causes a trend of increase in joint mobility and increased peripheral blood flow, which can reduce risks related to foot complications in patients with diabetes [21, 22]. However, on the same note, low compliance to exercise and physical activity in people with diabetes deteriorates their health and increases foot-related complication [23]. This review describes lower extremity complications associated with diabetes which may impact balance and increase risk of falling. In addition, we provide an overview of balance programs and their potential benefits and limitations for people with diabetes and foot disease.

Diabetic Peripheral Neuropathy

Diabetic peripheral neuropathy (DPN) is a serious complication of both type 1 and type 2 diabetes and is prevalent among nearly 50% of patients with diabetes over the age of 60 years [24, 25]. Symptoms of DPN include numbness, paresthesia, sharp pains, and cramps. About 30% of people with DPN will also experience muscle weakness, loss of ankle reflexes, and decreased balance and coordination.

DPN leads to sensory and motor deficits, resulting in mobility-related dysfunction. Common everyday functional task deficits related to complications in diabetes include poor postural balance [8, 26] and gait [27–29] thereby increasing fear and risk of fall in this population [29–33]. Furthermore, DPN has also been found to be one of the independent risk factors for increased risk of falls in older adults with diabetes [34–36]. Despite overwhelming evidence that older adults with diabetes have a significantly higher risk of falling than their peers, only a few studies have focused on improving balance and reducing falls in diabetic patients [35, 37–44]. Furthermore, fall-related injuries in diabetes often trigger a vicious circle as they have a detrimental influence on the physical activity levels. This vicious circle of low physical activity, functional deficits, and high fall risk further increases healthcare and economic costs. Among other factors, sedentary behavior has been reported to be associated risk of development of type 2 diabetes in healthy individuals [13, 45, 46]. If the physical activity and diabetes control deteriorate, DPN can progress, and foot ulcers can develop leading to hospitalization and possibly lead to loss of limb [14–17]. Improved postural balance, gait, increased level of activity, and compliance to exercise can reduce risk of diabetes-related complications.

Peripheral Artery Disease

Peripheral artery disease (PAD) is a common cardiovascular complication in patients with diabetes, which is characterized by atherosclerotic occlusive disease of the lower extremities [47]. PAD affects more than 202 million people globally, and its prevalence is sharply age related, rising >10% among patients in their 60s and 70s [48, 49]. It is estimated that 20% of symptomatic patients with PAD have diabetes [50], but this probably an underestimate, given that many more people with PAD are asymptomatic rather than symptomatic [47]. The most common symptom of PAD is a poor walking endurance associated with intermittent claudication [51, 52]. In addition to ambulatory limitation, PAD subjects have impairments in other domains of physical function such as reduced strength in the lower extremities, lower daily physical activity, worse self-perceived ambulatory function, lower health-related quality of life, impaired balance, and higher prevalence of falling [53]. Supervised exercise programs have been recommended as first-line therapy for treatment of claudication. These programs improve blood flow, enhance skeletal muscle metabolism and mitochondrial function, suppress inflammation, and reduce risk of falls [54]. However, poor walking endurance, pain, and ambulatory limitations are key barriers to engagement in routine exercise, in particular for unsupervised exercise and physical activities.

Benefits of Exercise in Diabetes

Balance training is considered to be an important aspect of a fall prevention program. Exercise and physical activity are also key components in the management of diabetes. Several studies have demonstrated benefits of exercise training have proved beneficial in improving postural balance and gait in diabetes, thereby reducing fall risk in populations [18–20]. Recent evidence also suggests that exercise causes a trend of increase in joint mobility, increased peripheral blood flow, improved glucose control, and improved insulin insensitivity, which can ultimately reduce risks related to foot complications in patients with diabetes [21, 22].

Types of Exercise

The conventional exercise programs for individuals with diabetes can be divided in three major categories: aerobic exercise, resistance exercise, and flexibility exercise [55].

Aerobic exercise is a physical activity, such as walking, bicycling, or jogging, that involves continuous, rhythmic movements of large muscle groups defined usually as moderate to vigorous activities and lasting for at least 10 min at a time [55]. Several clinical practice guidelines recommend that all patients with diabetes obtain at least 150 min of aerobic exercise per week [56]. Several studies have been suggested that moderate to high levels of aerobic physical activity are associated with substantial reductions in morbidity and mortality irrespective of gender or type of diabetes [55]. In addition, aerobic exercise can improve cardiorespiratory fitness and slow the development of peripheral neuropathy [57].

Resistance exercise is a physical activity involving brief repetitive exercises with weights, weight machines, resistance bands, or one's own body weight (e.g., push-ups) to increase muscle strength and/or endurance [55]. Although almost every clinical practice guideline recommends that adults with diabetes perform resistance training at least 2–3 days per week [55, 58], resistance training has tended to receive much less attention than aerobic training in individuals with diabetes [56]. However, recent studies highlight the additional values of resistance exercise in addition to aerobic exercise in individuals with diabetes in particular for improving glycemic control, decreasing insulin resistance, increasing muscular strength, increasing lean muscle mass, increasing bone mineral density, enhancing functional status, reducing risk of falls, and reducing vulnerability to trauma due to falls [56].

Flexibility exercise is a form of activity, such as lower back or hamstring stretching, that enhances the ability of joints to move through their full range of motion [55]. Some types of exercise, such as yoga, can incorporate elements of both resistance and flexibility exercise. To date, research on flexibility exercise (without component of aerobic and/or resistance exercise) is not as extensive or as definitive as the evidence for aerobic and resistance exercise [55].

Current exercise programs could be divided to supervised and unsupervised programs. In addition, each category could be divided to weight-bearing and non-weight-bearing exercise programs.

Supervised Versus Unsupervised Exercise Programs

Several systematic reviews highlighted the superior effectiveness of supervised exercise programs compared to unsupervised exercise programs. For example, a systematic review study by reviewing 47 randomized control trials ($n = 8538$ adult participants with type 2 diabetes) in which exercise programs including supervised training (i.e., aerobic or resistance or a combination of both) and unsupervised training (physical activity advice) were compared to control group found that supervised programs improved glycemic control in adults with type 2 diabetes, whether or not they included dietary co-intervention. However, unsupervised programs only improved glycemic control if there was concomitant dietary intervention [59]. However, the major barriers in providing supervised training are associated cost and the lack of insurance

coverage for such programs. The recent approval of the Diabetes Prevention Program for Medicare recipients may change this barrier, but it is unclear how it will be implemented. Additional patient- and physician-related factors may also limit the use of supervised exercise including physician referral, patient willingness to participate (see chapter on sedentary behavior and behavior change), availability of programs, time constraints and logistical issues, and medical comorbidities. Furthermore, patients with foot ulcers or rest pain or those who are planned to undergo surgery should defer exercise training until their condition has been treated and stablished [54].

Weight-Bearing Versus Non-weight-Bearing Exercise

Although considerable research has documented the benefits of exercise training for those with diabetes, little research has examined the effects of exercise among those with foot disease, probably due to concerns regarding the potential injuries due to lack of foot sensation caused by peripheral neuropathy [60]. The most common contributor for diabetic plantar ulcers is high plantar stresses in the presence of sensory neuropathy and foot deformity. There is concern that weight-bearing (WB) exercise or extensive aerobic activities could increase the risk of plantar ulcers, which is hard and costly to heal. On the other hand, inactivity may contribute to the deconditioning of the skin and lowering tolerance for WB activities. Non-weight-bearing (NWB) exercise performed could be alternative and effective strategy for improving balance as well as tolerance to WB activities in senior diabetes patients and thus could be recommended for those who may be at high risk of plantar ulcers during WB activities. In a randomized controlled trial of WB versus NWB exercise for patients with diabetic peripheral neuropathy [60], the WB group showed greater gains over time in 6-min walk distance and average daily step count, but the NWB showed greater gains over time in hemoglobin A1c values [60]. The NWB group also showed gains in range of joint motion, reductions in depression, and levels of participant satisfaction and perception of benefit on par with the WB group. Both groups also reported that they checked their feet more frequently after the exercise program than before, which could be beneficial to prevent ulcers. Finally, no skin breakdown injuries were reported in the NWB group, while 8% of participants in the WB group had a skin breakdown injury during the course of the exercise program. This evidence suggests that if an individual cannot or will not do WB exercise, they can still benefit from NWB exercise. If the NWB exercises are designed correctly, they can improve proprioception and kinesthesia to reduce fall risk and enhance blood flow to help prevent foot-related complications like ulcers.

Barriers to Exercise Training in Seniors with Diabetes

Conventional fall prevention exercise strategies may not well suited for patients with diabetes and foot disease because even moderate conventional exercise regimes can easily overtax them. In addition, these patients may not be able to perform exercises correctly and therefore may need visual feedback during exercise, which is critical given the impaired proprioception associated with neuropathy [61–63]. Furthermore, the selection of exercise modalities and intensities must avoid excessive plantar loading to avoid the risk of foot complications; thus, the exercise program should be tailored with respect to functional ability of patients and their level of risk for diabetic foot ulcers [64–66].

Largely because of peripheral neuropathy and loss of protective sensation which impact almost 50% of people with diabetes in particular in older age, lower extremity complications of diabetes constitute a major public burden in both the developed and developing world and affect 15–25% of those with peripheral neuropathy [67–70]. Due to peripheral neuropathy, the diabetic foot wound occurs most frequently when pressure and shear (cycles of stress) are multiplied by activity (episodes of initiating movement, walking, and standing) [71, 72].

Management of physical activity and its overall organization in patients with diabetic foot disease is poorly understood [72–75]. Thus, clinicians are cautious about advising extra activity to their patients with active diabetic foot ulcers (DFU) based upon a concern about excessive foot loading causing a delay with healing of DFU [76, 77]. However, the published data regarding this association are not entirely clear. Furthermore, there are few if any data evaluating the role of prolonged low-grade pressure on healing.

Decreased adherence to exercise recommendations and low motivation to exercise are another critical issue that is exacerbated in individuals who suffer from deconditioning due to habitual low physical activity behavior or lower extremity issues. In particular, weight-bearing exercises do not incorporate visual feedback of body center of mass and/or lower extremity position, which is critical given the impaired proprioception associated with neuropathy [61]. A recent review of fall prevention reported that exercise was the most promising approach for treating balance dysfunction in patients with diabetes [18, 78]. However, selection of intensity and type of exercise is crucial as excessive plantar loading can be associated with further foot ulceration [64, 65], given these patients are at high foot risk. Therefore, there is need to explore alternative approaches to increase physical activity and functional status in high-risk individuals that are motivational and fun while managing the risk.

Exergaming in Diabetes

With advancements in technology human-machine interface and virtual reality techniques, the use of game-based exercise programs or exergame has gained popularity as an alternative to conventional exercise for training of motor control in the elderly [62, 63, 79–82]. Benefits include concordance of visual and proprioceptive information, salient feedback from joint movement, as well as activation of motor-related areas of the brain [83, 84]. The interactive feature of these technologies allows for the design of game-based exercise programs that are personalized to the level of ability. This individualized approach avoids overtaxing people with limited functional mobility as well as managing the risk of plantar ulcers.

Barriers to conventional exercise in diabetes can be “lack of time” or “lack of mind to do it” [23]. Therefore, strategies to increase motivation are paramount to engage diabetes patients in regular exercise. Introduction to an enjoyable and motivational exercise program can motivate seniors with diabetes to engage in routine exercise. Exergame programs can fill the engagement gap by including entertainment features and providing different level of difficulties tailored based progress in performing each exercise task similar to usual games. In addition, they incorporate effective reward-based feedback about progress in motor performance, which could improve perception of benefit and enthusiasm to do it on regular basis [62, 82].

The exergame strategy is promising but not yet tailored to or tested in people with diabetes. However, commercially available exergame programs (Fig. 20.1) based on either force platform (e.g., Nintendo Wii Balance Board, Fig. 20.1b) or camera-based systems (Microsoft Kinect, Fig. 20.1a) are limited to either narrow force platforms (Fig. 20.1b) which may not be ideal for individuals with diabetes due to increased body weight and limited joint mobility or require continuous unobstructed sight of line and often unsuitable for older adults [79, 85, 86]. For example, while Kinect uses a low-cost camera to capture the subject’s motion and, thus, may be used as a low-cost method for an exergaming purpose, it needs a distance of at least 6 ft (~1.83 m) between the camera and subject. For older adults, this distance could be too far to see the computer screen and execute the tasks. Additionally, some of the commercially exergaming devices detect only movement of the controller and do not necessarily require participants to exert whole body movement which might not be ideal adaptive approaches for rehabilitation [80, 87]. Further, the options available to tailor the games for specific population group or individuals are limited as visual feedback is intended for gaming or fun purposes only [88, 89] rather than accuracy of performance or motor error feedback that

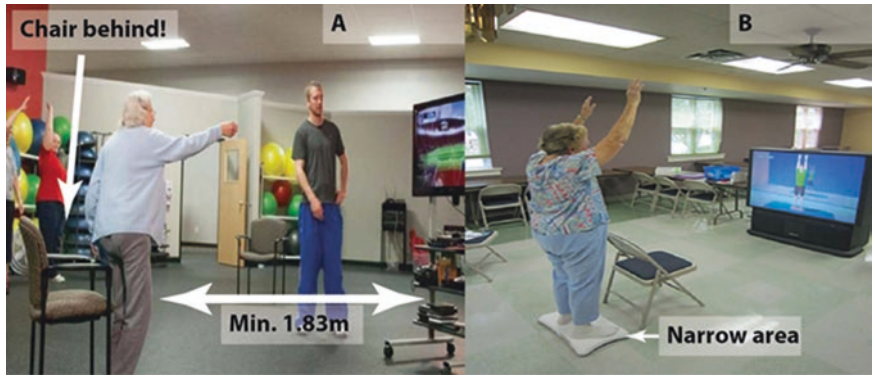

Fig. 20.1 Conventional exergame platforms may not be suitable for seniors who suffer from diabetes and have poor balance. For example, the exergame platform based on motion tracking cameras (**a**) need to have continuous unobstructed sightline thus limiting the usage of chair in front of the user, which is often required to avoid falling and give confidence to perform exercise tasks. In addition, it is often required a distance of at least 6 ft (~1.83 m) between the camera and subject, which could be problematic for those seniors with poor vision. Other exergame programs based on force platform (**b**) have also their own limitations. They are unable to provide visual feedback from body joint positions, and their narrow base of support makes it unsuitable for obese patients and those with high fear of falling, who may require wide base of support to safely perform exercise tasks

enhances learning. Biomechanical validation studies have also reported limited accuracy of such systems [90]. A tailored exergaming paradigm specifically for patients with diabetes needs to be developed and implemented that meets the capabilities of patients and maintains engagement.

Wearable Sensor-Based Exergaming

Thanks to recent advances in miniaturization of electronic circuits and mobile technologies, wearable technologies based on inertial sensors (e.g., accelerometer, gyroscope, and magnetometer) have provided a new avenue for accurately detecting and monitoring body motion including real-time tracking of body joint under free conditions and without use of traditional motion tracking cameras or other stationary motion tracking systems [78]. Unlike laboratory-based instruments, which need a dedicated controlled space, the wearable sensors can be used just about anywhere including at home [91]. These are highly transportable and do not require stationary units such as a transmitter, receiver, or camera. In addition, these sensors are inexpensive compare to sonic, magnetic, and optical motion capture devices [91]. They are easy to set up and use and do not require highly skilled operators. Wearable sensors can be used in real time, since the processing phase of detected signal is much shorter than the computing time of some standard systems using image processing and marker tracking algorithms [91]. In particular, combination of multiple accelerometers, angular rate sensors (gyroscopes), and magnetometer shows a promising design for a hybrid kinematic sensor module for measuring the 3D kinematics of different body segments [92]. These sensors incorporated with a high-speed data acquisition system enable measuring and recording of 3D body segment motion with sample frequency (up to several hundred hertz) with lower cost than camera-based systems. The high sample frequency is essential for virtual reality and exergaming applications, where creating an interactive human-machine interference is required to administer different exercise tasks, providing timely feedback about accuracy of execution of each motor task and providing timely reward-based feedback to engage the user and evaluate progression in motor performance, which is required to decide about level of complexity that user could tolerate. Another unique advantage of wearable technology is the ability of assessing gait and balance [78, 92, 93], which could be potentially used as

an objective outcome to evaluate and report the benefit of the exergame program in individual with diabetes. Additionally, wearable technologies allow designing exergame programs during both weight-bearing and non-weight-bearing conditions (Fig. 20.2) and incorporate both motor and cognitive exercises.

Wearable inertial sensors have significant advantages over competing technologies to provide visual feedback. Most virtual reality strategies for improving balance are based on biofeedback signals from force platforms, which reflect the center of pressure under the feet. This feedback modality does not reflect the ability of an individual to perceive lower extremity position errors and hence may not improve proprioceptive feedback [78, 94, 95]. Furthermore, the narrow platform surface provided by commercially available systems is often unsuitable for diabetic patients who have a fear of falling [96] and who may require a wide base of support to perform the exercises. Unlike camera-based systems, wearable sensors also do not require a continuous unobstructed sight line.

Recently exergaming using wearable technologies has been widely implemented in various patient populations, mostly using modifications of off-the-shelf commercial inertial sensors. These programs have been demonstrated to be effective in senior people with high risk of falling including those who were suffering from DPN, chemotherapy-induced peripheral neuropathy, and frail older adults [62, 63, 81, 82, 97].

Recent randomized control trial study from our group has demonstrated effectiveness of using wearable technology and exergame platform, which incorporates a series of repetitive ankle-reaching tasks and virtual obstacle to improve balance in individuals with confirmed DPN. Thirty-nine older adults with DPN were recruited (age, 63.7 ± 8.2 years; BMI, 30.6 ± 6 kg/m^2, 54% female) and randomized to either intervention (IG) or control (CG) group. The IG received sensor-based interactive exercise training tailored for people with diabetes (4 weeks/twice a week). Exercise focused on weight shifting and crossing virtual obstacles (Fig. 20.3). Body-worn sensors were

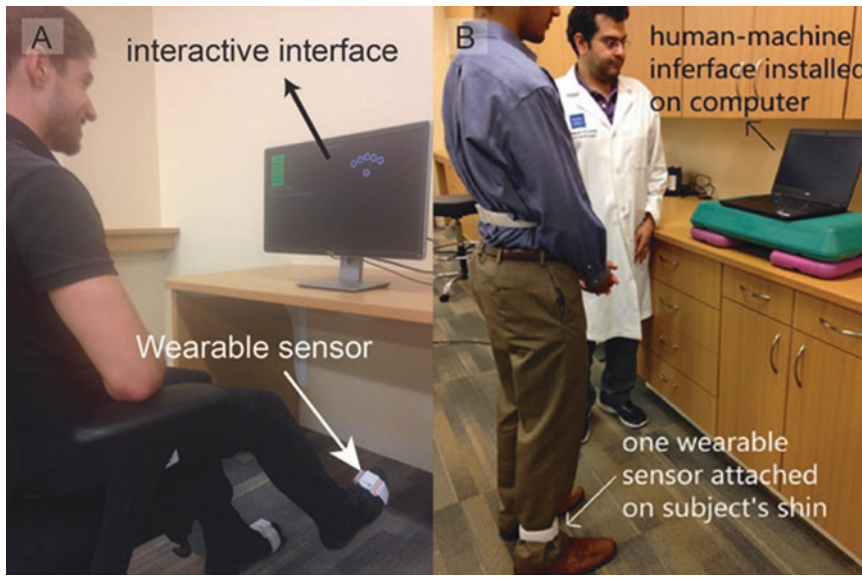

Fig. 20.2 Using wearable technologies allows creating cost-effective exergame programs for both non-weight-bearing (**a**) and weight-bearing (**b**) exercises. It also allows providing feedbacks from any joint of interest including the feet, ankle, knee, and upper body

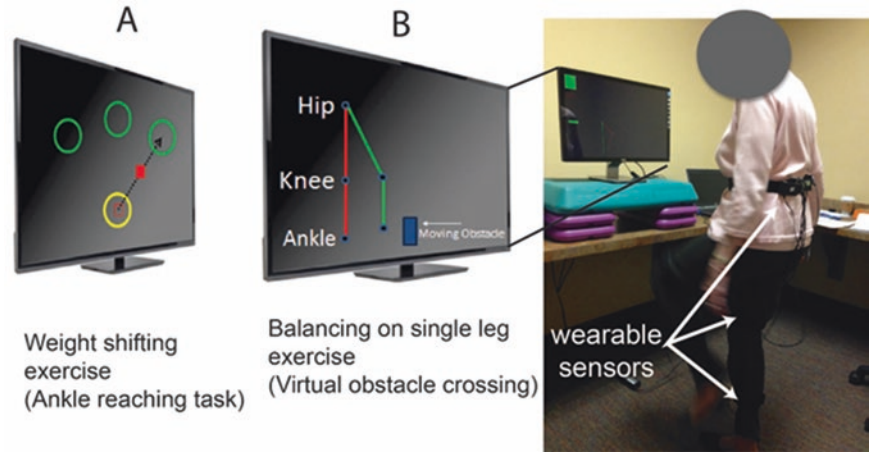

Fig. 20.3 A typical example of weight-bearing exergame platform to enhance balance in seniors suffering from DPN. The program includes repetitive and interactive exercises in a safe virtual environment including weight shifting (**a**) and virtual obstacle crossing (**b**) exercises. The simplicity of interface allows users to focus on joint of interest and better perceived motor errors, which are considered as major source of motor learning

implemented to acquire kinematic data and provide real-time joint visual feedback during exercise. Outcome measures included changes in center of mass (CoM) sway and ankle and hip joint sway measured during eyes open and closed balance test at baseline and post-intervention. In addition, spontaneous daily physical activities were monitored in a 48-h period at baseline and follow-up. Results of this randomized controlled trial demonstrate that people with diabetic peripheral neuropathy can significantly improve postural balance and activity level from the proposed exergame program. Specifically, compared with CG, patients who performed sensor-based exercise training significantly reduced CoM sway (59.8%, $p = 0.009$), ankle sway (62.2%, $p = 0.008$), and hip joint sway (72.4%, $p = 0.017$) in the IG during eyes open balance test. During eyes closed measurements, ankle sway reduced significantly for IG group (62.41%, $p = 0.037$). The number of steps walked showed a substantial but nonsignificant increase (+27.68%, $p = 0.064$) in IG following training. The results promote use of wearable technology in exercise training. However, future studies are warranted to demonstrate whether such technologies are feasible for home application with no or minimum supervision.

Summary

Diabetes and related complications can significantly compromise postural stability of patients, which in turn could profoundly affect people's ability to mobilize, to live long lives, and to exercise. Disturbances in executive function, particularly within the dimension of time sharing, may also contribute to gait abnormalities, increased risk for falls, and functional impairments in patients with diabetes. Exercise interventions have been shown to improve mobility and balance, reduce the incidence of falls, and improve peripheral blood flow among individuals with diabetes and associated complications such as peripheral neuropathy. However, uptake of exercise programs for senior individuals with diabetes has been limited. Recent exercise programs have been proposed to address the factors limiting uptake and adherence of therapeutic exercise such as game-based exercise (exergaming), which could motivate people with diabetes to be engaged in regular exercises tailored to their level of functional ability and their risk for diabetic foot ulcers. Such exercise programs may also address the current challenges associated with nonsupervised training via virtual supervision of exercise and provision of real-time feedback about accuracy and efficiency of executing each

exercise task. Advances in the design of wearable technologies have also opened new avenues to design tailored and cost-effective exergaming platform, which could effectively enhance balance and improve physical activities in people with diabetes and lower extremity disease.

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Cardiac Rehabilitation for Patients with Diabetes Mellitus

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Ray W. Squires and Kerry J. Stewart

Cardiac rehabilitation is a well-established and valuable component in the care of patients with most forms of cardiovascular disease. Evidence-based guidelines from the American Heart Association, the American College of Cardiology, and the American Association of Cardiovascular and Pulmonary Rehabilitation award cardiac rehabilitation a class I recommendation (the treatment is effective and should be performed) for patients with many forms of cardiovascular disease [1, 2]. Exercise training for patients with diabetes, irrespective of the diagnosis of cardiovascular disease, is also a class I recommendation [3].

Cardiac rehabilitation involves all of the accepted factors in the secondary prevention of adverse cardiovascular outcomes after an initial cardiovascular event, including exercise training, coronary risk factor identification and optimal modification, counseling and education regarding cardiovascular disease with special emphasis on avoidance of tobacco and healthy nutrition, emotional support, identification and treatment of depression, adherence to medications, and awareness and proper response to symptoms [4]. Cardiac rehabilitation programs generally utilize a variety of healthcare professionals functioning as an interdisciplinary team to provide comprehensive secondary prevention: physician (medical director), exercise physiologist or physical therapist, registered nurse, registered dietitian, and social worker/psychologist. The cardiac rehabilitation team routinely communicates with the patients' other healthcare providers including their primary care provider, cardiologist, internist, or endocrinologist. Cardiac rehabilitation typically begins during hospitalization for patients with an acute coronary event or after cardiothoracic surgery. However, hospital length of stays are typically only 2–6 days for most patients, and therefore, outpatient cardiac rehabilitation programs are the primary venue for providing these services. Outpatient cardiac rehabilitation ideally begins within one to 2 weeks, and not later than 1 month, after hospital discharge. The most common though not exclusive format for cardiac rehabilitation is three sessions per week over 3 months and includes supervised exercise training, education and counseling, and group support by interacting with other patients with cardiovascular diseases.

The Centers for Medicare and Medicaid Services and the vast majority of private insurers in the

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United States provide financial coverage for cardiac rehabilitation for the patients with the following diagnoses: acute myocardial infarction, percutaneous coronary intervention, coronary artery bypass surgery, stable angina pectoris, heart valve surgery (traditional replacement techniques, transcatheter aortic or mitral valve replacement [valve in valve], or various forms of valve repair), heart transplant, and chronic heart failure (CHF) with reduced left ventricular ejection fraction (≤35%, including patients with ventricular assist devices) [5, 6]. Some private insurers will also cover cardiac rehabilitation for patients with CHF with preserved left ventricular ejection fraction [7].

The established benefits of cardiac rehabilitation include [4, 8–14]:

- Increased exercise capacity, both aerobic and muscle strength and endurance
- Improved symptoms of fatigue, angina pectoris, and dyspnea
- Enhanced control of modifiable coronary risk factors, such as tobacco use, dyslipidemia, hyperglycemia, hypertension, and obesity
- Decreased mortality of 20–45% as reported in randomized, controlled trials and more recent observational studies using propensity matching statistical techniques to simulate randomization since further randomized trials are considered unethical given the class I indication for cardiac rehabilitation
- Better adherence to medical and lifestyle therapies for secondary prevention
- Reduced hospital readmissions
- Positive changes in vascular endothelial function and metabolism resulting from exercise training
- Emotional support for patients and families
- Identification and management of depression and other psychological conditions
- Coordination of care between patients' healthcare providers

Prevalence of Diabetes Mellitus in Cardiac Rehabilitation Programs

Diabetes is a potent and prevalent coronary risk factor. After an acute coronary event, patients with diabetes have a worse prognosis than patients without diabetes [15, 16]. Moreover, 50% of deaths in persons with diabetes are due to coronary heart disease [17]. The prevalence of diabetes in patients who participate in cardiac rehabilitation exceeds that of the general population without heart disease. In a cohort of 2991 patients with myocardial infarction who participated in cardiac rehabilitation in Olmsted County, Minnesota, 22% had a history of diabetes [14]. Estimates of the prevalence of diabetes in cardiac rehabilitation program participants range between 17 and 27%, and the prevalence has increased approximately 50% over the past decade [14, 18, 19].

The vast majority of patients with diabetes in cardiac rehabilitation programs have the type 2 form of the disease. While most patients with diabetes who participate in cardiac rehabilitation are aware of their diagnosis, it is not uncommon for the diagnosis of diabetes to be made at the time of hospitalization or during participation in cardiac rehabilitation. Thus, some patients who participate in cardiac rehabilitation may receive concurrent diagnoses of two serious chronic diseases, cardiovascular disease and diabetes. Potential complications of diabetes, such as blindness, nephropathy, peripheral neuropathy, peripheral artery disease and autonomic neuropathy, sinus tachycardia, orthostatic hypotension, absent angina pectoris with myocardial ischemia, peripheral artery disease with claudication, and limb amputation, may make participation in cardiac rehabilitation more challenging for some patients [20, 21].

Roles of Cardiac Rehabilitation Programs/Professionals in Patients with Diabetes

Cardiac rehabilitation professionals are experienced in collaborating with a variety of healthcare professionals who are involved in the care of cardiac rehabilitation patients outside of the cardiac rehabilitation environment. They should function as members of the diabetes management team for patients enrolled in cardiac rehabilitation [20]. Cardiac rehabilitation professionals interact closely with patients several times per month and have specific training and experience in secondary prevention of cardiovascular disease, including

identification of new symptoms, medication side effects, and comorbid conditions. As such, they are well qualified to provide care for their patients with comorbid conditions, such as diabetes. Specific roles for these professionals in the care of patients with diabetes include:

1. Assist in identification of new cases of diabetes. As mentioned previously, patients may receive the diagnosis of diabetes at the time of their hospitalization for cardiac disease or during routine blood testing during cardiac rehabilitation.
2. Monitor blood glucose in diabetic patients who start an exercise program.
3. Identify hypoglycemia or hyperglycemia.
4. Assist in treatment of hypoglycemia or hyperglycemia.
5. Supervised exercise training.
6. Referral to a Certified Diabetes Educator or registered dietitian.
7. Reinforcement of self-management skills and lifestyle education.
8. Facilitation of influenza and pneumococcal vaccination.
9. Identification and modification of coronary risk factors and diabetic goals for treatment through the following:
   (a) Provide medical nutrition therapy.
   (b) Assist with diabetes self-management education and counseling.
   (c) Help patients adequately control hypertension and dyslipidemia.
   (d) Provide the environment to facilitate body fat loss.
   (e) Reinforce tobacco avoidance.
   (f) Provide psychological assessment, especially screening for depression
   (g) Strive for adherence to cardioprotective medications, especially antiplatelet agents, statins, and angiotensin-converting enzyme inhibitors.
   (h) Assist in routine foot care for prevention of ulcers.
   (i) Identification of new or worsening symptoms, medication side effects, and comorbid conditions.

The cardiac rehabilitation team can provide important specific guidance for the management of diabetes, including the seven self-care behaviors promoted by the American Association of Diabetes Educators [22]:

1. Healthy eating
2. Physical activity
3. Monitoring blood glucose
4. Taking medications
5. Problem-solving
6. Reducing health risks
7. Healthy coping skills

Exercise Training

While cardiac rehabilitation programs provide a wide array of comprehensive services for secondary prevention of cardiovascular disease, exercise training is a visible and important factor in secondary prevention. Exercise is a key component in the treatment of both cardiovascular diseases and diabetes. Cardiac rehabilitation provides a medically supervised environment for patients to learn about exercise, progress in their exercise program safely, experience success in attaining an adequate exercise regimen, and the opportunity to identify the risks of hypoglycemia or hyperglycemia in diabetic patients who begin and gradually progress an exercise training program.

Though exercise participation in patients with diabetes and cardiac disease is considered safe and effective, health professional should recognize the inherent risks in these patients, [20, 23] which include:

- Major adverse cardiovascular events, such as acute myocardial infarction, sudden cardiac death, and symptomatic dysrhythmias; fortunately, these risks are extremely rare and the benefits of exercise training far outweigh these risks.
- Musculoskeletal injury.
- For patients with peripheral neuropathy and decreased sensation; skin breakdown of the feet and foot ulcers.
- Hypoglycemia and hyperglycemia.
- For patients with autonomic neuropathy: may be unable to experience angina pectoris during periods of myocardial ischemia; orthostatic or post-exercise hypotension, resting tachycardia,

and inability to increase heart rate appropriately during exercise.
- For patients with proliferative retinopathy: risk of vitreous hemorrhage and retinal detachment.

Exercise training results in improvements in many important variables for patients with diabetes, such as [23–25]:

1. Improvement in exercise capacity documented with graded exercise testing: 26% increase in estimated peak METs and 13% increase in directly measured VO_2 peak.
2. Reduced fasting blood glucose; the effects of exercise in lowering blood glucose persist for 48–72 h.
3. Improvement in Hg A1c of approximately −0.8%.
4. Improved insulin sensitivity and reduction in amounts of diabetic medications.
5. Reduction in body mass and body fat of 5.1% and 15.0%, respectively. Even modest weight loss may provide important clinical benefits listed above.
6. The improvements in glycemic control listed in #2 and #3 are independent of weight or body fat mass loss.
7. Improvement in systolic blood pressure of −6 mmHg and diastolic blood pressure of −1 mmHg.
8. Decrease in serum triglycerides of 27 mg/dL, increase in high-density lipoprotein cholesterol of 5 mg/dL.

Exercise training in an outpatient cardiac rehabilitation program for diabetics, as for all cardiac patients, should begin as soon as possible after hospital discharge, ideally no later than 1–2 weeks after leaving the hospital. Graded exercise testing by and large is recommended for all patients with cardiovascular diseases, including diabetics, prior to initiating an exercise program [23, 26]. The benefits of graded exercise testing include documentation of exercise capacity, assessment of the electrocardiographic, blood pressure, and symptom responses to exercise such as angina pectoris and dyspnea, and the presence and severity of myocardial ischemia. Graded exercise testing provides a sound basis for an individualized exercise prescription. However, there are medical system and local practice factors which may influence the decision to require a graded exercise test prior to beginning an exercise program. An alternative to graded exercise testing is performance of the 6-min walk test as an indication of tolerance of exercise [4].

Standard physiologic measurements and assessments during supervised exercise sessions in cardiac rehabilitation include continuous electrocardiographic telemetry to determine heart rate and rhythm; blood pressure measurement at rest, during each form of exercise, and during recovery; perceived exertion using the Borg Ratings of Perceived Exertion Scale [27] to assess subjective patient effort; symptoms of angina, dyspnea, lightheadedness, unusual fatigue, and lower limb claudication; and for diabetics taking insulin or an insulin secretagogue, warning symptoms of hypoglycemia.

Exercise prescription should be individualized for each patient, in terms of modes of exercise, warm-up and cooldown, duration of exercise, intensity of effort, beginning duration and intensity, as well as progression of duration and intensity. Table 21.1 provides general guidelines for the components of the exercise prescription. Aerobic, resistance, and flexibility exercise is prescribed. Balance improving exercises may be prescribed, based on patient need. Typical forms of aerobic exercise include walking (track or treadmill), upright or recumbent stationary cycle, combination arm-leg cycle, recumbent stepper, arm ergometer, elliptical trainer, rower, and walk/jog intervals or continuous jogging for more fit patients. Patients are generally encouraged to perform more than one type of aerobic exercise. Modes of resistance exercise include elastic bands, hand weights, free weights, weight machines, stability ball, and calisthenics using the patient's own body weight as resistance.

After a cardiac event, patients should begin exercise training conservatively. Typically, patients perform 10 min of warm-up activity including low-intensity aerobic exercise, such as walking, at less than 40% of heart rate reserve or a Rating of Perceived Exertion less than 12, static stretching of

Table 21.1 Summary of exercise prescription for cardiac rehabilitation, including patients with diabetes (Adapted from references [23, 24])

Type of exercise	Frequency	Intensity	Duration
Aerobic	3–7 days/week	Moderate, 40–59% of HRR or VO_2 peak	150+ min/week
		or RPE 12–13	30–45 min/session
Or in combination with			
Aerobic	3 days/week	Vigorous, 60–84% of HRR or VO_2 peak	90 min/week
		or RPE 14–16	20–30 min/session
And			
Resistance	2–3 days/week	RPE 12–14, 50–84% of 1RM, 10–15 repetitions without straining, exercises for the major muscle groups	30+ min/week

Source: American Heart Association, Inc.
HRR heart rate reserve (peak heart rate from graded exercise test minus rest heart rate),*VO_2 peak* oxygen uptake directly measured during graded exercise test, *RPE* Borg Perceived Exertion Scale, 6–20 version, *1RM* one repetition maximum

the major muscle groups to improve flexibility, and upper extremity range of motion exercises for patients with a median sternotomy. Moderate-intensity aerobic exercise usually begins at 5–10 min per session, although patients who have been exercising independently without symptoms or undue fatigue may perform 20 min at the first session. Cooldown is performed after the moderate-intensity aerobic exercise and includes low-intensity aerobic activity for 5 min and static muscle stretching. Cardiac rehabilitation professionals monitor and gradually increase the dose of exercise according to individual patients' capacity over a period of weeks. The duration of moderate-intensity aerobic exercise may be increased by 1–5 min per session, as tolerated, with a goal of 30–45 min per session (150+ min per week). Exercise frequency is five to seven sessions per week (three supervised sessions and at least two independent sessions per week with no more than two consecutive days without exercise). The intensity of exercise should be gradually increased as exercise tolerance improves to higher levels. Vigorous aerobic exercise training may be gradually incorporated into the exercise prescription when patients can easily accomplish 20 continuous minutes of moderate-intensity exercise. An interval training approach to incorporating vigorous-intensity exercise (alternating brief periods of higher-intensity and moderate-intensity exercise during an exercise training session) has been demonstrated to be more effective in improving aerobic capacity than traditional training and is becoming more prevalent in cardiac rehabilitation programs [28].

In patients who are motivated to lose a large amount of body fat, meticulous attention to permanent changes in dietary habits is required. In addition, in order to increase energy expenditure, exercise duration should be increased to 45–60 min with a frequency of five to seven sessions per week, at a moderate intensity, to achieve an exercise energy expenditure goal of 3000–3500 kcal per week. Such an approach has been shown to double the fat mass loss compared to standard cardiac rehabilitation exercise amounts [29].

Patients with lower extremity peripheral arterial disease, with or without symptoms of claudication, should spend at least a portion of their exercise time performing treadmill walking to the point of at least moderate discomfort or fatigue to improve walking ability [30]. If patients with peripheral artery disease are substantially limited by claudication and cannot achieve an appropriate target heart rate or Rating of Perceived Exertion with treadmill walking, a portion of their program should include combination arm and leg exercise, such as arm-leg cycle ergometer or recumbent stepper with arm involvement [21].

For patients with limited endurance, beginning with intermittent exercise (exercise for 3–7 min at

a comfortable intensity, rest for 3–5 min, repeat three to four times per session gradually increasing exercise duration and decreasing rest time over 2–5 weeks) is a helpful strategy [26].

A major challenge for patients who participate in cardiac rehabilitation for a few months and then graduate from the highly structured program is maintaining the recommended lifestyle changes over a lifetime. Many cardiac rehabilitation programs offer participation in the form of a "maintenance" exercise program. Another proven technique is periodic return visits with the cardiac rehabilitation staff to assess compliance with exercise, healthy nutrition, weight control, blood lipid and blood pressure control, as well as medication compliance [31].

Exercise Pearls for Patients with Diabetes Mellitus

The following are practical suggestions for dealing with specific diabetic complications [23]:

- Microvascular disease: in patients with proliferative retinopathy, avoid activities associated with the Valsalva maneuver which may greatly elevate systolic blood pressure and result in further retinal trauma.
- Diabetic nephropathy: recent evidence indicates that exercise does not need to be restricted in any way for these patients.
- Severe peripheral neuropathy: increases the risk of skin breakdown and ulceration, as well as development of a Charcot joint, due to reduced ability to sense pain; non-weight bearing forms of exercise are recommended to reduce this risk.
- Encourage inspection of feet for evidence of skin breakdown in patients beginning an exercise program; instruct patients to use proper fitting athletic shoes and cotton socks.
- Peripheral artery disease: emphasize foot care and avoid high-impact activities to minimize risk of skin ulceration.
- Patients too frail to accomplish the recommended amounts of exercise: some of the benefits of exercise are available for these patients with lesser amounts of exercise.

Managing Blood Glucose in Cardiac Rehabilitation Exercise Programs

There are no formal guidelines for the frequency of measurement of blood glucose for diabetics in the cardiac rehabilitation setting [3, 32]. For patients new to exercise training, it is prudent to review each patient's blood glucose log looking for evidence of hypoglycemia. It is also reasonable to measure blood glucose before and after exercise for the first few sessions to assess individual patient responses to an exercise session and to identify patients who should continue to monitor blood glucose with exercise sessions. Pre-exercise blood glucose should be measured immediately before exercise. Post-exercise blood glucose should be measured within 15 min of cessation of exercise.

The following factors are associated with an increased likelihood of exercise-related hypoglycemia [23]:

1. Diabetic medications which include various forms of insulin and insulin secretagogues, such as sulfonylureas and meglitinides. Current other non-insulin diabetic medications are unlikely to cause hypoglycemia.
2. Patients with consistently low blood glucose levels or variable blood glucose measurements.
3. Longer duration type 2 diabetes.
4. Low body mass index.
5. Impaired awareness of hypoglycemia.

Treatment of Hypoglycemia

For treatment of hypoglycemia, a 15–20 g glucose snack should be given to conscious patients. Blood glucose should be rechecked within 15 min, and if hypoglycemia is still present, another 15 g glucose snack should be given. For recurring episodes of hypoglycemia, adjustments in insulin or insulin secretagogue dosage should be made by the patient's diabetes provider. For patients with hypoglycemia who are unresponsive, intravenous glucagon or glucose should be infused according to the institutional policy of the particular cardiac rehabilitation program.

Management of Pre-exercise or Post-exercise Hypoglycemia (Blood Glucose <100 mg/dL)

In patients taking insulin or an insulin secretagogue, give a 15 g glucose snack which contains some protein and fat to slow absorption. For patients who are not taking insulin or an insulin secretagogue, a snack is not advised due to the very low risk of symptomatic hypoglycemia.

Post-exercise hypoglycemia warrants caution and additional monitoring until the patient's glycemic response to exercise is determined. For patients taking insulin or an insulin secretagogue, a 15 g glucose snack which contains some protein and fat is recommended. If blood glucose remains below 100 mg/dL or if symptoms of hypoglycemia persist in patients taking insulin or an insulin secretagogue, the diabetes provider should be notified.

For patients using an insulin pump, management of hypoglycemia is more complex. It is prudent for these patients to consult with their endocrinologist or Certified Diabetes Educator.

Most patients after an acute coronary event will be prescribed a beta-blocking medication. Concern has been raised regarding the effect of these medications on reducing the ability of patients to sense hypoglycemia due inhibition of the sympathetic nervous system response to hypoglycemia. However, the current consensus is that beta-blockers are not associated with an increased risk of hypoglycemia [20].

Management of Pre-exercise or Post-exercise Hyperglycemia (Blood Glucose >300 mg/dL)

For patients with type 2 diabetes and pre-exercise hyperglycemia, it is acceptable to proceed with the exercise session if the patient feels well and is adequately hydrated. For type 1 diabetics, exercise is permissible if there is no evidence of ketosis. If ketosis is present or there is concern for ketosis, exercise should be avoided. If pre-exercise hyperglycemia is a recurring problem, additional measures to improve glycemic control are required.

Post-exercise hyperglycemia is generally not a concern. Blood glucose levels may increase after vigorous exercise, even in patients with well-controlled diabetes. The mechanism for post-exercise hyperglycemia is catecholamine-mediated hepatic glucose production. Post-exercise hyperglycemia may persist for several hours and usually resolves without additional therapy. However, patients with symptomatic hyperglycemia should undergo an assessment with their diabetes provider.

Lifestyle Physical Activity

In addition to exercise training as discussed above, patients should be encouraged to engage in lifestyle physical activity outside of cardiac rehabilitation. Such activity has the following characteristics:

1. Informal in nature, includes various forms of activity and movement, such as standing rather than sitting and walking short distances as a means of transportation
2. Includes everyday activities: household tasks, shopping, and gardening
3. Is part of the normal routine
4. Provides health benefits and expends energy to facilitate body fat loss

Patients may benefit from measuring the number of steps taken per day using a pedometer or smartphone application. Prolonged sitting has been demonstrated to increase all-cause mortality [33]. In a large cohort of men and women without a history of cardiovascular disease, sitting for 10 or more hours/day was associated with a 31% increase in mortality after adjustment for a variety of potential confounding variables, including physical activity in leisure time and body mass index. Encouraging patients to spend less time sitting and more time standing is an important component of lifestyle physical activity.

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22 Peripheral Artery Disease and Exercise in Patients with Diabetes

Ryan J. Mays, Mary O. Whipple, and Diane Treat-Jacobson

Introduction

Peripheral artery disease (PAD) is a chronic condition characterized by atherosclerotic stenoses and/or occlusions in the arteries of the lower extremities. PAD has a significant negative influence on mobility and quality of life and is associated with increased morbidity and mortality [1, 2]. When PAD is present in addition to diabetes, outcomes are often far worse for patients. Thus, there is great importance for treating PAD and diabetes using currently established therapies as well as an impetus for developing novel treatment options to improve health outcomes. In this chapter, we will review (1) the scope of the problem of PAD among adults with diabetes, (2) the pathophysiology of PAD, (3) relevant diagnostic testing, (4) exercise program options and optimal prescription among adults with both conditions, (5) current findings related to the outcomes of exercise programs, and (6) recommendations for future trials to treat patients with both PAD and diabetes.

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Prevalence, Risk Factors, Health Impact, and Economic Burden

PAD affects an estimated 200 million adults worldwide, with a prevalence that dramatically increases with age [3, 4]. PAD has also been estimated to occur in approximately 10% of Americans over age 60 and 21% over age 80 [5]. There is a significant racial disparity; the rate of PAD among African Americans is approximately twice as high as among non-Hispanic whites, at any given age [5]. Using 2010 US census data, it appeared women age 40 and older had slightly higher prevalence of the disease than men [6].

Smoking, hypertension, and hyperlipidemia are highly related to the development of PAD. In particular, tobacco use via smoking is a key risk factor for developing PAD (odds ratio = 4.46; 95% confidence interval [CI] 2.25–8.84) [7].

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Diabetes is also a major risk factor for PAD as an estimated 20–30% of adults with diabetes are affected by PAD [8–11]. Approximately 30–40% of people with PAD experience claudication [3, 10], which is marked by ischemic pain and discomfort in the lower limbs with walking that subsides with cessation of walking. However, patients with PAD who also have diabetes are less likely to report classical symptoms of claudication, possibly due to altered pain perception related to the presence of peripheral neuropathy [12, 13]. Thus, the estimated rates of PAD in patients with diabetes are likely underestimated. Other concurrent health problems, such as heart failure and pulmonary disease, may prevent sufficient physical activity to produce limb symptoms; thus PAD may be underdiagnosed in these patient populations as well [4]. More severe or long-standing diabetes appears to increase the risk of developing PAD [14]. The combination of PAD and diabetes puts individuals at a greater risk of poor health outcomes, compared to either condition alone [15], and is particularly true in regard to cardiovascular complications. In fact, adults with PAD and diabetes have a 2–3.5-fold greater rate of mortality than those with PAD alone [16]. The survival curves depicted in Fig. 22.1 [17] show a greater risk of death within 10 years for patients with PAD and comorbid diabetes compared to those who have PAD without diabetes (risk ratio = 2.51; 95% CI, 1.72–3.66; $p < 0.001$). Patients with PAD and diabetes when compared to adults with PAD alone also have poorer lower extremity function [12] and self-reported quality of life [18]. In addition to affecting quality of life, increased severity of claudication is associated with impaired balance and physical function [19], and diabetes is believed to exacerbate the deterioration in these surrogate outcomes [20].

The milieu of factors present in concomitant disease in patients with PAD and diabetes results in not only a significant burden on the patient, but also leads to high economic costs for treatment. A seminal PAD-specific study examining Medicare enrollment and treatment utilization estimated an annual total cost of over $4 billion resulting from the disease [21]. When coupled with the staggering national costs of diabetes (estimated at ~$245 billion), this data clearly underscores the critical need for cost-effective treatment plans for patients with both diseases [22].

Pathophysiology

The pathophysiological and metabolic changes associated with diabetes are described elsewhere in Chap. 3. Much less is known about the disordered physiological processes brought on by the interaction of PAD and diabetes together. The proatherogenic changes linked to diabetes, including inflammation, endothelial cell dysfunction, and hypercoagulability, are also thought to be significant contributors to the development of PAD [13]. The principal cause of PAD is atherosclerosis, which causes progressive narrowing or occlusion of the arteries that supply blood and oxygen to the legs. Atherosclerosis results from a complex series of processes that include endothelial dysfunction and systemic inflammation. The vascular endothelium regulates blood flow by various mechanisms. Endothelial dysfunction is associated with a decrease in the ability of the blood vessel to dilate in response to changes in flow. The endothelium also produces several factors that can prevent thrombosis and promote thrombolysis. Disruption of these factors is the first step in the development of atherosclerosis. Increased low-density lipoprotein (LDL) cholesterol and increased plasma glucose contribute to activation of endothelial cells and recruitment of inflammatory cells into the intima. Hypertension and cigarette smoking also promote endothelial dysfunction and atherosclerosis. As this process continues, foam cells develop, which can be visualized as a “fatty streak” on the surface of the arterial wall. The next stage is the development of an atheroma, initiated by interactions between lymphocytes and macrophages. This can result in neovascularization, which is associated with interplaque hemorrhage and vascular remodeling to accommodate the growing atherosclerotic plaque. Advanced lesions contain a lipid pool within the plaque covered by a fibrous cap. Plaques that have a thick fibrous cap and smaller

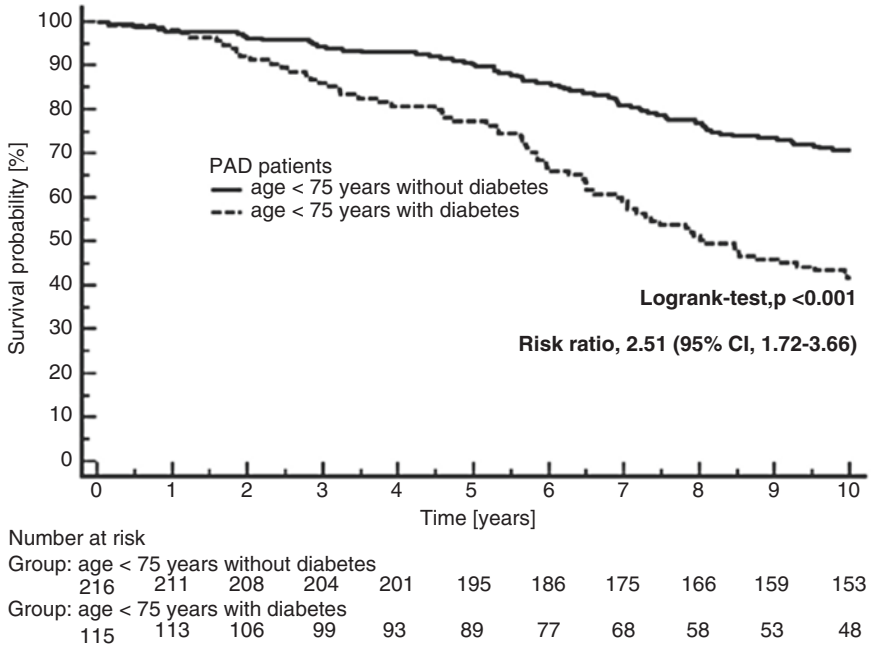

Fig. 22.1 Survival analysis in patients with peripheral artery disease only vs. those with both peripheral artery disease and diabetes. (Reprinted from Mueller et al. Mortality rates at 10 years are higher in diabetic than in non-diabetic patients with chronic lower extremity peripheral arterial disease. *Vascular Medicine* 2016; Oct 21 (5):445–452, with permission from Sage Publications. *PAD* peripheral artery disease)

lipid pool within the plaque are often more stable and less prone to rupture. These plaques cause narrowing of the arterial lumen and may result in chronic exertional ischemic symptoms such as those seen in patients with PAD. In contrast, plaques with a thin fibrous cap and larger lipid pool are more prone to rupture, exposing the thrombogenic material inside the plaque to blood, resulting in platelet activation and thrombus formation, often causing an acute event [23].

The narrowing of the vessel creates a turbulence of flow across the stenosis, further increasing the risk of platelet activation and thrombogenesis. Figure 22.2 [24] demonstrates the blood flow in a normal artery versus an artery narrowed by an arterial stenosis. In the normal artery, there is laminar flow of blood. Normally functioning endothelial cells regulate the vasodilation necessary to maintain optimal flow of blood and sufficient oxygenation of the skeletal muscle, even during lower extremity exertion. In the diseased artery, the stenosis creates high resistance, which may result in development of a collateral vessel, turbulent flow, decreased pressure across the stenosis, impaired endothelial function, and the inability to increase flow during exertion. This results in a mismatch of oxygen supply and demand, insufficient oxygenation to the skeletal muscles, and high oxidative stress.

Clinical Signs, Symptoms, and Diagnostic Testing for PAD

Clinical Presentation of PAD

Patients with PAD present across a spectrum of symptoms from asymptomatic to critical limb ischemia (CLI). It is estimated that up to 40% of patients with PAD report having no obvious exertional symptoms. However, there is evidence that PAD patients who report being asymptomatic actually have a slower gait speed and are more functionally impaired than people of similar age

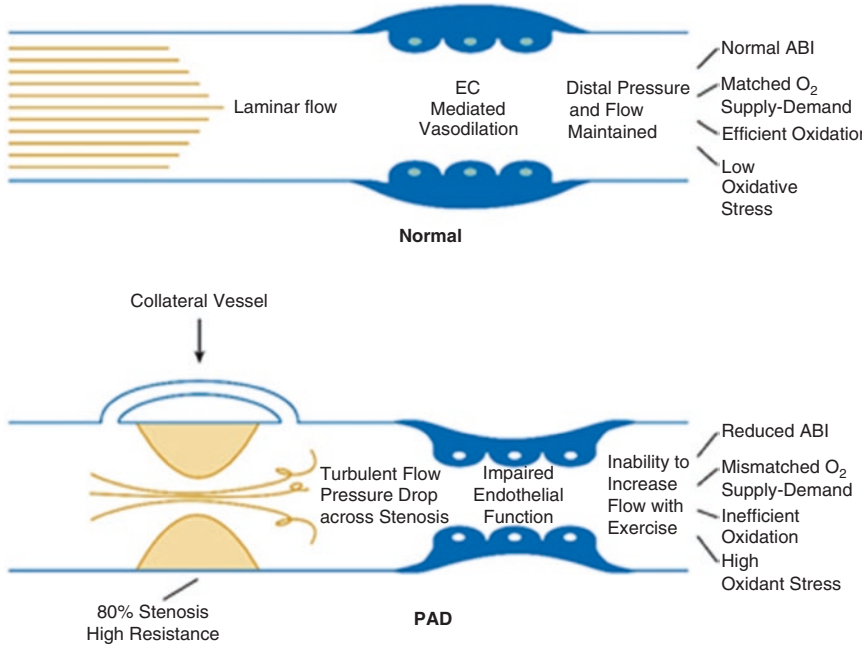

Fig. 22.2 Comparison of blood flow in normal vs. stenotic peripheral arteries. (Reprinted from *Vascular Medicine: A Companion to Braunwald's Heart Disease*, 2nd edition, Hiatt WR and Brass EP [24]. Pathophysiology of Peripheral Artery Disease, Intermittent Claudication, and Critical Limb Ischemia. Pp 223–230, 2013, with permission from Elsevier Inc. *ABI* ankle-brachial index, *EC* endothelial cell, *PAD* peripheral artery disease)

who don't have PAD [25]. Additionally, many asymptomatic patients will become symptomatic if they complete a peak walking test. This indicates their asymptomatic state is a result of not exerting themselves sufficiently during normal daily routine to reach the threshold where symptoms would occur.

The hallmark symptom claudication has several characteristics. It generally occurs in the lower extremities, although the term "claudication" has also been applied to upper limb pain as a result of subclavian stenoses/occlusions. Depending on the site of the partial or full blockage, claudication typically occurs in the calves, thighs, or buttocks. It is consistent and reproducible, it steadily increases as the exertion increases, and patients report not being able to walk through claudication if they try to continue at the same pace. In a majority of PAD patients who experience claudication, there is relief within 10 min of rest [26]. Patients will describe that they will go for a walk, and after a certain distance, they begin to get a cramping or aching feeling in their calf. If they keep walking, it gets continually worse, until finally they are forced to stop. Approximately 40–50% of patients who are symptomatic have an atypical presentation such that their lower extremity discomfort does not meet all the classic criteria of claudication [27, 28]. So, for example, the pain may be exertional, but doesn't consistently resolve with rest, or it may not consistently limit exercise at a reproducible distance and vary from day to day.

CLI is the most severe manifestation of PAD and is caused by severe progressive atherosclerosis. Blood flow to the lower extremity is insufficient to adequately supply tissue even at rest. As a result, progression to ulcers, gangrene, and amputation can occur [29, 30]. The pain at rest which can occur is characterized as an ache or a discomfort in the arch of the foot or toes, and it is usually exacerbated with leg elevation. Patients are most uncomfortable when lying flat with their legs elevated. The small loss of gravitational force when a patient lies down can cause a shift from the

tissue having sufficient blood flow to be comfortable, to progression to the ischemic rest pain. Often the pain is relieved when the foot is in a dependent position. This can interfere with sleep, and patients with rest pain will often describe waking up at night having pain in the ball or the arch of their foot and having to dangle the foot off the side of the bed to obtain relief. This poor circulation condition results from inadequate perfusion and triggers adverse responses in the microcirculation [31]. Circulating tissue factors associated with endothelial injury and activation of the clotting system further decrease blood flow and promote thrombosis in the arterial circulation [32]. This contributes to disease progression and perfusion that is insufficient to supply the distal tissue. CLI develops in 1% of patients with claudication per year, and approximately one million Americans present with CLI annually. The risk of progressing from claudication to CLI increases dramatically in those who have cardiovascular ischemic risk factors. Individuals with diabetes have a fourfold risk, and individuals who continue to smoke have a threefold risk of progressing from claudication to CLI [4]. Ulcerations as a result of CLI are typically found distally in the toe region and/or on the heels. They cause intense pain and may become dry, devitalized, or black at the end stage. Gangrene may also be an unfortunate consequence for those with CLI. Patients with ulcers and gangrene are more likely to progress to amputation than those with rest pain, and 1–3.3% of patients with claudication will progress to amputation. Patients with both diabetes and CLI carry a grave prognosis, as 5-year amputation rates have recently been defined to be as high as 34.1%, compared to patients with only CLI at 20.4% ($p = 0.015$) [33].

Diagnostic Testing for PAD

Ankle-Brachial Index The ankle-brachial index (ABI) is the most cost-effective tool that can confirm the diagnosis of PAD. It should be the first diagnostic test used when PAD is suspected. The concept of the ABI is that the systolic blood pressure in the leg should be approximately the same or slightly higher compared to the systolic blood pressure in the arm. The ABI should be a routine test for individuals who have a history or physical exam consistent with PAD, including an abnormal pulse exam, non-healing lower extremity ulcers, claudication or other exertional leg symptoms, or ischemic rest pain. An abnormal ABI is a very powerful predictor of future atherosclerotic cardiovascular events [34]. The lower the ABI, the worse the prognosis. The ABI can be performed in a clinician office with a manual blood pressure cuff and a handheld Doppler device. Sensitivity for ABI has ranged from 68 to 84% and specificities from 84 to 99% [35]. The interpretation of the ABI is as follows: 1.00–1.40 = normal; 0.91–0.99 = equivocal; and ≤0.90 diagnostic of PAD [36]. There are some limitations to the ABI. It can be falsely elevated when the pedal arteries are non-compressible because of the calcium deposits in the walls of the artery, therefore the blood pressure cuff cannot compress that artery and an accurate systolic pressure reading is not possible. This is most likely to occur in patients with diabetes, chronic kidney disease, or advanced age. Values >1.40 are considered abnormally elevated and in those individuals the ABI is nondiagnostic, and other tests need to be completed to confirm the diagnosis of PAD. Additionally, the ABI is insensitive to very mild occlusive disease and iliac occlusive disease. When the ABI is normal at rest, but there is a high suspicion of PAD because of symptoms or risk factors, additional tests can be performed to confirm the disease (e.g., exercise ABIs).

Toe-Brachial Index The toe-brachial index (TBI) is performed in the same manner as the ABI with the use of a special toe cuff. Measurements are made with a photoplethysmograph. This test is performed when the ABI is abnormally elevated and therefore nondiagnostic. A normal TBI value is ≥0.70.

Segmental Pressure Examination The segmental pressure examination is a physiologic test similar to the ABI with the addition of pressure measurements at multiple levels of the leg,

including the high thigh, low thigh, calf, and ankle. Measurement at multiple locations allows more precise understanding of the location of the lesion. A segmental pressure test is considered abnormal if there is more than a 20 mmHg decrease between a segment within the same leg, or between the original segment and the corresponding segment on the contralateral leg.

Pulse Volume Recording The pulse volume recording (PVR) reflects the change in volume of a leg segment with each pulse [37]. The waveform evaluation allows assessment of arterial flow in areas where arteries are calcified because it does not rely on compression of the artery to obtain a measurement [38]. Figure 22.3 shows images for PVR obtained during a segmental pressure test.

Exercise Testing Exercise testing in patients with PAD can aid in diagnosis and will provide valuable information about functional ability. In patients with symptoms consistent with claudication but a normal resting ABI, a treadmill test can be performed. The ABI is measured at rest prior to beginning exercise. During the exercise test, patients walk on a treadmill to a point of significant claudication symptoms. Immediately following the cessation of exercise, the ABI is repeated. Patients whose symptoms are a result of arterial insufficiency will have at least a 20 mmHg drop in ankle pressure following exercise. When that drop is compared with the elevated arm pressure usually seen with exercise, the ratio of ankle to arm pressure will be lower, which is diagnostic of PAD. A peak treadmill test will also measure how far a patient can walk before their symptoms force them to stop. This can be helpful in determining whether claudication is the limiting symptom versus other symptoms such as shortness of breath, angina, or musculoskeletal pain that does not arise from arterial insufficiency.

Diagnostic Imaging Procedures Duplex ultrasound is a noninvasive, relatively inexpensive imaging procedure that allows visualization of the lumen of the arteries of the lower extremity, and is indicated to determine diameter and location of stenoses. Computed tomography angiogram (CTA) and magnetic resonance angiogram (MRA) are noninvasive imaging procedures that allow visualization of the lower extremity arteries and are indicated to identify the location of atherosclerotic plaque. CTA requires the use of a contrast agent to maximize the quality of the images, and can be contraindicated in individuals with diabetes who are taking metformin or in those who have chronic kidney disease. MRA uses a contrast agent called gadolinium to enhance the images, which is less toxic than CTA contrast. MRA may not be an option for patients with implanted metal in addition to taking longer and being more expensive than a CTA. Because of the cost and exposure to contrast agents, both of these procedures are generally recommended to aid in planning a revascularization procedure. Digital subtraction angiogram (DSA) is an invasive imaging procedure that takes x-ray images of the lower extremity arteries, while injecting iodizing contrast material through a catheter threaded through the artery. Individuals with diabetes or chronic kidney disease are more at risk during this procedure because of the use of the contrast dye. Similar to CTA and MRA, DSA is indicated when a revascularization procedure is planned. Table 22.1 provides a summary of the diagnostic tests available for PAD.

Treatment Options for PAD and Diabetes

A full discussion of the various treatment options available for patients with both PAD and diabetes is beyond the intent of this chapter. Therapies are generally divided into noninvasive optimal medical treatment, revascularization, and in advanced stages, lower limb amputation. Optimal medical therapy targets several areas of health comprehensively, and further treatment is often dependent on the severity of the disease and subsequent symptom presentation. With all disease populations including those with PAD and diabetes, control of modifiable risk factors (e.g., smoking) is paramount to the treatment regimen. Reducing premature adverse cerebrovascular and cardiovascular events through pharmacological therapy (e.g., antiplatelet agents, statins,

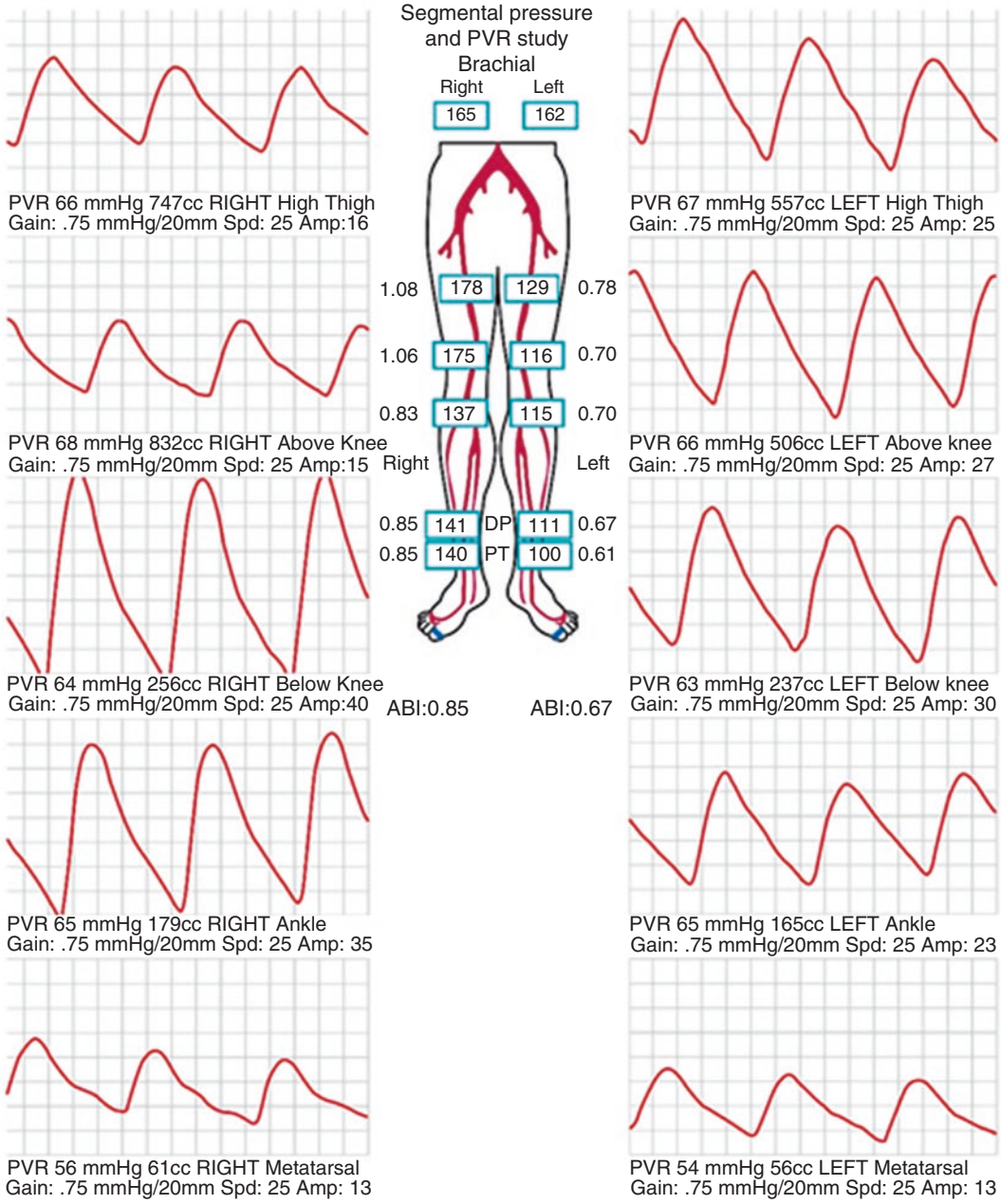

Fig. 22.3 Segmental pressure measurements and pulse volume recording. Right leg has a pressure drop between low thigh and calf consistent with superficial femoral/popliteal artery stenosis. Left leg has a pressure drop at level of high thigh consistent with iliofemoral artery stenosis. (Reprinted from *Vascular Medicine: A Companion to Braunwald's Heart Disease*, 2nd edition, Gerhard-Herman et al. [37]. Vascular Laboratory Testing. Pp 148–165, 2013, with permission from Elsevier. *ABI* ankle-brachial index, *PVR* pulse volume recording)

hypertension medications) is a mainstay in current medical therapy paradigms. Table 22.2 provides a brief summary of risk factors and treatment options for those factors in PAD patients with diabetes. A goal of any treatment method for PAD should focus on symptomology associated with the disease. For patients with claudication, medications have largely proven unsuccessful or demonstrated minimal

Table 22.1 Diagnostic testing for peripheral artery disease

Test	Description	Indication
Ankle-brachial index	Noninvasive procedure that assesses the ankle versus brachial systolic arterial pressure. Measured with a Doppler ultrasound device with a 4–8 MHz transducer.	To confirm diagnosis in patients with clinical suspicion of PAD. The ABI is somewhat less useful in patients with diabetes due to increased prevalence of medial artery calcification than can raise the ABI [114].
Toe-brachial index	Ratio of the systolic blood pressure measured at the great toe to that of the brachial artery. Measured with a Doppler ultrasound device and a photoplethysmograph.	To confirm diagnosis of PAD in patients with pedal artery calcification when ABI is nondiagnostic [114]. This is more commonly used in patients with diabetes [114].
Segmental limb pressures	Physiologic measurement of arterial systolic pressure in multiple limb segments compared to brachial pressure.	Useful in determining the location of arterial stenoses and/or occlusions. Generally, a pressure difference of ≥20 mmHg assessed at one cuff to the next is indicative of blockage.
Pulse volume recording	Measurement change in pulse volume of each leg segment using plethysmograph. Evaluates normalcy of waveforms.	To confirm diagnosis of PAD in patients with pedal artery calcification when ABI is nondiagnostic.
Exercise performance testing	Fixed or graded exercise test using primarily a treadmill. ABI can be performed before and immediately after the test to diagnose PAD in the presence of an equivocal ABI (0.91–0.99).	Useful for patients with high clinical suspicion of PAD but normal or borderline ABIs. Clarifies primary rate-limiter to exercise (e.g., claudication). Primary physical function test to determine effect of any clinical intervention.
Lower extremity duplex ultrasound	Noninvasive adjunct to physiologic testing. Peak systolic velocity and waveform analyses are used to quantify and localize extent of stenosis. Percentage reduction of diameter of the lumen is categorized.	Evaluation of location and severity of lower extremity arterial stenosis. Surveillance for recurrence of stenosis following endovascular or open revascularization.
Computed tomography angiogram	Noninvasive imaging study using a contrast agent to visualize lower extremity arteries. Higher risk of contrast-induced nephropathy in patients with CKD and/or diabetes.	To determine location of arterial lesions to inform planned revascularization procedures.
Magnetic resonance angiogram	Noninvasive imaging study using magnetic resonance techniques with gadolinium contrast to visualize lower extremity arteries. Higher risk of contrast-induced nephropathy in patients with CKD and/or diabetes.	Identifies the location of arterial lesions to inform planned peripheral revascularization procedures.
Digital subtraction angiogram	Invasive imaging procedure using x-ray and iodizing contrast agent to visualize lower extremity arteries. Associated with risk of hematoma and other procedural complications. Contraindicated in patients with CKD or diabetes because of the risk associated with the contrast dye, which is metabolized by the kidneys.	To determine location of arterial lesions to inform planned revascularization procedures.

ABI ankle-brachial index, *CKD* chronic kidney disease, *PAD* peripheral artery disease

Table 22.2 Summary of risk factors and therapy options for peripheral artery disease in patients with diabetes

Risk factors	Therapy options[a]	Discussion/considerations
Diabetes	Glucose control (pharmacological)	According to the AHA, ACC, and ADA, titration of dose and schedule of glucose-lowering therapies should aim to reduce and maintain HgbA1c to 7% with more rigorous control made on an individual basis [115, 116].
	1. Sulfonylureas	
	2. Meglitinides	
	3. DPP-4 inhibitors	
	4. GLP-1 receptor agonists	
	5. SGLT2 inhibitors	
	6. Thiazolidinediones	
	7. Insulin therapy	
Platelet aggregation	Antiplatelet agents	IWGDF recommendations include a low-dose aspirin or clopidogrel in patients with PAD and foot ulcers caused by diabetes [117].
	1. Aspirin	
	2. Clopidogrel	
Hypercholesterolemia	Statins	In a recent retrospective analysis [118], it was determined that patients with diabetes and PAD (and abdominal aortic aneurysms, carotid stenoses) had higher total and LDL cholesterol compared to patients with diabetes and CAD (152.0 ± 40.0 vs. 146.0 ± 42.0 mg·dl^{-1}, $p = 0.019$; 86.0 ± 35.0 vs. 80.0 ± 34.0 mg·dl^{-1}, $p = 0.04$). This in addition to lower statin usage compared to the latter (75% vs. 100%, $p < 0.001$).
	Niacin	
	Fibrates	
	Bile acid resins	
Hypertension	Beta-adrenergic blockers	The ACC/AHA practice guidelines [35] for the management of PAD highly recommends (IA) administration of antihypertensive therapy to reduce major cardiovascular event risk.
	Angiotensin-converting enzyme inhibitors	
	Diuretics	
	Calcium channel blockers	
Sedentary behavior and overall adverse risk profile	Therapeutic patient education and support	The ten standards within DSME and DSMS are defined by the National Standards for Diabetes Self-Management Education [119]. These standards provide guidance for ongoing support for people with diabetes by encouraging behavior change, maintaining healthy diabetes-related behaviors, and seek to address psychosocial issues. For PAD, compliance to smoking cessation and maintenance of an exercise program are key areas of focus for the patient [120]. Refer to section "Exercise Prescription in PAD and Diabetes" for more information on exercise therapy.
	Exercise therapy[b]	
Smoking	Behavior modification therapy	Interestingly, diabetes is associated with femoropopliteal and tibial disease in patients with PAD, whereas smoking is related to proximal disease in the aortoiliofemoral vessels [11, 13].
	Nicotine replacement therapy	
	Bupropion	

ACC American College of Cardiology, *ADA* American Diabetes Association, *AHA* American Heart Association, *CAD* coronary artery disease, *DPP-4* dipeptidyl peptidase-4, *DSME* Diabetes Self-Management Education, *DSMS* Diabetes Self-Management Support, *GLP-1* glucagon-like peptide-1, *IWGDF* International Working Group on the Diabetic Foot, *LDL* low-density lipoprotein, *mmHg* millimeters of mercury, *PAD* peripheral artery disease, *SGLT2* sodium-glucose co-transporter-2

[a]A full review of the relevant treatment options for these categories is not discussed due to the scope of this chapter.

[b]Note exercise therapy is recommended to positively impact the risk factor profile of patients with both peripheral artery disease and diabetes.

benefit in the USA for reducing leg pain and improving functional ability. Many of the initial systematic reviews examining the role of pentoxifylline to treat claudication have demonstrated lack of clinical effectiveness [39, 40]. A recent meta-analysis concluded that the role of pentoxifylline for improving walking performance endpoints remains uncertain, as the quality of trials in the analysis was low [41]. Based on this evidence, the 2016 AHA/ACC guidelines for the care of patients with lower extremity PAD have given pentoxifylline a class III, no benefit recommendation. Cilostazol is prescribed to treat claudication on a more routine basis in the USA, as it has demonstrated a modest improvement in walking and functional ability as well as quality of life [42, 43] of patients. It is generally recognized as having a greater clinical benefit but with more side effects (e.g., nausea) compared to pentoxifylline [44, 45]. Rendell et al. [46] reviewed pooled data from eight randomized controlled trials that demonstrated an improvement in peak walking distances (distance walked on a graded treadmill prior to test termination by the patient due to severe claudication pain) for patients with PAD and diabetes taking cilostazol (+51.4%) vs. placebo (+32.6%). Several studies have identified a signal of significant benefit for cilostazol in PAD and diabetes, particularly for improving claudication and ulceration prevention [47, 48]. However, other studies have shown less benefit, if any, for the drug to treat diabetes alone or the diseases when present in combination, in particular the symptom of peripheral neuropathy [49, 50]. There are other pharmacologic options available in Europe such as naftidrofuryl that show promise in PAD; however, it is still unclear if it is efficacious for treatment of PAD patients with diabetes [51].

Because the risk of limb loss is higher in patients with concomitant PAD and diabetes, revascularization therapies including lower extremity bypass or peripheral endovascular therapy are potential options for these patients. Endovascular interventions in particular have emerged as a less invasive option to open peripheral bypass procedures. The concern with endovascular revascularization is the lower patency rates over the long term when compared to open procedures, but the rates are improving with enhancements in technology [52]. The choice of treatment is largely dependent on the arterial segments that are affected, the severity and volume of lesions located in the peripheral artery anatomy, and whether the plaque is calcified. Restenosis often leads to a return of leg symptoms in PAD; thus the vascular specialist is cautioned to evaluate the risk/benefit ratio carefully before considering this as an option to treat the patient. In general, a more aggressive approach is adopted in younger active patients without comorbidities that may contribute to functional limitation and with more favorable disease anatomies (e.g., aortoiliac vs. femoropopliteal, stenosis vs. occlusion, focal vs. diffuse disease, non-calcified vs. calcified plaque). However, because of the markedly improved benefits, peripheral revascularizations using endovascular techniques are commonly used to treat PAD at all levels of symptom severity. Because of the significant risk of limb loss for patients with both diabetes and PAD, CLI should be treated aggressively using the most durable procedures in order to prevent amputation. Patients with PAD and diabetes do tend to have poorer outcomes following revascularization procedures than patients with PAD alone [53] and have a higher risk of lower extremity amputation than patients without diabetes [16, 54] as mentioned previously. One factor that may be partially responsible for the reduced effectiveness of revascularization procedures in patients with PAD and diabetes is that patients with both conditions tend to have more diffuse femoropopliteal and tibial disease, rather than focal aortoiliofemoral stenoses [55]. Regardless, it has been suggested that revascularization for the PAD patient with diabetes should be considered due to promising short-term clinical improvements in these patients [56].

Exercise Prescription in PAD and Diabetes

Exercise therapy in controlled settings such as hospitals and clinics is noninvasive, cost-effective, and considered the gold standard treatment option for patients with PAD (IA practice guideline rating) [35]. Programs of walking specifically lead to incremental improvement of

physiological parameters such as peak oxygen uptake (VO_{2peak}), walking performance both in time and distance during graded exercise tests, as well as enhancement of quality of life [4]. Current guidelines do not provide classification of recommendation/level of evidence in the existence of concomitant PAD and diabetes. However, the benefits of exercise for patients with diabetes are well known [57]. Individual limitations such as disease severity, age, and other comorbidities (e.g., lung disease) guide the exercise prescription for PAD and diabetes patients. The Claudication Symptom Rating Scale [58], which ranges from 1–5 (1 = no pain; 2 = onset of claudication; 3 = mild pain; 4 = moderate pain; 5 = severe pain) is used by the patient to rate pain according to their perception of discomfort. Exercise in patients with claudication is intermittent in nature with the walking being continued until the onset of moderate leg pain [35]. Patients then rest to allow for a reduction in claudication, if not a complete resolution of pain. It is preferable for patients to sit for rest periods so that exercise can begin again as soon as possible. Recent focus group studies with PAD patients indicated barriers to continuing to exercise include a lack of seating options being readily available [59]; however, no randomized controlled trials have evaluated the effects of sitting vs. standing during training for improvement of any composite, direct, or surrogate endpoints. The total duration that includes the walk/rest ratios of time should be approximately 35–50 min. Frequency should be three times a week, and ideally the program should continue for not just a discrete period of time (3–6 months) but rather throughout the patient's lifetime. When beginning a walking exercise program for the first time, the healthcare providers should input treadmill parameters (i.e., speed and grade) at an intensity great enough to elicit moderate claudication in 3–5 min. Depending on the patient's functional level at the onset of a new program, the initial sessions should start at lower durations and progress to 50 min as tolerated. For the PAD patient who has received peripheral revascularization or has other comorbidities that limit exercise (e.g., arthritis), ratings of perceived exertion (RPE) can be used to regulate intensity of exercise at moderate exertional levels. The most common metrics used to assess a patient's RPE include the Borg Scales and the OMNI Picture System of Perceived Exertion Scales [60, 61]. The former scales have been used successfully in PAD patients who do not experience claudication [62, 63] and thus are a valid alternative to pain scales for regulating exercise intensity.

Supervised exercise training is often not utilized despite being a highly recommended therapy for PAD. This is due to a number of problems including time constraints, habitual sedentary behavior of patients, proximity to clinics and healthcare facilities, and inadequate transportation [64–67]. Thus, unsupervised exercise programs are often provided, which consist of PAD patients being informed by their healthcare provider to walk at home or in their respective community [68–72]. There are many weaknesses to this approach that lead to the failure of these programs, including little follow-up from providers and a lack of taking into account barriers (e.g., absence of seating for rest) that may prevent the successful completion of any prescribed program. The majority of studies and subsequent results in this area support the concept that a lack of optimal training, monitoring, and coaching for the home exercise program simply does not work [73]. Thus, creating novel programs with components inclusive of those found in successful supervised programs may improve the likelihood of exercise therapy to be successful in community settings. Despite inclusion of individuals with diabetes in studies of exercise outcomes in PAD, few studies have directly compared outcomes among individuals with and without diabetes, and two recent systematic reviews on the topic have yielded conflicting findings about the role of diabetes in outcomes of exercise therapy in PAD [74, 75].

Several other modalities additional to walking have been evaluated to determine their impact on health outcomes in PAD alone, although for all modalities there has been far less research than that of supervised walking programs. Briefly, alternative modes of exercise to treat PAD include strength training, cycle and arm ergometry, pole

striding, and active pedal plantar flexion [76–80]. Strength training may offer health benefits to vascular disease patients and may consist of upper and/or lower limb movement [81]. Generally, the strength training program consists of standard guidelines utilized in healthy populations [82].

Treatment of those with diabetes and PAD should include some special considerations. Diabetes treatment includes a comprehensive program of exercise that includes resistance training to offset the decline of atrophy of the skeletal muscle. It has also been suggested that resistance and aerobic exercise for patients with only diabetes may be more beneficial to the patient than one singular modality [57]. Although strength training targets an important component of health, it should only be prescribed as a supplement to a walking exercise regimen for PAD patients. PAD incurs a high level of detriment on the cardiovascular and microvascular systems; thus aerobic exercise is primarily recommended. This makes the decision process for the clinical care provider a difficult one, when faced with a patient who has concomitant PAD and diabetes. Determination of comorbidities and any substantial physical limitations (e.g., CLI, amputations) should be considered by the provider before prescribing the mode of exercise. For example, upper body strength training and in particular arm ergometry may be valid alternatives for patients to improve the primary limiter of claudication [79]. However, more research is still needed from large trials to establish whether these alternative modes of exercise are indeed effective.

The importance of appropriate foot care is critical in patients with PAD and diabetes. Although there is no known risk of exercise therapy to causing irreversible ischemic damage to the muscles of the lower limbs as is the case in myocardial ischemia, the vascular complications of diabetes should be assessed closely due to potential skin breakdown and infection. This can be attributed to a higher vascular permeable environment, impaired regulation of blood flow, and poor vascular tone, all of which may be present in PAD patients as well [83]. Thus, caution is advised for patients with neuropathy performing a walking exercise program, as changes in gait may occur due to impaired sensory perception. One issue is that undue pressure could be placed on portions of the foot as the patient attempts to attenuate or avoid neurogenic pain. Abnormal friction could also go unnoticed by the patient without protective foot sensation. The presentation of peripheral symptoms from diabetes could result in pressure-induced necrosis from abnormal foot to ground contact patterns [84]. Shoes that do not fit properly or trauma as the result of poorly trimmed toenails could also cause ulcerations and potentially lead to amputation, a problem that is exponentially amplified in diabetes with PAD [56]. Footwear should consist of depth shoes that provide ample room in the toe box, and toenails should ideally be cut by an appropriate healthcare provider (e.g., podiatrist). Skin fissures and dryness should be avoided; thus lotion can be applied to the feet in the absence of nonhealing wounds [84]. Regular visual inspection of skin integrity is highly recommended.

Effects of Exercise Training in PAD and Diabetes

Numerous studies have evaluated the effects of exercise training in adults with PAD. However, there is a relative dearth of trials evaluating the impact of exercise therapy programs when both diseases are present. We will discuss the available literature. Key outcomes of interventions include assessment of walking ability and functional status, objective physiological endpoints such as VO_{2peak} and endothelial dysfunction, and patient-reported outcomes via questionnaires.

Walking Performance Outcomes and Functional Ability

The most objective modality for evaluating a patient's walking ability is a treadmill walking test. This type of test has been well validated for use in patients with PAD [85, 86]. Treadmill testing can be used to establish claudication onset time or distance (time or distance of initial presentation of any claudication pain), as well as

peak walking time or distance (point at which claudication pain becomes so severe that the patient is forced to stop). Several different treadmill protocols have been used in PAD populations to test for leg pain and evaluate other potential limiting factors in response to exercise [87]. A typical exercise protocol uses a graded exercise test in which the speed is maintained at 2 mph and the grade is incrementally increased 2% every 2 min [88]. Patients are instructed to walk as long as possible until they are unable to continue. The time walked prior to the onset of pain and the total time walked are both important in the evaluation of function, and are often included in studies of exercise interventions. This type of testing has been used in patients with PAD and diabetes.

The 6-min walk test is a performance-based functional measure that requires minimal equipment or training for staff administering the test [89]. Initially developed and validated in patients with respiratory disease as well as heart failure, the test has emerged as an important tool to determine the functional ability of patients with PAD [90, 91]. To perform the 6-min walk test, the patient is instructed to walk a defined course for 6 min, covering as much ground as possible in that time period, although they are permitted to stop and rest if needed. The total distance walked, as well as the distance covered prior to the patient's first report of leg symptoms, is recorded. The 6-min walk test has been used extensively in cardiovascular and pulmonary disease research, including PAD, as a method of monitoring disease status and the effects of interventions [92, 93]. It has been found to be a valid and reliable measure of functional ability in patients with PAD [94]. A significant recent trial also used the total distance walked during the 6-min walk test as an outcome (via a post hoc analysis) in patients with both PAD and diabetes [95].

Surprisingly little data exists as to the efficacy of exercise rehabilitation among adults with PAD and diabetes, when compared to those with PAD alone. In addition, existing data are conflicting. While exercise has been shown to be an effective therapy for improving pain-free and peak walking distance among adults with PAD [96, 97], some research suggests that individuals with PAD and diabetes may experience a blunted response to exercise therapy. In one study, 40% of patients with PAD and diabetes did not respond to exercise rehabilitation, and their risk ratio for nonresponse was 4.7, when compared to adults without diabetes [98]. Similarly, another study found that maximal walking distances did not improve in patients with PAD and diabetes with a 6-month exercise program [99]. Results are not consistent; another report found that patients with diabetes improved to a similar extent compared to nondiabetes patients [100]. It is unclear why this discrepancy exists, but it has been suggested that diabetes may contribute to reduced blood volume expansion and slower oxygen kinetics in the calf muscles during exercise [101, 102], thus reducing exercise-mediated improvements typically seen in measures of claudication.

Physiological Endpoints

There are a number of objective physiological endpoints, including VO_{2peak} and endothelial dysfunction that have been evaluated as outcomes from exercise training in patients with PAD and diabetes. A recent systematic review and meta-analysis concluded that exercise training improves cardiorespiratory fitness as measured by VO_{2peak} in adults with PAD when compared to usual care, although the differences were small (0.62 $ml \cdot kg^{-1} \cdot min^{-1}$; 95% CI, 0.47–0.77) [103]. This is consistent with the lack of major change observed in markers of endothelial dysfunction among adults with both PAD and diabetes. In a study examining endothelial dysfunction as measured via brachial artery flow-mediated dilation following 3 months of structured exercise therapy, the PAD-only group demonstrated an improvement in endothelial function (+1.9%, $p < 0.05$); however there was no change in the group with both PAD and diabetes (+0.75%, $p = 0.8$) [104]. Thus, the presence of diabetes in combination with PAD appears to attenuate improvements in endothelial function and net plasma nitrite. Markers of inflammation, including intercellular adhesion molecules, vascular

cell adhesion molecules, total cholesterol, triglycerides, and low-density lipoprotein cholesterol, do appear to be positively influenced by exercise therapy in adults with PAD and diabetes [105].

Patient-Reported Outcomes

Functional impairment and other relevant patient-reported outcomes of exercise programs for patients with PAD can be subjectively assessed through validated questionnaires. The Medical Outcomes Study Short-Form 36-item (SF-36) questionnaire is commonly used to assess quality of life in this population [106], and results can be used to compare outcomes across patient populations. There are a number of disease-specific questionnaires that have been used to characterize PAD-related symptoms, physical limitations, and mental, social, and emotional function. A full review of patient-reported outcome questionnaires in PAD is described elsewhere [106], but briefly, common metrics used in PAD include the Walking Impairment Questionnaire (WIQ) [107], Vascular Quality of Life Questionnaire (VascuQOL) [108], Peripheral Artery Questionnaire (PAQ) [109], Peripheral Artery Disease Quality of Life (PAD-QoL) [110], and the San Diego Claudication Questionnaire [27]. Each of these questionnaires has been used and validated in a population of adults with PAD and are frequently included as secondary outcomes of large PAD exercise trials. Studies have demonstrated improvement in self-report functional status and quality of life as a result of exercise interventions, and these improvements appear to be maintained long-term if individuals continue to exercise [111]; however the effect of exercise on these outcomes among patients with PAD and diabetes when compared to patients with PAD alone is unclear [99, 100]. Table 22.3 provides an overview of trials that evaluated outcomes following exercise therapy in patients with PAD and diabetes.

Conclusions and Future Directions

In conclusion, the primary aim of this chapter was to describe the role of exercise for treating symptomatic PAD in patients with diabetes. Importantly, relatively little is known about the interaction of the pathophysiologic effects of the two diseases in combination, although concomitant PAD and diabetes are relatively common. Each disease has its own challenges regarding patient symptom limitations. It appears that those with diabetes and PAD may benefit less from exercise training with regard to ambulatory endpoints than those with PAD alone or diabetes alone. However, exercise therapy remains a key therapeutic modality given its benefits for the diabetic metabolism, and it should be aggressively pursued as a front-line option by clinicians. Optimal medical therapy especially when including exercise is important due to its low risk and high benefits. Exercise training can improve the patient-reported outcomes, functional capacity, and metabolic risk profile of these patients while also reducing healthcare costs. Revascularization is critical for improving patient symptoms in addition to potentially reducing morbidity (amputation) for PAD and diabetes patients.

The current state of the healthcare system limits the treatment options for PAD and diabetes patients. Exercise as a method to improve health is unfortunately underused in current clinical practice. Although supervised exercise programs for PAD were recently approved for reimbursement by the Centers for Medicare and Medicaid, many patients are relegated to self-monitored exercise programs at home or in the community, which have been largely unsuccessful. Most of these programs that occur in the patients natural environment consist of recommendations for patients to walk as much as they can [112, 113] but without feedback or follow-up to ensure an adequate dose of exercise is performed to derive benefit. Thus, more research is needed to improve the effectiveness of these programs, particularly increasing exercise adoption and long-term adherence for those with diabetes and PAD.

Table 22.3 Results from exercise trials evaluating cohorts of only peripheral artery disease and concurrent diabetes or trials that performed subanalyses comparing those with concomitant disease vs. peripheral artery disease patients only

First author and year	Sample size[a]	Exercise intervention(s); study design (duration[b])	Results
Treat-Jacobson 2009 [79]	PAD only = 26; PAD and DM = 15	Arm ergometry, treadmill walking, combination of the two, or control; RCT (12 weeks)	PWD change scores (mean ± SD) were significantly greater for all exercise therapy groups (arm ergometry: +182.1 ± 126.7 m); treadmill walking: +294.7 ± 163.5 m; combination group: +217.2 ± 72.7 m) compared to patients randomized to the control arm (+45.3 ± 92.7 m, $p < 0.003$). Additionally, COD improved in the arm ergometry group (+89.6 ± 74.0 m) vs. controls (+4.0 ± 45.4 m, $p = 0.03$). The improvements in COD were also similar in those with and without DM.
Collins 2011 [99]	PAD and DM = 145	Home-based walking and behavioral intervention or control; RCT (6 months)	No significant difference in PWD (primary outcome) change scores between intervention and attention-control patients (+24.5 vs. +39.2 m, $p = 0.598$). However, differences were found for patients' perception of walking speed from the WIQ (+5.7 vs. −1.9%, $p = 0.034$) as well as the SF-36 mental component summary score (+3.2 vs 1.9% −2.4%, $p = 0.01$).
van Pul 2012 [100]	PAD and DM = 230; PAD only = 545	Supervised walking on a treadmill; open-label, nonrandomized design (6 months)	At 6 months, there was no difference ($p = 0.48$) in change from baseline for PWD between patients with PAD and comorbid DM (+270 m) compared to PAD patients without DM (+400 m).
Collins 2013 [105][c]	PAD and DM = 55	Home-based walking and behavioral intervention or control; RCT (6 months)	An exploratory pilot trial using liberal alpha parameters, a numerical trend ($p < 0.20$) was exhibited for improvement in specific lipid panel components (total cholesterol, triglycerides) for intervention group patients compared to those in the control arm.
Allen 2014 [104]	PAD and DM = 13; PAD only = 14	Supervised walking intervention; open-label design with PAD only patient data derived from a previous trial [121] (3 months)	Supervised walking exercise was associated with a within-group improvement ($p \leq 0.01$) in PWT for both patients with concomitant PAD and DM (+29%) and PAD only (+52%). Other exercise performance endpoints (e.g., COT, VO_{2peak}) and endothelial function improved in the PAD-only group; however no significant change was found among those with DM.
Gardner 2014 [98][d]	PAD and DM=25[e]; PAD only = 35[e]	Home-based and supervised walking interventions; RCT (3 months)	A sex by diabetes interaction effect was present (with total exercise strides built in as a covariate) as men with PAD and DM had a greater change in COT compared to women (mean ± SD: +273 ± 212 vs. +52 ± 155 s, $p < 0.05$). The change in COT from baseline to post-3 months was not significantly different ($p > 0.05$) between men (+189 ± 146 s) and women (+139 ± 191 s) without DM.

ABI ankle-brachial index, *COD* claudication onset distance, *COT* claudication onset time, *DM* diabetes mellitus, *FMD* flow-mediated dilation, *PAD* peripheral artery disease, *PWD* peak walking distance, *PWT* peak walking time, *RCT* randomized clinical trial, *SD* standard deviation, *SF-36* Medical Outcomes Study Short-Form 36-item Questionnaire, VO_{2peak} peak oxygen consumption, *WIQ* Walking Impairment Questionnaire

[a]Randomized patients

[b]Trial duration for the primary outcome

[c]Subanalysis of patients from previously published parent study [99]

[d]Secondary analysis from separate randomized controlled trial [122]

[e]Sample from 60 total patients who completed the trial

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