Stress and Skin Disorders

Basic and Clinical Aspects

Katlein França
Mohammad Jafferany
Editors

Springer

Stress and Skin Disorders

Katlein França • Mohammad Jafferany
Editors

Stress and Skin Disorders

Basic and Clinical Aspects

Springer

Editors
Katlein França, MD, PhD
Centro Studi per la Ricerca
Multidisciplinare e Rigenerativa
Department of Dermatology
Università degli Studi Guglielmo Marconi
Rome
Italy

Mohammad Jafferany, MD, FAPA
Department of Psychiatry
Central Michigan University
College of Medicine
Saginaw
Michigan
USA

ISBN 978-3-319-46351-3 ISBN 978-3-319-46352-0 (eBook)
DOI 10.1007/978-3-319-46352-0

Library of Congress Control Number: 2016960769

Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer International Publishing AG
The registered company address is Gewerbestrasse 11, 6330 Cham, Switzerland

I dedicate this book to my father and mother, Reginaldo and Aparecida França, who have encouraged and guided me in my professional and personal evolution.
I dedicate this book to the rest of my lovely family. I am very fortunate to have you all.
I dedicate this book to my patients, professors, mentors and friends. Thank you for the inspiration and support.

Katlein França

I dedicate this book to Professor Bryan H. King, for his support and encouragement in my interest in Psychodermatology during my fellowship training at University of Washington Seattle Children's Hospital.
I also dedicate this book to my family for having the patience with me for having taken yet another challenge which decreases the amount of time I can spend with them. They have been my inspiration and motivation for continuing to pursue my passion towards Psychodermatology.

Mohammad Jafferany

Foreword

The relationship between stress and skin disorders has long been recognized. It is commonly believed that many inflammatory skin diseases including psoriasis, atopic dermatitis, acne and rosacea are exacerbated by stress. A number of clinical studies suggest that this is true although difficulties in appropriate controls and various confounding variables make this conclusion less than absolute. Nonetheless, there is extensive evidence from animal models that various forms of stress can exacerbate certain inflammatory dermatoses, lead to mast cell degranulation and result in faster growth of immunogenic transplantable malignancies. Furthermore, in a mouse model, exposure to both chronic stress and ultraviolet radiation induced more rapid appearance of skin tumors compared to animals exposed to ultraviolet radiation without stress. Additionally, convincing evidence in animal models demonstrates that stress delays wound healing and inhibits perturbed skin barrier repair.

In addition to effects of stress on inflammatory skin disorders, the experience of having skin disorders, as well as the disturbance of interpersonal relations secondary to some of these diseases, may lead to psychological stress. Additionally, it is well known that some recognized dermatologic conditions (such as delusions of parasitosis), are primarily psychiatric disorders.

As the brain is the seat of the mind and both processive and systemic stressors manifest their effects through the nervous system, it is important to elucidate the mechanisms by which the nervous system impacts on cutaneous and systemic immunity. In this regard, much work has been done to elucidate neurohormonal regulatory mechanisms as well as influences of the peripheral nervous system on immunity and inflammation in the skin. Studies have demonstrated anatomical links between peripheral nerves and a variety of immune cells in the skin and draining lymph nodes. Furthermore, blood vessels within the dermis and elsewhere are associated with both sensory and sympathetic nerves and endothelial cells lining vessels are known to have inflammatory and immune functions. Recent work has demonstrated that products of nerves (including both neuropeptides and classic neurotransmitters) have regulatory functions on epidermal Langerhans cells, dermal dendritic cells, mast cells and endothelial cells, amongst others. This area of research is highly significant, not only for elucidating pathways by which stress and the nervous

system may regulate immunity and inflammatory skin disorders, but also because targets are likely to be identified that may be amenable to therapeutic manipulation. It is the hope of investigators in the field that a greater understanding of the pathways by which stress and the nervous system regulate immune and inflammatory processes in the skin will lead to new and novel methods to prevent and treat skin diseases for the benefit of our patients.

It is in this context that the book by Katlein França and Mohammed Jafferany, two experts in the field, is so timely and important. Chapters in this book discuss pathways of the brain-skin connection, the psychoneuroimmunology of stress and psychological states that impact skin disorders. Other portions of the book provide a comprehensive review of the relationship of stress to many inflammatory skin disorders and some non-inflammatory skin disorders as well as stress effects on hair and nails. Importantly, a chapter deals with stress and itch, the predominant symptom of many skin disorders.

This book will be of great interest to both investigators and clinicians interested in stress effects on the skin and will be especially useful for dermatologists, psychiatrists and other clinicians dealing with patients suffering from stress-associated skin diseases. Drs. Franca and Jafferany have done a great service by producing this valuable resource.

New York, NY, USA Richard D. Granstein, MD

Acknowledgments

If I have seen further it is by standing on the shoulders of giants

–Isaac Newton

We sincerely thank all the authors of this book, whose untiring efforts in writing chapters are highly appreciated. Without your help and contribution, the production of this book would not have been possible. We are also inspired with the work of Association for Psychoneurocutaneous Medicine of North America (APMNA), European Society of Dermatology and Psychiatry (ESDaP), Psychodermatology Group of the Brazilian Society of Dermatology, Japanese Society of Psychosomatic Medicine and UK Psychodermatology group. All these organizations, societies and groups have inspired us tremendously to edit a book on this important subject, which is the basis of psychodermatology. We are also indebted to our families for their patience and support during the entire time we were working on editing this book. Our patients who suffered psychocutaneous diseases also inspired us and gave us a new perspective of diagnosis and treatment in more a holistic way. We are also thankful to Springer for providing the opportunity to bring this book for the readership. It has been a pleasure working with them in this inspiring project.

Katlein França, MD, PhD
Mohammad Jafferany, MD

Contents

Contributors

Adam S. Aldahan, BS Department of Dermatology and Cutaneous Surgery, University of Miami Miller School of Medicine, Miami, FL, USA

Eloisa Leis Ayres, MD Fluminense Federal University – Niterói, Rio de Janeiro, Brazil

Annelyse Cristine Ballin, MD CEFOR (Center of the Face and Otolaryngology), Curitiba, Brazil

Christopher Bridgett, MD Chelsea and Westminster Hospital, Imperial College London, London, UK

José Carlos Cardoso, MD Dermatology Department, Coimbra Hospital and University Centre, Coimbra, Portugal

Bettina Carvalho, MD Otolaryngology Department, Federal University of Parana, Curitiba, PR, Brazil

Flavia Lira Diniz, MD Department of Otolaryngology, University of São Paulo, São Paulo, Brazil

Clinton Enos, MD Eastern Virginia Medical School, Norfolk, VA, USA

Bárbara Roque Ferreira, MD Dermatology Department, Coimbra Hospital and University Centre, Coimbra, Portugal

Reginaldo de França, MSc Universidad de Buenos Aires, Buenos Aires, Argentina

Aparecida Porto França, BS, PhD Instituto Universitario Italiano de Rosario, Rosario, Argentina

Katlein França, MD, PhD Centro Studi per la Ricerca Multidisciplinare e Rigenerativa, Università Degli Studi "G. Marconi", Rome, Italy

Department of Dermatology and Cutaneous Surgery, Department of Psychiatry and Behavioral Sciences, Institute for Bioethics and Health Policy, University of Miami Miller School of Medicine, Miami, FL, USA

Madhulika A. Gupta, MD Department of Psychiatry, University of Western Ontario, London, ON, Canada

Aditya K. Gupta, MD Department of Medicine, University of Western Ontario, London, ON, Canada

Zeba Hasan Hafeez, MD Touro University College of Osteopathic Medicine, Vallejo, CA, USA

Ingrid Herskovitz, MD Department of Dermatology and Cutaneous Surgery, University of Miami Miller School of Medicine, Miami, FL, USA

Josie Howard, MD Private Practice Psychiatry, Departments of Dermatology and Psychiatry, University of California, San Francisco, CA, USA

Vincent M. Hsu, BS Department of Dermatology and Cutaneous Surgery, University of Miami Miller School of Medicine, Miami, FL, USA

Sarah H. Hsu, MD Department of Dermatology, Boston University School of Medicine, Boston, MA, USA

Olivia Hughes, BS Department of Dermatology and Cutaneous Surgery, University of Miami Miller School of Medicine, Miami, FL, USA

Mohammad Jafferany, MD Department of Psychiatry and Behavioral Sciences, Central Michigan University, College of Medicine, Saginaw, MI, USA

Jonette Keri, MD, PhD Department of Dermatology and Cutaneous Surgery, University of Miami Miller School of Medicine, Miami, FL, USA

Robert S. Kirsner, MD, PhD Department of Dermatology and Cutaneous Surgery, University of Miami Miller School of Medicine, Miami, FL, USA

Torello Lotti, MD Centro Studi per la Ricerca Multidisciplinare e Rigenerativa, Università degli Studi Guglielmo Marconi, Rome, Italy

Flor MacQuhae, MD Department of Dermatology and Cutaneous Surgery, University of Miami Miller School of Medicine, Miami, FL, USA

Stephanie Mlacker, BS Department of Dermatology and Cutaneous Surgery, University of Miami Miller School of Medicine, Miami, FL, USA

Ladan Mostaghimi, MD Department of Dermatology, University of Wisconsin, Madison, WI, USA

Peter Noren, MD Department of Dermatology, Uppsala University, Uppsala, Sweden

Keyvan Nouri, MD Department of Dermatology and Cutaneous Surgery, University of Miami Miller School of Medicine, Miami, FL, USA

Tulsie Patel, MD Department of Dermatology and Cutaneous Surgery, University of Miami Miller School of Medicine, Miami, FL, USA

Shailee Patel, MD Department of Dermatology and Cutaneous Surgery, University of Miami Miller School of Medicine, Miami, FL, USA

Adele Rakosi, MD Department of Dermatology and Cutaneous Surgery, University of Miami Miller School of Medicine, Miami, FL, USA

Radomir Reszke, MD Department of Dermatology, Venerology and Allergology, Wroclaw Medical University, Wroclaw, Poland

Lidia Rudnicka, MD, PhD Department of Dermatology, Medical University of Warsaw, Warsaw, Poland

Sahal Samarkandy, MD Department of Dermatology and Cutaneous Surgery, University of Miami Miller School of Medicine, Miami, FL, USA

Department of Dermatology, King Abdulaziz Medical City, Jeddah, Saudi Arabia

Maria Helena Lesqueves Sandoval, MD Department of Dermatology, Cosmiatric Clinic, Hospital Cassiano Antonio De Moraes, Vitória, Brazil

Wilmarie Cidre Serrano, MD Department of Psychiatry, Stanford University, Stanford,CA, USA

Vidhi V. Shah, BA Department of Dermatology and Cutaneous Surgery, University of Miami Miller School of Medicine, Miami, FL, USA

Philip D. Shenefelt, MD Department of Dermatology and Cutaneous Surgery, College of Medicine, University of South Florida, Tampa, FL, USA

Anna Skrok, MD Department of Dermatology, Medical University of Warsaw, Warsaw, Poland

Jacek C. Szepietowski, MD Department of Dermatology, Venerology and Allergology, Wroclaw Medical University, Wroclaw, Poland

Kinza N. Tareen, BS Michigan State University, East Lansing, MI, USA

Ruqiya Shama Tareen, MD Department of Psychiatry, Western Michigan University, Kalamazoo, MI, USA

Neelam A. Vashi, MD Department of Dermatology, Boston University School of Medicine, Boston, MA, USA

Chapter 1
Psychoneuroimmunology of Stress and Psychodermatologic Disorders

Ruqiya Shama Tareen and Kinza N. Tareen

Introduction

Stress or more precisely psychological stress is defined in many ways but a simple definition captures the essesnce of it "a state of psychological strain or pressure due to a adverse or demanding situation." A stressor or a stress full event is the one, which either disrupts or threaten to disrupt an organisms' homeostasis. The stress full event can be a good event like a job promotion, marriage, having a child or a bad one like divorce, financial stress or death of a loved one, or it can be just a internal or external change in normal homeostasis like move, interpersonal relationship difficulties, suffering from pain or having a medical illness. It does not matter what kind of stress one faces, what matter most is how our mind and body respond to it and how we cope with it over all. All organisms are equipped to deal with stress no matter where they are on the ladder of evolution as specie. We as human have extensive and intricate systems and subsystems that work in tandem to help us cope with any stressor both emotionally and physically. However, our ability to respond to psychological stress depends on various variables. Age when the stressor occurred, early age of psychological stress can have much significant impact on psychological and physical well being. Nature of the stressor and its importance to the person in stress is also important as not every stressor has same impact for every one. While one might take job promotion in stride and deals with initial challenges of it with some difficulty another person may struggle to overcome the same kind of challenges, becoming psychologically overwhelmed and it may impact their physical

R.S. Tareen, MD (✉)
Associate Professor, Department of Psychiatry,
Western Michigan University School of Medicine, 1000 Oakland Drive, Kalamazoo, MI 49008, USA
e-mail: shama.tareen@med.wmich.edu

K. N. Tareen, BS
Michigan State University, College of Human Medicne, Lansing, MI, USA

K. França, M. Jafferany (eds.), *Stress and Skin Disorders*,
DOI 10.1007/978-3-319-46352-0_1

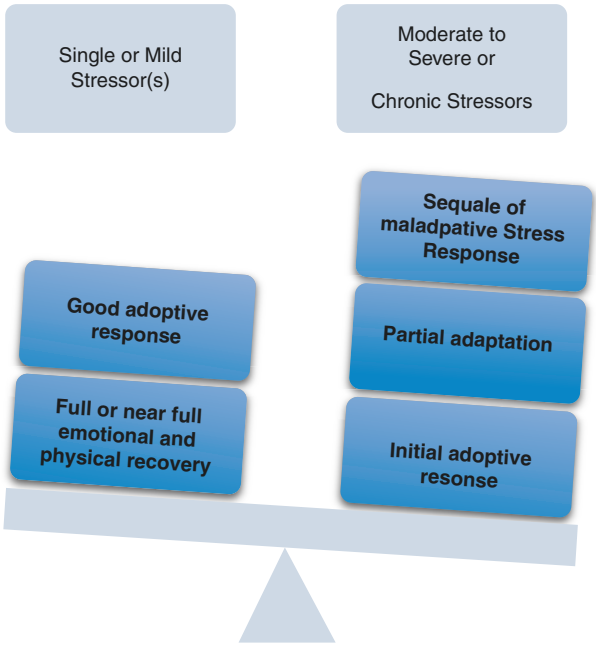


Fig. 1.1 Role of Stress in neuroimmunological response

well being. Chronicity of the stressor can overwhelm a person's adaptive level of responding to stress adequately. A child growing up in a dysfunctional family is under stress earlier on and exposed to some kind of stress on regular basis, constantly challenging his or her neuro-endocrine-immune response system to cope with stress, resulting in constant activation and ultimately failure of the stress response system.

The role of chronic stress in the pathogenesis of skin disease has been proposed by patients and physicans alike since the early days of modern medicine. It is only in last few decades we have achieved good scientific grounds to establish this connection [1]. The sophisticated relationship of stress and expression of dermatologic disease in different organ system is well established but it is nowhere so transparent as in skin and psychiatric disease. Skin is very well connected with the neuro-endocrine-immune system and plays that plays a fundamental role in maintaining homeostatis when faced with internal or external stress (Fig. 1.1).

Psychoineuroimmulongy

Psychoneuroimmunology, a relatively new field which relates to the study of complex and synchronous activation and interactions of behavioral, neural, endocrine, and immune systems leading to a successful defense response to an internal or external challenge including psychosocial stress. This intriguing phenomenon

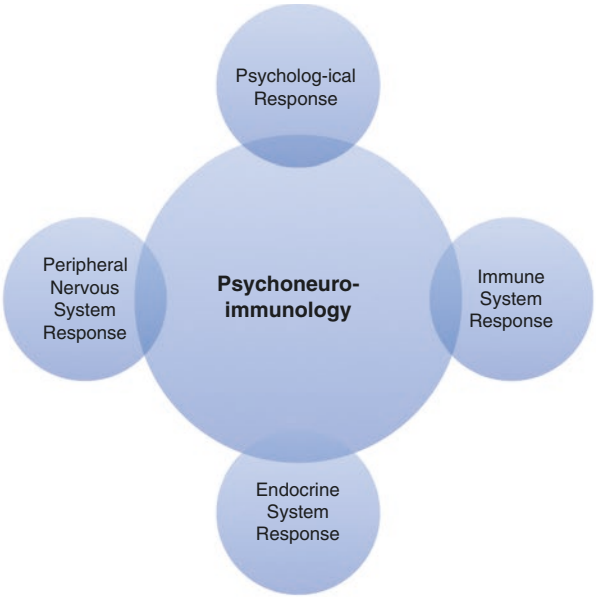


Fig. 1.2 A simple representation of psychoneuro-immunological response to a stressor

explains that immune system is rather one part of a multisystem response of a body challenged by an internal or external threat or psychological stress. This multisystem interplay that initiates and orchestrate a defense response helps us understand the complexities and intricacies of stress and adaptation of a body to it and how imbalance caused by severe or continual stress in can be detrimental to physical and mental wellbeing (Fig. 1.2).

The intricate multidimensional workflow of central and peripheral nervous systems, endocrine and immune system when gets overwhelmed or gets disturbed by high level of stress it results in expression of a disease process, including skin diseases. These three systems while respond to stress on their own they also interact with each other to orchestrate a stress response. The interaction of these three systems prepare body and mind to adapt to the stess induced changes by utilizing a series of neuropetides, neurotransmitters, and neurohormones. While stress affects a person at different levels, stress can impact each and every cell and organ in a body. Skin being the most outer, biggest and most innervated organ can show the burden of stress in most obvious way. Stress plays amajor role in the pathogenesis and expression of many skin diseases and dermatological diseases can appear de novo or relapse in response to psychological stress. Skin and brain both share an embryological origin from the single layer of germinal cells; the ectoderm. A specialized population of multi-potent cells known as neural crest cells emerge from the junction of neural and surface ectoderm; these cells can develop in different types of cells like epidermis, sympathetic nervous system, peripheral sensory neurons, and melanocytes [2] under the influence of neurotrophins such as nerve growth factor and other chemical signals that attract or dispel certain

cells, ensuring growth and expansion of the sensory peripheral nerve cells, ganglion, and interconnection between the neuronal system within different organs and in skin in the right direction [3, 4].

The complex relationship between stress and skin disease can not be fully explained unless we understands the mecahnisms by which the body responds to stress at macro and micro levels.

Nervous System Response to Stress

Central nervous system (CNS) modulates the immune response to stress via three distinct mecahnisms; activation of hypothalamic-pituitary-adrenal axis (HPA axis) and autonomic nervous system (ANS) and modulation of microglia on local level. This two prong activation of ANS as well as HPA axis ensures a prompt yet sustained respose to a particular stress stimuli as long as it is needed. Both of these systems work in-synch to each other in a bidirectional way to maintain the equilibirium in the stess response and to rheostat the intensity and duration of immune response [5]. Initiation of both of these pathways also leads to production of biologically active molecules that in turn can interact with immune cells directly and cn further modulate the stress immune respose [5].

ANS activation starts the releases of norepinephrine from the adrenal cortex. Most of the organs are innervated with noradrenergic postganglioning nerver fibers and lymphoid argans are no exception. Primary and secondary lymphoid organs like spleen, thymus, bone marrow, mucosal lymph glands and lymph nodes are activated through release of norepinephrine via peptidergic nerve fibers. The sympathetic innervations generally follow a similar pattern in different tissues. The nerve fibers are more dense in T-cell zones as compared to the B-cell zone. These nerve fibers makes neuroeffector junctions with lymphoid cells like macrophages to exert effect on immune systems. It has been known that any inturruption of this pathway can lead to impairment in immune response [5]. The function of sympathetic innervation is to modulate the innate immune response in such a way that a specific immune response is in proportion to the stimulus strength and not to continue beyond what is needed. The noradrenergic innervated areas within the lymphoid cells are also rich with neuromoulatory neuropeptides like somatostatin, substance P, neuropeptide Y, calcitonin gene-related peptide, opiate peptides, and vasoactive intestinal peptide [5, 6].

The release of norephnephrine within lyphoid cells can activate different receptors like β- adrenergic receprtors to influence the direction of stress response in certain way thus fine tunning the immune response to a particular offender. Norepinephrine has shown to modulate immune resonse by modulating thymocyte mitogenesis, lymphocyte proliferation in some lymph nodes, cell expression of antigens, antibody response, deters complement activation, and inhibits macrophages mediated lysis of certain cancerous or infectious cells. Lymphoid tissues have catecholamine and various neuropeptide-specific receptors. Catecholamines and

other neurotransmitters released from nerve fibers can activate theses receptors and can modulate the immune response via intracellular signals influencing a particular cell line proliferation, antibody and cytotoxin production etc. This can lead to vasodilation and adhesions of leukocytes which can further modulate local inflammatory response in response to stress Watson and Nance [6].

The third pathway the CNS mediated stress response is through microglia that are inactive or resting magrophages found all over the brain and spinal cord. In response to a stress stimuli, these resting microglia can become active. Activation of microglia can leas to expression of cell-surface markers such as major histocompatibility complex (MHC) molecules, complement receptors, and CD4 cells. Microglia then morphologically change to become active phagocytes. These microglia/macrophages are weak phagocyt when compared to the peripheral macrophages. However, when over activated they release certain pro-inflammatory cytokines such as platelet-activating factor, reactive oxygen molecules, and nitric oxide that can lead to neuronal injury [6].

Endocrine Response to Stress

The endocrine system plays a vital role in maintaining homeostatis in response to acute or chronic stress. The relationship of stress and disease expression in different organ system is well established. The HPA is a multilevel endocrine system playing the central role in defending body from stessful stimuli. Stress response starts from the hypothalamus leading to a synchronized activation or down regulation of pituitary and adrenal glands which is the vital system of body to respond and adapt to all kinds of stress. HPA axis have a cause and effect relationship with many skin diseases. When HPA axis is looses its ability to maintain basal and stress related homeostasis it can results in disease expression especially in skin diseases [7].

At the anterior pituitary gland the stress response is co-mediated by arginine vasopressin (AVP) and other nonapeptides. Corticotropin releasing hormone (CRH) and AVP are secreted in near synchronized pulses, inducing the secretion of adrenocorticotropin hormone (ACTH) [7]. Stress triggers CRH release from the hypothalamus in starting hormonal cascade of HPA axis. CRH receptors has a wide distribution of in various neural circuits like limbic system, and sympathetic arousal system both in the brain and spinal cord. Once these receptors are stimulated it leads to a well-coordinated chain of events including physiologic, behavioral changes like changes in appetite, arousal, sexual and activity levels Kyrou and Tsigos [7].

The CRH stimulate secreation of ACTH in a diurnal fashion with highest peak secreations occuring between 6:00 AM to 8:00 AM and lowest trough happening at midnight. This diuranal pulse secretion of ACTH is greatly affected by levels of stress. ACTH exerts its action by binding with melanocortin receptors 2 (MC2) found in all three layers of adrenal cortex, stimulating adenyl cyclase and generating cAMP that activates downstream enzyme pathways in steroidogenesis [7] Glucocorticoid synthesis mainly takes place in the zona fasciculata of the adrenal

cortex; this in turn is responsible for initiating the negative feedback loop to put a brake to the stress response at the level of suprahypothalamic centers, hypothalamus, and pituitary gland.

This self-regulatory stress response cycle prevents adverse consequences of prolonged adaptive changes such as catabolism and immunosuppression [7]. When stress is chronic and unrelenting the self regulatory negative feedback does not occur leading to continual hypersecretion of CRH, perpetuating a constant activation of HPA-axis. The constant excitation of HPA-axis result is a syndromal state characterized by behavioral disturbances such as depression, anxiety disorders, eating disorders as well as many systemic sequelae that include central obesity, hyperthyroidism, diabetes mellitus, metabolic syndrome, osteoporosis, atherosclerosis, immunosuppression, and increased susceptibility.

The HPA-axis is not the only nuroendocrine stress reponse there are many other neuroendocrine mechanisms that plays important role in mounting a stress response. Leukocytes that plays the first line defence in stress repsose have specific neuroendocrine receptors, such as receptors for growth hormone (GH), β-endorphin, thyroid hormone, luteinizing hormone-releasing hormone, and somatostatin. Deficiency of GH can lead to attenuate production of antibodies, activity of natural killer cells as well as T-cell lymphocytes. On the other hand prolactin can inhibit cellular and antibody response predisposing to certain infections [5, 6]. When there is an interruption in this neuroendocrine pathway as a result of a lesion in anterior hypothalmic region can lead to suppression of cellular response from spleen and thymus and antibody production as well as diminished natural killer cells response [5].

Dermatologic Response to Stress

Skin is richly innervated an has an extensive immuno-neuro-endocrine network can be compromised by stress and be not able to respond to predictable stressors such as seasonal changes or an unpredictable stressor such as a psychosocial stress. Skin is very well connected with the endocrine system and plays a vital role in maintaining homeostatis when faced with internal or external stress. The intricate relationship of stress and causation of disease in different organ system is well established but it is nowhere so transparent as in skin when expressed in form of dermatologic disease.

Any type of stress results in what is calles as allostatic overload, causing various levels of dysregulation ranging from inflammation to immunosuppression [8]. Skin mast cells are crucial in maintaining an allostatic balance and they are labeled as “central switchboard” of skin-stress-response [8]. Skin mast cells are activated by stress mediators such as CRH, ACTH, nerve growth factor (NGF), substance P (SP) and stem-cell factor while glucocorticoids and cathecholamines can inhib the skin mast cell activity [8]. Several bderamtological conditions represent a classic model of the stress and expression of disease paradigm; some common expamles include atopic dermatitis, psoriasis, hair disorders, urticaria, angioedema, and skin infections [8].

Skin mast cells has specific neuropeptides receptors on their surface making them a central player in the psycho-immuno-neuro-endocirne axis. They also produce various pro-inflammatory substances leading to the local effects of inflammation within the skin initiating the classic itch-scratch cycle. Any stressful event leading to psychological stress can cause a flare up of AD initiating and exacerbating itch and scratch cycle that is central to many dermatological conditions [9]. Pruritus associated with skin diseases can cause stigma leadig to anxiety and mood problems giving rise to major psychiatric difficulties. Selective serotonin reuptake inhibitors (SSRIs) and related medications have been shown to be effective in these instances [9].

Stress Diathesis and Dermatologic Diseases

The concept of psychosomatic medicine was initially proposed around 400–500 BC by Hippocrates, Plato, and Aesculapians alluding that soma and psych are interconnected and these intricate interaction or disturbance of can lead the expression of a disease [10, 11]. However, this was not the first time that a skin–mind connections was mentioned. The earliest mention of such connection was even found in Biblical and ancient literature. Despite that early conceptulization it was not until 1930s and 1940s that a more cohesive concept of how the stress, psychological burden, psychiatric conditions and its expression in dermatologic conditions emerged more clearly, this is the field that is now known as psychodermatology [10]. The current and most commonly used classification proposed by Koo and Lebwohl [12], classifies the psychodermatoses into three main groups:

Psychophysiologic disorders Dermatologic diseases with a well established etiologic role of psychological stress. They include psoriasis, alopecia areata, atopic dermatitis, acne vulgaris, and others [12].

Primary psychiatric disorders Psychiatric disorder with manifestation of dermatologic symptoms like dermatitis artefacta, delusional infestation, trichotillomania, neurotic excoriations, and others [12].

Secondary psychiatric disorders A dermatologic condition due to the disfiguring lesions leading to the development of a psychiatric condition like cystic acne, vitligo, alopecia areata, ichthyosis and others skin conditions leading to stigma and psychological stress [12].

In this section we are going to focus on some well known dermatological conditions with well established role of stress and psychological distress leading to expression and maintanance of disease.

Atopic dermatitis is an archetype disease to understand the psychoneuroimmunology phenomenon playing a part in an expression and continuance of a dermatologic condition. The bidirectional relationship of stress to atopic dermatitis is very interesting to observe. The psychological stress can impact an individual at any stage of life, however the impact of stress can be devastating if the individual is at a

stage of life when it is completely dependent on others for it's survival; in infancy. This is the stage of life when stress can cause an ineradicable damage to the psyche and as we have learned on soma of an individual who is still trying to figure out its surrounding in most basic way and who's neuronal, hormonal, and immunological systems are still evolving.

Atopic dermatitis is a disease of early childhood where early life stress has been plays an important role. Stressful early life experiences as severe as neglect, abuse and abondonment or as mild as improper or inconsistent care by the primary care giver that in most instances is the mother can be very stressful to an infants who is compleltly dependent on mother for their basic needs for survival in this world. The love, affection and care a mother conveys to her neonate when lovingly providing basic care conveys the sense of safety and assurance via skin to skin touch; neonates very first and most important mode of communication [13]. This tactile communication is very important for neonate as it has been shown by animal studies and behavior studies in premature infants that tactile communication plays an important role in neuronal cell growth and maturation [13, 14].

Psychological stress in early days, months and even in early years of development can lead to initiation and permanance of a sense of rejection, abandonment and helplessness which can over sensitize the neuro-immune system predisposing the infant to develop some dysregulation of immune responses. Production of histamine one of the main mediators of the itch and scratch cycle is released in response to classical conditioning of repeated stress in guinea pigs [15].

Under stress the sympathetic system causes release of catecholamine that in turn can increase the production of histamine, prostaglandins, ND leukotrienes starting the cycle of scratch-itch that can initiates the chronic pruritus [15, 16]. The evidence to suggest the existence of such neuroimmunological response to stress in patients with atopic dermatitis comes from the finding that CD8 lymphocyte production increases in response to psychological stress and remains elevated even one hour after the initial stressful event, suggesting that a heightened autonomic response to a stressful events may be pathognomic in atopic dermatitis [15, 16]. Presence of various neuropeptides receptors on the surface of skin mast cells help them play a central role in this psycho-immuno-neuro-endocirne interactions in atopic dermatitis. On the other hand skin mast cells also produce various pro-inflammatory substances caussing inflammation within the skin that can recruit and perpetuate the classic itch-scratch cycle. In event of a psychological trauma exacerbation of this itch-scratch cycle can lead to a flare up of atopic dermatitis [15–17].

In a child who has chronically overactive HPA-axis it can lead to increased productions of catecholamines and glucocor to ticoids. This triggers production of T lymphocyte helper T_H1 and overproduction of T_H2. This altered ratio of T_H1 and T_H2 cells caused up-regulation of T_{H2} mediated antibody production including IL-4, IL-10, and IL-13 [16, 17]. The stress also causes stimulation of cytokines and proteases [18]. Release of neuropeptides such as Substance P (SP), nerve growth factor, and calcitonin gene related peptide from efferent nerve fibers [16–18].

The constant trauma of itch-scratch can lead to disruption of of the epidermal barrier causing further worsening of eczematious lesions and perpetuating the

itch-scratch cycle all over again. The unrelenting pruritus of an eczematious lesion and the stigma of the physical appearecnce when the lesions are visible to others can cause significant anxiety and mood disturbances in patients with atopic dermatitis. Use of psychotropic medications such as selective serotonin reuptake inhibitors are indicated in such patients and have been shown to be effective in improving the quality of life in such patients by improving the psychological conditons [9].

Conclusion

The skin is our largest organ and our most important and very first interface with the environment we live in. It is our shield that protect us from onslaught of environmental toxins, pollutants, infections, and other noxious agents. Psychological stress can cause dysregulation of the immune system, resulting in weakening of the skin defense system resulting in inoculation of new pathogens or reactivation of dormant pathogens. For decades we have studied different organ systems in isolation and while we understood that the interplay among different systems we tend to omit the most important contributor to maintain the harmony among these systems, the psyche. Psychoneuroimmunology teaches us that psychological stress can be detrimental to an organism's successful existence as it plays a much important role in our psychical wellbeing and attention to a patient's psychological wellbeing is an essential part of their care.

References

1. The concise corsini encyclopedia of psychology and behavioral science. http://www.credoreference.com.libproxy.library.wmich.edu/entry/wileypsych/psychoneuroimmunology. Accessed on 26 Feb 2016.
2. Motohashi M, Aoki H, Chiba K. Multipotent cell fate of neural crest-like cells derived from embryonic stem cells. Stem Cells. 2007;25(2):402–10.
3. Le Douarin NM, Calloni GW, Dupin E. The stem cells of the neural crest. Cell Cycle. 2008;7(8):1013–9.
4. Le Douarin NM. Cell line segregation during peripheral nervous system ontogeny. Science. 1986;231:1515–22.
5. Ader R, Cohen N, Felten D. Psychoneuroimmunology: interactions between the nervous system and the immune system. Lancet. 1995;345:99–103.
6. Watson SCL, Nance DM. nervous system–immune system interactions. In: Michael Conn P, editor. Chapter 30 in neuroscience in medicine. 3rd ed. Totowa: Humana Press; 2008.
7. Kyrou I, Tsigos C. Hypothalamic-pituitary-adrenal axis. In: Linos D, Heerden J, editors. Adrenal glands. Berlin/Heidelberg: Springer; 2005. p. 19–32.
8. Paus R, Theoharides TC, Arck PC. Neuroimmunoendocrine circuitry of the 'brain-skin connection'. TRENDS Immunol. 2008;27(1):32–9.
9. Suárez AL, Feramisco JD, Koo J, Steinhoff M. Psychoneuroimmunology if psychological stress and atopic dermatitis: pathophysiologic and therapeutic updates. Acta Derm Venereol. 2012;92:7–15.

10. Rodríguez-Cerdeira C, Pera-Grasa JT, Molares A. Psychodermatology: past, present and future. Open Dermatol J. 2011;5:21–7.
11. Koblennzer PJ. A brief history of psychosomatic dermatology. Psychodermatology. Dermatol Clin. 1996;14(3):395–7.
12. Koo J, Lebwohl A. Psychodermatology: the mind and skin connection. Am Fam Physician. 2001;64:1873–8.
13. Walser A. Bodies in skin: a philosophical and theological approach to genetic skin diseases. J Relig Health. 2010;49:96–104.
14. Schneider G. Psychosomatic aspects and psychiatric conditions. In: Misery L, Ständer S, editors. Pruritus. Berlin: Springer; 2010. p. 211–5.
15. Gieler U, Ehlers A, Hohler T, Burkard G. The psychosocial status of patients with endogenous eczema: a study using cluster analysis for the correlation of psychological factors with somatic findings. Hautarzt. 1990;41:416–23.
16. Arndt J, Smith N, Tausk F. Stress and atopic dermatitis. Curr Allergy Asthma Rep. 2008; 8:312–7.
17. Faulstich ME, Williamson DA, Duchmann EG, Conerly SL, Brantley PJ. Psychophysiological analysis of atopic dermatitis. J Psychosom Res. 1985;29:415–7.
18. Seiffert K, Hilbert E, Schaechinger H. Psychophysiological reactivity under mental stress in atopic dermatitis. Dermatology. 2005;210:286–93.

Chapter 2
Evaluating the Role of Stress in Skin Disease

Madhulika A. Gupta and Aditya K. Gupta

Definition of Stress

In psychosomatic dermatology, the term stress is generally used to refer to stimuli (such as experiences of stigmatization related to a cosmetically disfiguring condition, major life events such as bereavement, and traumatic life experiences such as earthquake or war where the patient's coping capacities may be overwhelmed) that pose a challenge to homeostasis. The stress response is viewed as having a degree of specificity based upon the particular challenge to homeostasis, the organism's conscious and subconscious perception of the stressor, and the organism's perceived ability to cope with the stressor [1]. Various clinical factors such as the developmental stage of the patient (e.g., the adolescent patient's reaction to a skin condition may appear excessive and be out of proportion to the clinical dermatological severity), medical comorbidities (e.g., metabolic syndrome) and psychiatric comorbidities (e.g., major depressive disorder, posttraumatic stress disorder) can play a moderating role in the relation between stress and dermatologic disease.

M.A. Gupta, MD, FRCPC (✉)
Department of Psychiatry, Schulich School of Medicine and Dentistry, University of Western Ontario, 585 Springbank Drive, Suite 101, London, ON, Canada, N6J 1H3
e-mail: magupta@uwo.ca

A.K. Gupta, MD, PhD, FRCPC
Department of Medicine, University of Toronto, Toronto, ON, Canada

Mediprobe Research, London, ON, Canada

K. França, M. Jafferany (eds.), *Stress and Skin Disorders*,
DOI 10.1007/978-3-319-46352-0_2

Table 2.1 Psychosocial stressors and the stress- reactive dermatologic disorders

Psychosocial stressor	Predisposing factors	Precipitating factors	Perpetuating factors
Dermatologic disease – related stress, i.e., stress and daily hassles from impact of skin disorder upon the quality of life. Children and adolescents may experience bullying. Important factor in cosmetically disfiguring disorders		Onset/exacerbation of stress- reactive dermatoses that tend to be cosmetically disfiguring e.g., acne, psoriasis, atopic dermatitis	Stress and hassles from having to live with a chronic and usually cosmetically disfiguring dermatologic condition can be a perpetuating factor
Major stressful life events – e.g., loss of job, marital stress, death of spouse		Onset/exacerbation of a wide range of stress-reactive dermatoses	Unresolved stressors may lead to perpetuation of dermatologic disorder
Traumatic life events i.e., events that overwhelm the patient's coping capacity e.g., history of severe neglect, sexual abuse, trauma of war etc. May affect patient years after the initial event, as patients may get triggered by a person or event that reminds them of the trauma. May be associated with autonomic nervous system (ANS) dysregulation	Autonomic dysregulation and hyperarousal may predispose to exacerbations stress-reactive and self-induced dermatoses	Onset/exacerbation of a wide range of stress-reactive dermatoses, especially disorders associated with autonomic hyperarousal e.g, urticaria. May precipitate self-induced dermatoses. Also onset of other stress-reactive dermatoses e.g., psoriasis	Perpetuation of a wide range of stress-reactive dermatoses, especially disorders associated with autonomic hyperarousal. Factor in chronic idiopathic urticaria and chronic self-induced dermatoses e.g., acne excoriee, dermatitis artefacta

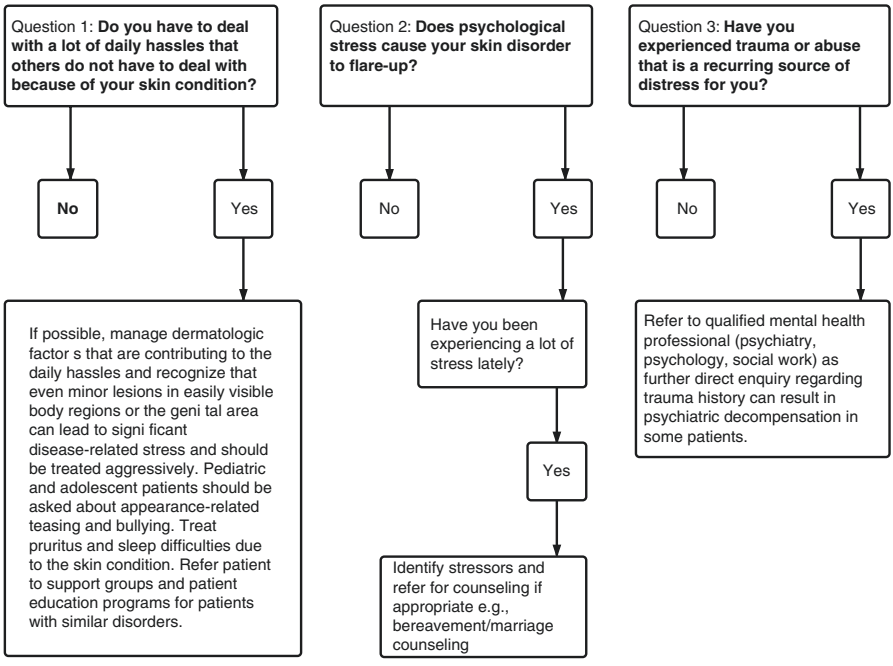
Adapted from Gupta and Gupta [3], with the permission of publisher and author
Types of stress in a clinical setting that may act as predisposing, precipitating or perpetuating factors in stress-reactive dermatologic disorders

Stress and Clinical Dermatology

Psychosocial stress and psychiatric factors are important in about one-third of dermatologic disorders [2]. In the clinical literature stress, which can be a predisposing, precipitating or perpetuating factor in stress-reactive dermatoses, is associated with skin diseases in three main situations (Table 2.1) [3]: (i) when stress arises secondary to the effect of the skin disease upon quality of life. Heightened interpersonal sensitivity and perceived stigmatization and social alienation are some of the most

important factors in the psychological morbidity and stress associated with a cosmetically disfiguring dermatologic condition [4]. There are a large number of instruments that measure health-related quality of life in dermatologic disease [5]. The Dermatology Life Quality Index (DLQI) [6] is an extensively validated, brief and easy-to-follow generic dermatology specific quality of life instrument that has been widely used in clinical and research settings [7]. The skin disease-related stress increases the morbidity associated with the condition, and in some instances may contribute to clinical exacerbations of some stress-reactive dermatoses such as psoriasis [2]; (ii) when stress exacerbates a stress-reactive skin disorder e.g., psoriasis, atopic dermatitis, acne, chronic idiopathic urticaria; and (iii) when the dermatologic disorder is essentially a cutaneous sign of a psychiatric disorder (e.g., obsessive-compulsive and related disorders, dissociative disorders, posttraumatic stress disorder) where stress plays a central role e.g., skin picking disorder, trichotillomania, dermatitis artefacta. Three major types of stressors are encountered clinically (Table 2.1) [3]: (a) stress from daily hassles secondary to impact of the skin disorder upon the quality of life; (b) major external life events such as bereavement and marital problems; and (c) major catastrophic/traumatic life events such as sexual assault, where the individual's coping capacities are overwhelmed. It is important for the clinician to be able to delineate the nature of the stressor, as each situation requires a different management approach (Table 2.2) [3].

Table 2.2 A practical approach to the initial assessment and management of psychosocial stressors in the dermatology patient



Adapted from Gupta and Gupta [3], with the permission of publisher and author

Theoretical Perspectives

Stress and Immune Function of the Skin

The skin serves as both (i) an immune organ and metabolically active interface between the individual and the outside world during sleep and wakefulness, (ii) an organ of communication throughout the life span- at neurobiological, psychological and social levels [8]. Due to its strategic location, the skin plays a critical role in preserving homeostasis [9], as it is regularly exposed to potentially dysregulating stimuli, both physical and psychosocial. A critical function of the epidermis is permeability barrier homeostasis, and acute psychological stress can prevent skin barrier function recovery in humans which can lead to exacerbations of conditions like atopic dermatitis, psoriasis and contact dermatitis [10]. It is important to recognize that the relationship between stress and immune function is complex [11], as the enhanced immuno-protection (e.g., increased efficacy of immunization and wound healing) that may be associated with acute (typically lasting minutes to hours) psychological stress, can also exacerbate immune-mediated dermatologic disorders such as psoriasis and atopic dermatitis [11]. Sleep disruption and deprivation, and circadian-rhythm disruption (e.g., due to rotating shift work) are associated with increased stress, and can exacerbate many dermatologic disorders as a result of an enhanced pro-inflammatory state [12].

The Skin as an Organ of Communication

Changes Over the Life Cycle

The skin plays an important role as an organ of communication across the life span- this role of the skin also forms a basis for the relation between skin disorders and psychosocial stress. Right after birth skin-to-skin contact between the neonate and the mother is known to have a significant beneficial impact on the infant's capacity for autonomic regulation [13] and socialization in later life [14] – both these factors are directly associated with better capacity for managing stress. The psychosocial development of an infant with dermatologic disease may be adversely affected if the caregiver is reluctant to sufficiently touch or hold the infant. In later life, a cosmetically disfiguring dermatologic disorder, affecting the 'emotionally charged' body regions such as the genital region and the easily visible body regions, especially the face [15], can lead to significant stress due to feelings of stigmatization and social exclusion [16]. The overall appearance of the skin, even when minimally flawed, can have a profound effect on the body image especially during adolescence and young adulthood when the individual is especially vulnerable to peer disapproval and social exclusion including bullying [16]. The skin, especially facial skin, is one of the most easily visible indicators of chronological age. The idea that

chronological age itself does not signal the beginning of old age, and that one can get older without the signs of aging, has become increasingly prevalent [17]. Over the last several decades old age has started to acquire increasingly negative connotations and often normal intrinsic aging is viewed as a medical and social problem that needs to be addressed by health care professionals and an aging appearance can be a source of significant distress [17]. Cutaneous body image dissatisfaction and resultant interpersonal sensitivity and feelings of social alienation have been associated with increased suicide risk [4].

Cultural and Ethnic Factors

The clinician should be sensitive to the fact that the dermatology patient's cultural and ethnic background may have an important effect on how their skin disorder affects their quality of life and resultant disease-related stress. There are also cultural differences in the physiology of the stratum corneum barrier which plays an important role in stress reactive dermatoses. Studies have shown that a lighter skin tone is preferred by both individuals of European Caucasian descent and cultures and ethnic groups with a darker skin color [16, 18]. The term 'ethnic skin' has been used in the medical literature to describe skin of color, traditionally of Fitzpatrick skin types III-VI [19]. This does not define any particular race, ethnicity, or culture. The clinician should be aware that in many cultures the preference for fair or lighter colored skin is quite pervasive, as lighter skin is associated with several perceived benefits including job, beauty and marriage opportunity [20, 21], and the perception that an individual's skin is not 'fair' enough can be a source of social stigmatization and stress for the individual. As a result harmful practices like skin bleaching may be carried out [16], which can further enhance the dermatologic morbidity associated with the skin condition. It is important for the clinician be sensitive to these issues and make an effort to mitigate the perpetuation of stress resulting from deep-rooted belief systems regarding preferred skin color [16, 20].

A Biopsychosocial Approach

A biopsychosocial approach (Table 2.3) that takes into consideration the patient's social, psychological/psychiatric and general medical status in addition to dermatologic symptoms, is suggested when assessing the role of stress in skin disease. The patient should be assessed within the context of their developmental stage and cultural background. A cosmetically disfiguring condition in an adolescent patient may be a lot more stressful for the patient, and the perceived stress may be grossly out of proportion to the dermatologic severity of the skin disorder. The patient should be screened for medical (e.g., metabolic syndrome) and psychiatric (e.g., body dysmorphic disorder, major depressive disorder, posttraumatic stress disorder) including substance use disorders, that are likely to enhance 'allostatic load' and

disease-related stress [22]. It is important to recognize that sleep and circadian-rhythm disruption play an important mediating role in stress associated flare-ups of skin disorders [12]; they can also exacerbate other comorbidities such as metabolic syndrome and major depression.

Table 2.3 Some general clinical factors that can moderate the relation between stress and skin disease

1. Demographic
Age – developmental stage of patient e.g., an adolescent patient's concern about the effect of a cosmetically disfiguring disorder upon their appearance can be grossly out of proportion to the clinical severity of the disorder
Culture and ethnicity – individual factors e.g., perceived social benefits of lighter skin in many cultures
Gender – men and women usually equally affected; earlier literature reported greater impact on quality of life of women versus men
Socioeconomic factors – homelessness has been associated with increased dermatologic morbidity; proper nutrition
2. General physical
Sleep – sleep restriction, and sleep and circadian rhythm disruption (e.g., related to rotating shift-work) can lead to a heightened pro-inflammatory state and autonomic dysregulation which can exacerbate many inflammatory skin diseases and decrease pruritus threshold
Body mass index – obesity is associated with higher risk of a range of skin disorders some of which e.g., psoriasis are known to be reactive to stress
Lesions in genital and other 'emotionally charged' regions – lesions in such regions know to be associated with greater stress and greater impact on quality of life; patients may not volunteer information about lesions in these regions for fear of stigmatization
Other symptoms of skin disorder – ask patient 'What bothers you the most about your skin condition?' Patients may be most stressed by symptoms that are not considered to be important from a clinical dermatologic perspective and hence may get over-looked
Physical skin-to-skin contact – in the case of infants and children, ask parents/caregivers if they are reluctant to touch or hold their child because of the skin disorder e.g., for fear of adversely affecting the disorder. Counsel parents/caregivers regarding the importance of skin-to-skin contact and nurturance of the child by touch
3. Psychiatric factors
Suicide risk – the psychosocial impact of disorders such as acne and psoriasis has been associated with increased suicide risk
Substance use – tobacco smoking, alcohol use, other substance use disorders
Psychiatric comorbidity – may be present in upto one-third of dermatology patients, and can affect the patient's perception of stress and ability to manage stress- comorbidities include major depressive disorder, obsessive-compulsive and related disorders, social anxiety disorder, posttraumatic stress disorder, body dysmorphic disorder and dissociative disorders
4. Medical comorbidities
Obesity – obesity and metabolic syndrome is being increasingly recognized as a factor in inflammatory dermatoses e.g., psoriasis and atopic dermatitis
Other conditions – depending upon the primary dermatologic disorder, assess patients for other comorbidities that may be contributing the stress reactivity of the skin disorder

References

1. Goldstein DS, Kopin IJ. Evolution of concepts of stress. Stress. 2007;10(2):109–20.
2. Gupta MA, Levenson JL. Dermatology. In: Levenson JL, editor. The American Psychiatric Publishing Textbook of psychosomatic medicine: psychiatric care of the medically ill. 2nd ed. Washington, DC: American Psychiatric Association; 2011. p. 667–90.
3. Gupta MA, Gupta AK. A practical approach to the assessment of psychosocial and psychiatric comorbidity in the dermatology patient. Clin Dermatol. 2013;31(1):57–61.
4. Gupta MA, Gupta AK. Cutaneous body image dissatisfaction and suicidal ideation: mediation by interpersonal sensitivity. J Psychosom Res. 2013;75(1):55–9.
5. Both H, Essink-Bot ML, Busschbach J, Nijsten T. Critical review of generic and dermatology-specific health-related quality of life instruments. J Invest Dermatol. 2007;127(12):2726–39.
6. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)–a simple practical measure for routine clinical use. Clin Exp Dermatol. 1994;19(3):210–6.
7. Basra MK, Fenech R, Gatt RM, Salek MS, Finlay AY. The dermatology life quality index 1994–2007: a comprehensive review of validation data and clinical results. Br J Dermatol. 2008;159(5):997–1035.
8. Gupta MA, Gupta AK. Current concepts in psychodermatology. Curr Psychiatry Rep. 2014;16(6):449.
9. Slominski AT, Zmijewski MA, Skobowiat C, Zbytek B, Slominski RM, Steketee JD. Sensing the environment: regulation of local and global homeostasis by the skin's neuroendocrine system. Adv Anat Embryol Cell Biol. 2012;212:v, vii, 1–115.
10. Orion E, Wolf R. Psychological stress and epidermal barrier function. Clin Dermatol. 2012;30(3):280–5.
11. Dhabhar FS. Psychological stress and immunoprotection versus immunopathology in the skin. Clin Dermatol. 2013;31(1):18–30.
12. Gupta MA, Gupta AK. Sleep-wake disorders and dermatology. Clin Dermatol. 2013;31(1):118–26.
13. Morgan BE, Horn AR, Bergman NJ. Should neonates sleep alone? Biol Psychiatry. 2011;70(9):817–25.
14. van Rosmalen L, van der Horst FC, van der Veer R. Of monkeys and men: Spitz and Harlow on the consequences of maternal deprivation. Attach Hum Dev. 2012;14(4):425–37.
15. Orion E, Wolf R. Psychologic consequences of facial dermatoses. Clin Dermatol. 2014;32(6):767–71.
16. Gupta MA, Gupta AK. Evaluation of cutaneous body image dissatisfaction in the dermatology patient. Clin Dermatol. 2013;31(1):72–9.
17. Gupta MA. Aging skin: some psychosomatic aspects. In: Farage AM, Miller WK, Maibach IH, editors. Textbook of aging skin. Berlin/Heidelberg: Springer; 2015. p. 1–19.
18. Swami V, Furnham A, Joshi K. The influence of skin tone, hair length, and hair colour on ratings of women's physical attractiveness, health and fertility. Scand J Psychol. 2008;49(5):429–37.
19. Talakoub L, Wesley NO. Differences in perceptions of beauty and cosmetic procedures performed in ethnic patients. Semin Cutan Med Surg. 2009;28(2):115–29.
20. Verma SB. Obsession with light skin–shedding some light on use of skin lightening products in India. Int J Dermatol. 2010;49(4):464–5.
21. Hamed SH, Tayyem R, Nimer N, Alkhatib HS. Skin-lightening practice among women living in Jordan: prevalence, determinants, and user's awareness. Int J Dermatol. 2010;49(4):414–20.
22. McEwen BS. Stress, adaptation, and disease. Allostasis and allostatic load. Ann N Y Acad Sci. 1998;840:33–44.

Chapter 3
Anxiety, Depression, and OCD: Understanding Common Psychiatric Conditions in the Dermatological Patient

Josie Howard and Wilmarie Cidre Serrano

Depressive Disorders

Overview and Epidemiology of Depressive Disorders

Depression is one of the most common psychiatric disorders and a leading cause of disability and disease burden worldwide [1]. According to the World Health Organization, approximately 350 million people suffer from depression worldwide [2]. In the US alone the lifetime incidence of depression is approximately 12 % in men and 20 % in women [3]. Depression is two times more prevalent in women compared to men and is less prevalent in the elderly compared to young adults [4]. It's estimated that 25–30 % of dermatological patients have psychiatric diagnoses [5, 6]. While depression is common and associated with significant morbidity and mortality, it remains highly under-diagnosed and undertreated.

Depression is currently understood as a group of heterogeneous illnesses with a common phenotype that is characterized by a low, sad, empty or irritable mood that affects a person's social and/or cognitive function. To diagnose depression, a distinct change in mood must be present and is often accompanied by psychophysiological cognitive as well as neurovegetative symptoms, including changes in sleep, appetite, and energy levels. The change in mood cannot be explained entirely by external or medical circumstances and often seems disproportionate to the precipitating events. While depression's course can be highly variable, it is usually charac-

J. Howard, MD (✉)
Private Practice Psychiatry, Departments of Dermatology and Psychiatry, University of California, 490 Post Street, Suite 1703, San Francisco, CA 94118, USA
e-mail: josie.howard@ucsf.edu

W.C. Serrano, MD
Department of Psychiatry, Stanford University, Stanford, CA, USA

K. França, M. Jafferany (eds.), *Stress and Skin Disorders*,
DOI 10.1007/978-3-319-46352-0_3

terized as an episodic and chronic illness. Left untreated, depression can lead to chronic disability or suicide.

Risk factors for the development of depression include the following: family history of depression, female gender, neuroticism (personality trait characterized by a propensity to experience negative emotional state in response to conflict), negative cognitive bias (focus on negative memories and thoughts), stressful life events, and adverse childhood experiences [7]. While there is no one established mechanism for the development of depression, depression involves abnormal functioning of neurotransmitters and implicates brain circuits like the anterior cingulate, dorsolateral prefrontal cortex, orbitofrontal cortex, amygdala, ventral striatum, and hippocampus in the development of depression. Twin studies suggest a 37 % heritability of depression [8], yet no specific genes have been reliably linked to the development of depression. Most of the current pharmacological treatments for depression target the neurotransmitter imbalance that has been theorized to drive the development of depression.

Depressive Disorders and the DSM

The American Psychiatric Association's DSM, the most commonly used diagnostic manual for psychiatric disorders, was last updated in 2013 and published as the DSM-5 [9]. In past editions of the DSM, depressive disorders were listed with other mood disorders under the chapter "Bipolar and Related Disorders." In the DSM-5, however, depressive disorders are listed in a separate chapter and include the following disorders: *Major Depressive Disorder, Persistent Depressive Disorder, Disruptive Mood Dysregulation Disorder, Premenstrual Dysphoric Disorder, Substance or Medication-Induced Depressive Disorder, Depressive Disorder Due to Another Medical Condition, Other Specified Depressive Disorder and Unspecified Depressive Disorder*.

The main depression and related disorders **DSM-5 changes** include [9, 10]:

- Addition of Disruptive Mood Dysregulation Disorder and Premenstrual Dysphoric Disorder
- The specifier "with mixed features" was added to characterize patients with major depressive episode and manic features that do not meet criteria for a manic episode.
- The specifier "with anxious distress" was added to characterize patients with a major depressive episode and anxious features. This was done as anxiety is an important prognostic value and affects the treatment choice.
- Dysthymia was eliminated and now falls under the category of persistent depressive disorder, which includes both chronic major depressive disorder and the previous dysthymic disorder.
- The bereavement exclusion, which used to advise clinicians against the diagnosis of depression within 2 months of the loss of a loved one, has now been eliminated. This change comes from the recognition that bereavement lasts longer than 2 months and can be complicated by depression soon after the loss of a loved one (see Table 3.1 for more details).

Table 3.1 DSM-5 MDD diagnostic criteria

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of rest or pleasure. (**Note:** Do not include symptoms that are clearly attributable another medical condition)
1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad empty, hopeless) or observation made by others (e.g., appears tearful). (**Note:** In children and adolescents, can be irritable mood.)
2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation)
3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5 % of body weight i a month), or decrease or increase in appetite nearly every day. (**Note:** In children, consider failure to make expected weight gain.)
4. Insomnia or hypersomnia nearly every day
5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)
6. Fatigue or loss of energy nearly every day
7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)
9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide
B. he symptoms cause clinically significant distress or impairment in social, occupational, or other important as of functioning
C. he episode is not attributable to the physiological effects of a substance or to another medical condition
Note: Must meet Criteria A–C to represent a major depressive episode
Note: Responses to a significant loss (e.g., bereavement, financial ruin, losses from a natural disaster, a serious medical illness or disability) may include the feelings of intense sadness, rumination about the loss, insomnia, poor appetite, and weight loss noted in Criterion A, which may resemble a depressive episode. Although such symptoms may be understandable or considered appropriate to the loss, the presence of a major depressive episode in addition to the normal response to a significant loss should also be carefully considered. This decision inevitably requires the exercise of clinical judgment based on the individual's history and the cultural norms for expression of distress in the context of loss. In distinguishing grief from a major depressive episode (MDE), it is useful to consider that in grief the predominant affect is feelings of emptiness and loss, while in MDE it is persistent depressed mood and the inability to anticipate happiness or pleasure. The dysphoria in grief is likely to decrease in intensity over days to weeks and occurs in waves, the so-called pangs of grief. These waves tend to be associated with thoughts or reminders of the deceased. The depressed mood of MDE is more persistent and not tied to specific thoughts or preoccupations. The pain of grief may be accompanied by positive emotions and humor that are uncharacteristic of the pervasive unhappiness and misery characteristic of MDE. The thought content associated with grief generally features a preoccupation with thoughts and memories of the deceased, rather than the self-critical or pessimistic ruminations seen in MDE. In grief, self-esteem is generally preserved, whereas in MDE feelings of worthlessness and self-loathing are common. If self-derogatory ideation is present in grief, it typically involves perceived failings vis-à-vis the deceased (e.g., not visiting frequently enough, not telling deceased how much he or she was loved). If a bereaved individual thinks about death and dying, such though are generally focused on the deceased and possibly about "joining" the deceased, whereas in MDE such thoughts focused on ending one's own life because of feeling worthless, undeserving of life, or unable to cope with the n of depression

Table 3.1 (continued)

D. The occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders
E. There has never been a manic episode or a hypomanic episode. (**Note:** This exclusion does not apply if all of the manic-like or hypomanic-like episodes are substance-induced or are attributable to the physiological effects of another medical condition.)

Reference: American Psychiatric Association's DSM-5 [9]

Major Depressive Disorder

Major depressive disorder is the most common depressive disorder. Table 3.1 lists the DSM-5 criteria for the diagnosis of MDD [9].

The DSM-5 includes the following new specifiers for MDD: "with anxious distress" and "with mixed features." These specifiers allow for the characterization of additional symptoms. In addition, the DSM-5 expands the specifier "postnatal onset" to include onset during pregnancy by substituting "postnatal onset" with "perinatal onset."

The following is a complete list of the DSM-5 specifiers for MDD [9]:

- With anxious distress
- With mixed features
- With melancholic features
- With atypical features
- With mood-congruent psychotic features
- With mood-incongruent psychotic features
- With catatonia
- With peripartum onset
- With seasonal pattern

When considering a diagnosis of depression, it is of utmost importance to screen for symptoms of current or past mania. Manic symptoms include: decreased sleep, racing thoughts, pressured speech, distractibility, increased risky behavior, and inflated self-esteem or sense of grandiosity. In order to be considered a manic episode, the patient must have noticeable difficulty keeping his social and work responsibilities, need hospitalization, or suffer from delusions. A floridly manic patient should be taken to the Emergency Room for evaluation. SSRI's should not be prescribed in patients with a history of mania or hypomania as they may precipitate a manic episode.

A thorough assessment of suicidality must be undertaken in any patient suspected of being depressed. This evaluation includes an assessment of ideation, plan, and intent. We recommend the following screening questions:

- Ideation: It seems like thing have been difficult recently, has it ever gotten so bad that you have thought of taking your life?
- Plan: Have you thought about how you would kill yourself? Have you made any plans? Do you have access to firearms or weapons?

- Intent: Do you think you would carry out these plans? Have you ever tried to kill yourself in the past?

Patients at risk for suicide must be taken to the nearest Emergency Room for evaluation.

Treatment of Depressive Disorders

Overview

The goal of depression treatment is remission, or return to baseline. The initial treatment for unipolar depression consists of pharmacotherapy, psychotherapy, or both. Evidence suggests that the combination of pharmacotherapy and psychotherapy is more effective than either therapy alone [11, 12]. Given issues of patient openness to psychotherapy referrals as well as limited availability of psychotherapy providers in some areas, it may also be helpful to encourage patients to seek support or counseling as is appropriate and available in their social context.

Pharmacology

SSRIs, a type of second-generation anti-depressant, are the most commonly prescribed antidepressants given their efficacy and tolerability. Table 3.2 details the doses and most common side effects of SSRIs. Since their efficacy is comparable, choosing among this list of antidepressants is usually based on factors like side effects, safety, patient preference, cost, and comorbidities. The most common side effects include: diarrhea, nausea, vomiting, and sexual dysfunction.

Psychotherapy

The most commonly used therapies for depression include cognitive behavioral therapy (CBT), interpersonal therapy (IPT), psychodynamic psychotherapy, and supportive therapy.

Table 3.2 SSRI antidepressant medications

Antidepressant name (trade name)	Starting dose	Target daily dose
Citalopram (Celexa)	10	20–40
Escitalopram (Lexapro)	5	10–20
Fluoxetine (Prozac)	10	20–60
Paroxetine CR (Paxil CR)	12.5	25–50
Sertraline (Zoloft)	25	50–200

This table was modified and abbreviated version of Table 3.7: Antidepressant Medications in *The American Psychiatric Publishing Textbook of Psychopharmacology* [13]. Starting doses were halved to reduce side-effects and increase compliance; this is commonly done by psychiatrists. Medications should be slowly titrated up to the target dose as needed for symptom relief and as tolerated

CBT is a skill-oriented and time-limited psychotherapy where the therapist helps patients change the relationship that they have with their thoughts and identify cognitive distortions. CBT also teaches participants to recognize maladaptive thoughts or behaviors and substitute them with adaptive ones.

IPT is also a time-limited psychotherapy that focuses on interpersonal relationships. This therapy rests on the theory that there is a relationship between a person's mental health and how they interact with people.

Depressive Disorders Subsection Take Home Points

- Main Changes introduced in DSM-5:
  - The following disorders were added: Disruptive mood dysregulation and premenstrual dysphoric disorder.
  - Dysthymia was eliminated and is now included under the diagnosis of persistent depressive disorder.
  - Specifiers 'with mixed features' and 'with anxious distress' were added to MDD.
  - The bereavement exclusion was eliminated
- Major Depressive Disorder is the most common depressive disorder and can be treated with psychopharmacology and/or psychotherapy. Clinicians should assess suicidality when considering a diagnosis of MDD.

Unlike CBT and IPT, psychodynamic psychotherapy focuses on the unconscious and is based on the idea that events in the past affect how we experience the present through our unconscious.

Supportive psychotherapy is a type of listening therapy where the therapist's main role is to form an alliance with the patient and provide support.

Anxiety Disorders

Overview and Epidemiology of Anxiety Disorders

Anxiety and fear can be normal and adaptive human emotions. Anxiety often manifests itself as uneasiness towards anticipated and imagined dangers, whereas fear is triggered by a real and present danger and is usually associated with the stress response, that is to say, the body's response to a real or perceived threat. When these normal stress responses become unmanageable symptoms, an anxiety disorder or medical condition exacerbated by anxiety should be considered.

Anxiety disorders are characterized by a chronic state of persistent, excessive, and debilitating anxiety and/or fear that is often accompanied by avoid-

ance behaviors. Anxiety disorders are the most common mental health disorder worldwide [14] and their lifetime prevalence is over 25 % in the US [15]. High risk groups include those with a history of childhood adversity or trauma, low-income women, as well as middle-aged widowed, separated, or divorced individuals [16, 17].

Anxiety Disorders and the DSM

The following anxiety disorders are described in the DSM-5 [9]: *Separation Anxiety Disorder, Selective Mutism, Specific Phobia, Social Anxiety Disorder, Panic Disorder, Agoraphonia, Generalized Anxiety Disorder, Substance/Medication-Induced Anxiety Disorder, Anxiety Disorder due to Another Medical Condition, Other Specified Anxiety Disorder, and Unspecified Anxiety Disorder*.

The main anxiety disorders-related **DSM-5 changes** include the following [10]:

- Anxiety disorders are listed in a separate chapter and no longer include obsessive-compulsive disorders or post-traumatic stress disorder.
- Individuals over 18 no longer need to recognize that their fear is excessive in order to be diagnosed with agoraphobia, social anxiety disorder, or specific phobia
- The minimum 6-month duration for the diagnosis of agoraphobia, social anxiety disorder, and specific phobia was extended to all ages (in the DSM-IV the 6 month duration minimum was limited to individuals under 18 years of age).
- Different types of panic attacks are now described as expected or unexpected.
- Panic disorder and agoraphobia are two separate diagnoses whereas in the DSM-IV one could diagnose panic disorder with agoraphobia, panic disorder without agoraphobia, and agoraphobia without history of panic disorder.
- Social phobia is now called social anxiety disorder and the "generalized" specifier was eliminated and replaced by "performance only."
- Separation Anxiety Disorder and Selective Mutism are now classified as anxiety disorders, whereas in the DSM-IV they were under the subsection "Disorders usually first diagnosed in infancy, childhood or adolescence."
- The criteria for diagnosis of Separation Anxiety Disorder no longer include an age of onset before 18 years of age.

We will focus on Generalized Anxiety Disorder, as it is the anxiety disorder that we have observed to most often complicate the treatment of dermatological patients.

Generalized Anxiety Disorder

Generalized Anxiety Disorder (GAD) is a chronic condition characterized by excessive and uncontrollable worry over numerous aspects of ones life that often interferes with functioning and is accompanied by behavioral changes and somatic

Table 3.3 DSM-5 criteria for diagnosis of generalized anxiety disorder

A. Excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 months, about a number of events or activities (such as work or school performance)
B. The individual finds it difficult to control the worry
C. The anxiety and worry are associated with three (or more) of the following six symptoms (with at least some symptoms having been present for more days than not for the past 6 months):
Note: Only one item is required in children
1. Restlessness or feeling keyed up or on edge
2. Being easily fatigued
3. Difficulty concentrating or mind going blank
4. Irritability
5. Muscle tension
6. Sleep disturbance (difficulty falling or staying asleep, or restless, unsatisfying sleep)
B. The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
C. The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition (e.g., hyperthyroidism)
D. The disturbance is not better explained by another mental disorder (e.g., anxiety or worry about having panic attacks in panic disorder, negative evaluation in social anxiety disorder [social phobia], contamination or other obsessions in obsessive-compulsive disorder, separation from attachment figures in separation anxiety disorder, reminders of traumatic events in posttraumatic stress disorder, gaining weight in anorexia nervosa, physical complaints in somatic symptom disorder, perceived appearance flaws in body dysmorphic disorder, having a serious illness in illness anxiety disorder, or the content of delusional beliefs in schizophrenia or delusional disorder)

Reference: American Psychiatric Association's DSM-5 [9]

symptoms. In order to diagnose GAD, symptoms must be present for at least 6 months. Table 3.3 details the complete DSM-5 criteria for the diagnosis of GAD [9].

GAD is highly prevalent in primary care settings and has a 12-month prevalence of approximately 2 % [16, 18]. Its age of onset is generally late adolescence or early adulthood and risk factors for its development are similar to the risk factors for the development of depressive disorders. GAD is two times more common in women compared to men and is often comorbid with other psychiatric disorders; the lifetime comorbidity with other disorders has been reported to be as high as 90 % [17].

GAD first appeared in the DSM in its third edition. Since then, the diagnostic criteria have changed significantly [16]. Before the DSM-III, GAD was considered a residual condition. As such, it wasn't until after 1980 that clinicians started understanding and diagnosing GAD as a separate diagnosis. Even then, the DSM-III prohibited the diagnosis of GAD when there were other psychiatric diagnoses. With the DSM-IIIR, GAD could be diagnosed with other psychiatric conditions. There have not been any significant changes in the diagnostic criteria for GAD between the DSM-IV and DSM-5 [10].

When considering a diagnosis of GAD, careful attention must be paid to other medical or psychiatric conditions that could be primary or comorbid. If an older patient presents with excessive worrying, weight loss and cognitive changes, consider

other medical causes to explain these changes. It is also important to gather a complete social, substance use, and family psychiatric history when considering a diagnosis of GAD. Of note, GAD can be diagnosed with or without panic attacks, which are characterized by discrete periods of intense fear accompanied by bodily symptoms like heart palpitations, dizziness, chest pain, or shortness of breath. The occurrence of panic attacks is not sufficient for the diagnosis of panic disorder, which is outside the scope of this chapter.

Treatment of Generalized Anxiety Disorder

Traditionally the goal of GAD treatment had been treatment response, however the field has been moving towards considering remission, or >70 % improvement from baseline, to be the new treatment goal [13]. Like MDD, GAD can be treated with psychopharmacology and/or psychotherapy. Because all of the psychotherapies delineated in the MDD section are applicable to the treatment of GAD, this subsection will focus on psychopharmacology. It should be noted, however, that psychotherapy is a critical component in the treatment of anxiety disorders. Please refer to the psychotherapies for MDD section for more detail.

Psychopharmacology Treatments

Selective Serotonin Reuptake Inhibitors

SSRIs are the first-line treatment of GAD. Because the anxiolytic effects of SSRIs are quite similar across the different drugs, factors that guide selection of specific SSRIs include side-effect profile, family history (first degree relatives with a response to a particular agent), cost/availability, and patient preference. Table 3.2 details the SSRI doses used in MDD, which are similar to those used in GAD. Note that the starting dose for GAD is often lower to avoid initial exacerbation of symptoms and the target dose is often higher to treat anxiety disorders. Additionally, the titration schedule is often slower in an effort to avoid exacerbation of somatic symptoms in anxious, vigilant patients. Patients with GAD may show some early response to SSRIs within 4 weeks, but often require 6–8 weeks to see the full benefit. Patients should be counseled about this timeline to set expectations appropriately. It should also be noted that any side effects that emerge are most likely to be experienced within the first 6–8 weeks and often dissipate after that time. If the patient shows only partial improvement, the SSRI dose can be increased after this timeframe. A different medication trial is recommended if the patient does not show any response after a 6–8 week trial. A trial of a second SSRI is recommended before moving on to an agent in another class (most often an SNRI). When switching SSRIs, the clinician can choose between a cross-taper or a full switch. Since SSRIs have the same mechanism of action, switching SSRIs with equivalent doses is generally well

tolerated by patients and is probably the simplest choice. Clinicians must remember that, upon discontinuation, antidepressants need to be tapered at a rate of about 25 % reduction per week given the risk for discontinuation syndrome. While not physiologically dangerous, antidepressant discontinuation syndrome can be quite uncomfortable for patients and includes anxiety, irritability, nausea, dizziness, fatigue, and muscle aches. Paroxetine is notorious for its discontinuation syndrome and utmost care must be taken when tapering this antidepressant.

Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)

Duloxetine and Venlafaxine are SNRIs that have been approved for the treatment of GAD. The starting doses in milligrams for duloxetine and venlafaxine are 30 and 37.5 (if XR), respectively. The target dose range in milligrams for duloxetine and venlafaxine is 60–120 and 75–225, respectively. Blood pressure must be monitored when starting patients on venlafaxine since this medication can cause small increases in blood pressure. Discontinuation should be done in a similar manner to SSRI's to avoid discontinuation syndrome.

Benzodiazepines

While benzodiazepines have historically been initiated early in the treatment of anxiety disorders, there is increasing concern regarding their potential for physical dependence, abuse, and withdrawal. As such, we do not recommend benzodiazepines as first line agents for the treatment of GAD. Benzodiazepines can be used as short-term therapy (2–6 weeks) bridge treatment to help patients cope with their anxiety while the effects of the SSRIs commence. Due to their sedative effects, benzodiazepines should be avoided in the elderly in order to prevent confusion and falls. Short-acting benzodiazepines like alprazolam or Xanax should be avoided altogether, as their risk for dependence is higher than long-acting agents and it is very difficult to take patients off short-acting benzodiazepines. Table 3.4 details the most commonly used benzodiazepines. If benzodiazepines are prescribed, utmost care should be taken to prescribe the minimum amount required for short-term

Table 3.4 Commonly used Benzodiazepines and their characteristics

Benzodiazepine Medication	Brand name	Dose (mg)	Oral absorption	Half-life (hours)
Alprazolam	Xanax	1–4	Intermediate	14
Clonazepam	Klonopin	0.5–3	Intermediate	30–40
Diazepam	Valium	5–40	Fast	40–100
Lorazepam	Ativan	1–6	Intermediate	14

This table was modified from Table 24.1 in the *Manual of Clinical Psychopharmacology*, Eighth Edition [19]

treatment and only one clinician should be responsible for prescribing benzodiazepines per patient.

Patients often use complementary and alternative treatments to reduce their stress and anxiety [20]. Exercise and meditation are important and effective anxiolytics that should be recommended to patients. Herbal remedies like kava, St. John's Wart, and valerian root are often used to relieve anxiety even though their effectiveness has not been studied well. **Kava** has been reported in numerous randomized trials to have anxiolytic effects, yet its safety is questionable and there have been multiple case reports of liver failure associated with the use of kava [21–23]. **St John's Wart** is a plant that is commonly used as an anxiolytic or anti-depressant. Clinicians should know that combining St John's wart with SSRIs must be avoided as it can lead to serotonergic syndrome [24]. **Valerian Root** is commonly used for insomnia. While there is not much literature to back up the use of valerian root in patients with anxiety, it is relatively safe with minimal side-effects.

Anxiety Disorder Subsection Take Home Points

- Main Changes introduced in DSM-5:
  - Obsessive Compulsive disorders and PTSD are no longer part of the Anxiety Disorders chapter and were granted their own separate chapters in the DSM-5.
  - Patients no longer need to recognize that their fear is excessive in order to be diagnosed with an anxiety disorder
  - The minimum 6-month duration for the diagnosis of agoraphobia, social anxiety disorder, and specific phobia was extended to all ages
  - Panic disorder and agoraphobia are two separate diagnoses
- Generalized Anxiety Disorder is a common condition with high comorbidity with other anxiety and mood disorders. First line treatments include psychotherapy (CBT) and SSRIs. Benzodiazepines are NOT a first-line treatment for GAD. Always rule-out bipolar disorder before starting an SSRI or SNRI.

Obsessive Compulsive and Related Disorders

A Overview and Epidemiology of Obsessive Compulsive and Related Disorders

Obsessive Compulsive and related-disorders are a mixed group of diagnoses that share the presence of obsessions and/or compulsions. Obsessions are recurrent and unwanted thoughts. Compulsions are repetitive ritualized behaviors that occur as a response to obsessive thoughts. While the presence of some repetitive thinking is psychologically normal, when obsessions and compulsions interfere with daily life, an obsessive compulsive and related disorder should be considered.

Many obsessive compulsive and related disorder patients suffer from dermatological conditions that are exacerbated, if not caused, by their psychiatric diagnoses. As such, dermatologists have significant contact with this population. Given that many patients with obsessive compulsive and related disorders remain undiagnosed and untreated, dermatologists can play a key role in the much-needed identification and appropriate referral of these patients who often suffer undiagnosed for many years.

Obsessive Compulsive and Related Disorders and the DSM

The following Obsessive Compulsive and related disorders are listed in the DSM-5 [9]: *Obsessive-Compulsive Disorder, Body Dysmorphic Disorder, Hoarding Disorder, Trichotillomania (Hair-Pulling Disorder), Excoriation (Skin-picking) Disorder, Substance/Medication-Induced Obsessive-Compulsive and Related Disorder, Obsessive-Compulsive and Related Disorder due to Another Medical Condition, Other Specified Obsessive-Compulsive and Related Disorder, Unspecified Obsessive-Compulsive and Related Disorder*.

Obsessive Compulsive and Related Disorders were previously included in the anxiety chapter of the DSM. However, they are now listed in their own, separate chapter in the DSM-5. Changes introduced in the DSM-5 also include the following [10]:

- The following new disorders were added: Hoarding Disorder, Excoriation (Skin-Picking) Disorder, Substance/Medication-Induced Obsessive-Compulsive and Related Disorder, and Obsessive-Compulsive and Related Disorder Due to Another Medical Condition
- Impulse-Control Disorders were eliminated as a category.
- Trichotillomania, which was previously listed as an Impulse-Control Disorder, is now under Obsessive-Compulsive and Related Disorders.
- Insight specifiers (good or fair insight, poor insight, or absent/delusional insight) were added to Obsessive-Compulsive Disorder, Body Dysmorphic Disorder, and Hoarding Disorder.
- An additional diagnostic criterion was added to Body Dysmorphic Disorder and characterizes the presence of repetitive behaviors or mental acts in response to appearance concerns.
- The specifier ‘with muscle dysmorphia’ was added to Body Dysmorphic Disorder.

Obsessive Compulsive Disorder

As the name denotes, Obsessive Compulsive Disorder (OCD) is a chronic disorder characterized by severe, recurrent, and time-consuming obsessions, compulsions, or both. Patients with OCD usually spend more than an hour daily attending to their obsessions and/or compulsions and experience these as unwanted and intrusive. While the content of obsessions vary widely, common themes include:

contamination, safety, forbidden thoughts, thoughts of harm, and doubt of ones memory. The most common compulsions include: counting, cleaning, lock checking, list making, or arranging objects. The DSM-5 diagnostic criteria for OCD are described in Table 3.5 [9].

Table 3.5 DSM-5 diagnostic criteria for obsessive compulsive disorder

A. Presence of obsessions, compulsions, or both:
Obsessions are defined by (1) and (2):
1. Recurrent and persistent thoughts, urges, or images that are experienced, at some time during the disturbance, as intrusive and unwanted, and that in most individuals cause marked anxiety or distress
2. The individual attempts to ignore or suppress such thoughts, urges, or images, or to neutralize them with some other thought or action (i.e., by performing a compulsion)
Compulsions are defined by (1) and (2):
1. Repetitive behaviors (e.g., hand washing, ordering, checking) or mental acts (e.g., praying, counting, repeating words silently) that the individual feels driven to perform in response to an obsession or according to rules that must be applied rigidly
2. The behaviors or mental acts are aimed at preventing or reducing anxiety or distress, or preventing some dreaded event or situation; however, these behaviors or mental acts are not connected in a realistic way with what they are designed to neutralize or prevent, or are clearly excessive
Note: Young children may not be able to articulate the aims of these behaviors or mental acts
B. The obsessions or compulsions are time-consuming (e.g., take more than 1 h per day) or cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
C. The obsessive-compulsive symptoms are not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition
D. The disturbance is not better explained by the symptoms of another mental disorder (e.g., excessive worries, as in generalized anxiety disorder; preoccupation with appearance, as in body dysmorphic disorder; difficulty discarding or parting with possessions, as in hoarding disorder; hair pulling, as in trichotillomania [hair-pulling disorder]; skin picking, as in excoriation [skin-picking] disorder; stereotypies, as in stereotypic movement disorder; ritualized eating behavior, as in eating disorders; preoccupation with substances or gambling, as in substance-related and addictive disorders; preoccupation with having an illness, as in illness anxiety disorder; sexual urges or fantasies, as in paraphilic disorders; impulses, as in disruptive, impulse-control, and conduct disorders; guilty ruminations, as in major depressive disorder; thought insertion or delusional preoccupations, as in schizophrenia spectrum and other psychotic disorders; or repetitive patterns of behavior, as in autism spectrum disorder)
Specify if:
With good or fair insight: The individual recognizes that obsessive-compulsive disorder beliefs are definitely or probably not true or that they may or may not be true
With poor insight: The individual thinks obsessive-compulsive disorder beliefs are probably true
With absent insight/delusional beliefs: The individual is completely convinced that obsessive-compulsive disorder beliefs are true
Specify if:
Tic-related: The individual has a current or past history of a tic disorder

Reference: American Psychiatric Association's DSM-5 [9]

The lifetime prevalence of OCD is 2.3 % [25] and its mean age of onset is 19.5 years [25]. The age of onset for men is typically earlier than that for women. The disorder is considered chronic, even though particular obsessions and compulsions may wax and wane. OCD is highly comorbid with other psychiatric disorders; the lifetime prevalence of another DSM disorder in individuals with OCD is approximately 90 % [25]. Anxiety and mood disorders are the two most common disorders comorbid with OCD.

OCD is often severely impairing. Patients with OCD have an average of 45.7 days of disability in a 12- month period; this number increases to 129.4 days in patients with severe OCD [25]. The quality of life and function of patients with OCD and a comorbid disorder is lowest compared to patients with OCD alone and healthy controls [26].

Dermatologists often encounter patients with OCD. In two separate studies, the prevalence of OCD in dermatological clinics was estimated to be above 20 % [27, 28]. Since rates of OCD remission are low without treatment and absent insight is rare in OCD patients, we believe that dermatologists can have an incredible impact in patient's lives by simply screening for OCD symptoms and making the appropriate referral to psychiatric care. We recommend the following screening questions: How often do you hand wash (if there is evidence on exam that hand washing may be excessive)? Do you ever feel like your hand-washing gets out of hand? Do you have any rituals? Are you fearful of germs? Do you find yourself repeatedly checking the locks? If so, how much time does this take out of your day?

Treatment of Obsessive Compulsive Disorder

Patients with a suspected diagnosis of OCD should be referred to a psychiatrist for treatment. The treatment for OCD usually involves psychopharmacology and/or psychotherapy. SSRIs are commonly used as initial treatment. With the exception of citalopram and escitalopram, all SSRIs listed in Table 3.2 are FDA approved to treat OCD. Patients with OCD are usually treated with higher doses of SSRIs compared to patients with MDD given that there is a dose–response relationship in the treatment of OCD with SSRIs [29]. CBT, which is described in section I.D, has been shown to successfully treat OCD [30].

Trichotillomania and Excoriation Disorder

The essential features of trichotillomania and excoriation disorders are hair pulling and skin picking, respectively. These two disorders were first introduced as diagnoses under obsessive compulsive and related disorders in the DSM-5. The diagnostic criteria for trichotillomania and excoriation disorder are listed in Tables 3.6 and 3.7, respectively [9].

Table 3.6 DSM-5 criteria for the diagnosis of trichotillomania

A. Recurrent pulling out of one's hair, resulting in hair loss
B. Repeated attempts to decrease or stop hair pulling
C. The hair pulling causes clinically significant distress or impairment in social, occupational, or other important areas of functioning
D. The hair pulling or hair loss is not attributable to another medical condition (e.g., a dermatological condition)
E. The hair pulling is not better explained by the symptoms of another mental disorder (e.g., attempts to improve a perceived defect or flaw in appearance in body dysmorphic disorder)

Reference: American Psychiatric Association's DSM-5 [9]

Table 3.7 DSM-5 criteria for the diagnosis of excoriation disorder

A. Recurrent skin picking resulting in skin lesions
B. Repeated attempts to decrease or stop skin picking
C. The skin picking causes clinically significant distress or impairment in social, occupational, or other important areas of functioning
D. The skin picking is not attributable to the physiological effects of a substance (e.g., cocaine) or another medical condition (e.g., scabies)
E. The skin picking is not better explained by symptoms of another mental disorder (e.g., delusions or tactile hallucinations in a psychotic disorder, attempts to improve a perceived defect or flaw in appearance in body dysmorphic disorder, stereotypies in stereotypic movement disorder, or intention to harm oneself in nonsuicidal self-injury)

Reference: American Psychiatric Association's DSM-5 [9]

Most of the epidemiological studies on trichotillomania have examined its prevalence in adolescents and college students. The lifetime prevalence of trichotillomania in college students is estimated to be 0.6 % [31]. There are no studies evaluating the prevalence of trichotillomania in the community. Trichotillomania impacts the social, occupational and psychological wellbeing of patients [32]. In a study of 1667 patients with trichotillomania, 23 % reported that their illness interfered with work and 36 % avoided participating in group activities [32].

Trichotillomania patients often present to the dermatology clinics with hair loss in various body sites characterized by regrowth at multiple stages. The most commonly affected areas are the scalp, eyebrows and eyelashes [32]. Alopecia areata and tinea capitis are part of the differential diagnosis [33]. Dermatologists should ask patients about hair-pulling behavior and refer patients who endorse symptoms of trichotillomania to a psychiatrist.

Excoriation disorder is not foreign for most dermatologists. The prevalence of excoriation disorder in adults is 1.4 % [34] but it is estimated to be much higher in dermatology patients. In a study of 60 patients with skin picking disorder, subjects endorsed picking at their skins for an average of 107.6 minutes per day. In the same study 38.3 % of the sample had a psychiatric comorbidity, with trichotillomania being the most common of these [35]. Other studies have reported that over 40 % of

patients with skin picking also meet criteria for depression and over 60 % meet criteria for an anxiety disorder [36].

The clinical presentation and severity of the excoriations varies, but usually includes various polymorphic lesions at different stages and in different parts of the body. The face is the most common site for excoriations. The distribution of lesions is also significant for occurring only in areas that a patient can reach (i.e. butterfly sign). Patients may also have scars or hypo/hyper pigmentation due to chronic inflammation.

Screening questions for excoriation disorder and trichotillomania include the following: *Do you ever pick at your skin or pull out your hair? How much time do you spend engaging in these behaviors on a daily basis? Does it ever feel out of control or like you want to stop but you can't?*

Treatment of Excoriation Disorder and Trichotillomania

Once primary skin disorders are ruled out, we recommend psychiatric referral for patients with a suspected diagnosis of excoriation disorder or trichotillomania [37]. Dermatological treatment may be required to treat any infections that occur secondary to excoriations. Dermatologists can also be incredibly helpful by identifying any underlying cutaneous dysesthesias (an abnormal, usually unpleasant, sensation in or on the skin) that may trigger skin picking. The clinician should ask about any sensations under the skin such as itching, creeping, crawling, pin prick, or biting sensations and then consider prescribing the appropriate agent (i.e. doxepin, hydroxyzine, neurontin), which can augment the psychiatric treatment of the patient. Other triggers that should be discussed include acne lesions (maximizing acne treatment can be helpful) as well as keratosis pilaris.

In our experience, it is not helpful to instruct the patient to stop these behaviors, as by definition they are unable to do so. However, it is helpful to empathize, normalize, identify, and refer. The clinician could use the following phrase: "Many people experience similar symptoms and there are treatments available…" If time allows, it can be incredibly comforting and helpful to explain your diagnostic impression and provide appropriate psychiatric referrals. An excellent resource for patients is the Trichotillomania Learning Center www.trich.org, which provides patient education, support, and referrals for patients with trichotillomania and skin picking disorders.

Psychiatric treatment of excoriation disorder includes SSRIs and occasionally pimozide. Delusional ideation should be ruled out. Trichotillomania patients are usually treated with behavioral psychotherapy as it has been shown to have the best outcomes [38, 39].

OCD and Related Disorders Section Take-Home Points

- Main Changes Introduced in DSM-5:
  - Impulse-Control Disorders were eliminated as a category
  - Excoriation Disorder, Substance/Medication-Induced Obsessive-Compulsive and Related Disorder, and Obsessive-Compulsive and Related Disorder Due to Another Medical Condition were added as Obsessive-Compulsive and Related Disorders.
  - Insight specifiers were added to Obsessive-Compulsive Disorder, Body Dysmorphic Disorder, and Hoarding Disorder.
- Dermatologists often serve as initial points of contact for patients with OCD, excoriation disorder, or trichotillomania. As such, they can play a major role in the identification of these patients and their appropriate referral to psychiatric care.
- OCD is a chronic disorder that can be severely impairing. Patients can present to the dermatologist with dermatitis from excessive hand washing or cleaning rituals. Please refer to a psychiatrist if you suspect your patient might have OCD.
- Skin picking and trichotillomania are psychiatric conditions that need to be treated by a psychiatrist. It is usually not therapeutic to ask patients to simply stop these behaviors.

References

1. Ferrari AJ, Charlson FJ, Norman RE, Patten SB, Freedman G, Murray CJ, Vos T, Whiteford HA. Burden of depressive disorders by country, sex, age, and year: findings from the global burden of disease study 2010. PLoS Med. 2013;10(11):e1001547.
2. WHO | Depression. In: WHO. http://www.who.int/mediacentre/factsheets/fs369/en/. Accessed 6 Jan 2016.
3. Kessler RC, Berglund P, Demler O, Jin R, Koretz D, Merikangas KR, Rush AJ, Walters EE, Wang PS. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA. 2003;289:3095–105.
4. Pedersen CB, Mors O, Bertelsen A, Waltoft BL, Agerbo E, McGrath JJ, Mortensen PB, Eaton WW. A comprehensive nationwide study of the incidence rate and lifetime risk for treated mental disorders. JAMA Psychiatry. 2014;71:573–81.
5. Picardi A, Abeni D, Melchi CF, Puddu P, Pasquini P. Psychiatric morbidity in dermatological outpatients: an issue to be recognized. Br J Dermatol. 2000;143:983–91.
6. Hughes JE, Barraclough BM, Hamblin LG, White JE. Psychiatric symptoms in dermatology patients. Br J Psychiatry. 1983;143:51–4.
7. Fava M, Kendler KS. Major depressive disorder. Neuron. 2000;28:335–41.

8. Sullivan PF, Neale MC, Kendler KS. Genetic epidemiology of major depression: review and meta-analysis. Am J Psychiatry. 2000;157(10):1552–62.
9. American Psychiatric Association, American Psychiatric Association, editors. Diagnostic and statistical manual of mental disorders: DSM-5. 5th ed. Washington, DC: American Psychiatric Association; 2013.
10. Association AP, Association AP, et al. Highlights of changes from DSM-IV-TR to DSM-5. Arlingt. VA Am Psychiatr Assoc. 2013:1–19. http://www.dsm5.org/documents/changes%20from%20dsm-iv-tr%20to%20dsm-5.pdf
11. Cuijpers P, Dekker JJM, Hollon SD, Andersson G, et al. Adding psychotherapy to pharmacotherapy in the treatment of depressive disorders in adults: a meta-analysis. J Clin Psychiatry. 2009;70(9):1219–29.
12. Cuijpers P, van Straten A, Warmerdam L, Andersson G. Psychotherapy versus the combination of psychotherapy and pharmacotherapy in the treatment of depression: a meta-analysis. Depress Anxiety. 2009;26:279–88.
13. Schatzberg AF, Nemeroff CB. The American Psychiatric Publishing textbook of psychopharmacology. Washington, DC: American Psychiatric Pub; 2009.
14. Kessler RC, Aguilar-Gaxiola S, Alonso J, Chatterji S, Lee S, Ormel J, Üstün TB, Wang PS. The global burden of mental disorders: an update from the WHO World Mental Health (WMH) surveys. Epidemiol Psichiatr Soc. 2009;18:23–33.
15. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005;62:593–602.
16. Grant BF, Hasin DS, Stinson FS, Dawson DA, June Ruan W, Goldstein RB, Smith SM, Saha TD, Huang B. Prevalence, correlates, co-morbidity, and comparative disability of DSM-IV generalized anxiety disorder in the USA: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Psychol Med. 2005;35:1747–59.
17. Wittchen H-U, Zhao S, Kessler RC, Eaton WW. DSM-III-R generalized anxiety disorder in the National Comorbidity Survey. Arch Gen Psychiatry. 1994;51:355–64.
18. Grant BF, Stinson FS, Dawson DA, Chou SP, Dufour MC, Compton W, Pickering RP, Kaplan K. Prevalence and co-occurrence of substance use disorders and independent mood and anxiety disorders. Alcohol Res Health. 2006;29:107–20.
19. Schatzberg AF, DeBattista C. Manual of clinical psychopharmacology. Washington, DC: American Psychiatric Publishing, a division of American Psychiatric Association; 2009.
20. Bystritsky A, Hovav S, Sherbourne C, Stein MB, Rose RD, Campbell-Sills L, Golinelli D, Sullivan G, Craske MG, Roy-Byrne PP. Use of complementary and alternative medicine in a large sample of anxiety patients. Psychosomatics. 2012;53:266–72.
21. Cases N. Fatal fulminant hepatic failure induced by a natural therapy containing kava. Med J Aust. 2003;178:442–3.
22. Kraft M, Spahn TW, Menzel J, Senninger N, Dietl KH, Herbst H, Domschke W, Lerch MM. [Fulminant liver failure after administration of the herbal antidepressant Kava-Kava]. Dtsch Med Wochenschr. 2001;126:970–2.
23. Clouatre DL. Kava kava: examining new reports of toxicity. Toxicol Lett. 2004;150:85–96.
24. Mannel M. Drug interactions with St John's wort. Drug Saf. 2004;27:773–97.
25. Ruscio AM, Stein DJ, Chiu WT, Kessler RC. The epidemiology of obsessivecompulsive disorder in the National Comorbidity Survey Replication. Mol Psychiatry. 2010;15:53–63.
26. Huppert JD, Simpson HB, Nissenson KJ, Liebowitz MR, Foa EB. Quality of life and functional impairment in obsessive–compulsive disorder: a comparison of patients with and without comorbidity, patients in remission, and healthy controls. Depress Anxiety. 2009;26:39–45.
27. Fineberg NA, O'Doherty C, Rajagopal S, Reddy K, Banks A, Gale TM. How common is obsessive-compulsive disorder in a dermatology outpatient clinic? J Clin Psychiatry. 2003;64:152–5.
28. Demet MM, Deveci A, Taskin EO, Ermertcan AT, Yurtsever F, Deniz F, Bayraktar D, Ozturkcan S. Obsessive–compulsive disorder in a dermatology outpatient clinic. Gen Hosp Psychiatry. 2005;27:426–30.

29. Bloch MH, McGuire J, Landeros-Weisenberger A, Leckman JF, Pittenger C. Meta-analysis of the dose-response relationship of SSRI in obsessivecompulsive disorder. Mol Psychiatry. 2010;15:850–5.
30. Gava I, Barbui C, Aguglia E, Carlino D, Churchill R, De Vanna M, McGuire HF. Psychological treatments versus treatment as usual for obsessive compulsive disorder (OCD). Cochrane Database Syst Rev. 2007;(2):CD005333.
31. OMIM PGS. Estimated lifetime prevalence of trichotillomania in college students. J Clin Psychiatry. 1993;54:72–3.
32. Woods DW, Flessner CA, Franklin ME, Keuthen NJ, Goodwin RD, Stein DJ, Walther MR. The Trichotillomania Impact Project (TIP): exploring phenomenology, functional impairment, and treatment utilization. J Clin Psychiatry. 2006;67:1877.
33. Sah DE, Koo J, Price VH. Trichotillomania. Dermatol Ther. 2008;21:13–21.
34. Keuthen NJ, Koran LM, Aboujaoude E, Large MD, Serpe RT. The prevalence of pathologic skin picking in US adults. Compr Psychiatry. 2010;51:183–6.
35. Odlaug BL, Grant JE. Clinical characteristics and medical complications of pathologic skin picking. Gen Hosp Psychiatry. 2008;30:61–6.
36. Wilhelm S, Keuthen NJ, Deckersbach T, Engelhard IM, Forker AE, Baer L, O'Sullivan RL, Jenike MA. Self-injurious skin picking: clinical characteristics and comorbidity. J Clin Psychiatry. 1999;60:454–9.
37. Koo J, Lebwohl A. Psycho dermatology: the mind and skin connection. Am Fam Physician. 2001;64:1873–8.
38. McGuire JF, Ung D, Selles RR, Rahman O, Lewin AB, Murphy TK, Storch EA. Treating trichotillomania: a meta-analysis of treatment effects and moderators for behavior therapy and serotonin reuptake inhibitors. J Psychiatr Res. 2014;58:76–83.
39. Rothbart R, Amos T, Siegfried N, Ipser JC, Fineberg N, Chamberlain SR, Stein DJ. Pharmacotherapy for trichotillomania. Cochrane Database Syst Rev. 2013;(11):CD007662.

Chapter 4
Skin Aging and Stress

Maria Helena Lesqueves Sandoval and Eloisa Leis Ayres

Introduction

The skin provides the body's first means of contact with the external world and is therefore the primary organ for sensory communication. The skin has the finely tuned ability to react to signs of conflict and emotions, as well as expressing our state of health, mood and well-being [1].

The connection between psychosocial stress and disease has been the focus of an increasing number of investigations since it was first recognized in the 1970s. The study demonstrated how viral diseases of mucous membranes developed at a faster rate and became more severe upon exposure to stress. While there is still little concrete evidence proving the mechanism by which chronic stress can contribute to the aging of the skin, today we have new insights into epidemiology, psychoneuroimmunology, and molecular psychosomatics which reveal the multiple interactions which occur between a disease and the endocrine, nervous, and immune systems [2].

Therefore, when treating chronic skin disease, one must also take into consideration the complexity and multi-dimensional nature of the aging process, paying particular attention to the clinical signs of photoaging and recognizing the mounting evidence suggesting that psychological stress may be an important extrinsic factor which influences this process.

Furthermore, when treating an elderly patient a physician should be aware of the high levels of stress which often appear during this stage of life. There are a range of procedures available to help improve appearance, however, the patient should

M.H.L. Sandoval, MD (✉)
Department of Dermatology, Cosmiatric Clinic, Hospital Cassiano Antonio De Moraes, Vitória, Brazil
e-mail: mhlsand@terra.com.br

E.L. Ayres, MD
Fluminense Federal University – Niterói, Rio de Janeiro, Brazil

K. França, M. Jafferany (eds.), *Stress and Skin Disorders*,
DOI 10.1007/978-3-319-46352-0_4

also be assessed to evaluate the possible need for psychological support or other treatments to help reduce anxiety and increase their emotional, social and spiritual welfare [3].

The Aging Skin

The aging process is the result of multiple intrinsic factors that occur naturally over time and extrinsic factors, including ultra violet (UV) radiation, pollution and stress. Aging is caused by both genetics and environmental factors such as smoking, unhealthy diet and lack of exercise. As we grow older, there are common changes that can be seen on the epidermis and dermis of the skin: abnormality in epidermal maturation, the skin becomes drier, the appearance of age spots, more wrinkles, actinic keratosis or even the emergence of skin cancers. Furthermore, after an injury, older skin tends to heal more slowly [4]. The collagen and elastin fibers that keep the skin firm weaken. The skin becomes loose and lax, and turns fragile, thin and loses fat tissue. Bone remodeling becomes more evident in the face [5]. There are many signs of aging skin which could be easily treated by a dermatologist (Table 4.1).

Photoaging is a highly evident and significant trait of aging skin caused by the accumulation of UV radiation and leads to a transformation of the skin and visible skin damage. Other signs that are often present include color changes, solar lentigines, melanosis, wrinkles, roughness, telangiectasias, xerosis and actinic keratosis [4, 6].

Comparing normal skin (no exposure to sun radiation) to exposed skin, a remarkable difference can be observed (Fig. 4.1).

Visible signs of aging on the exposed skin are a constant reminder to the patient of his or her decrepitude. Comments and questions about these marks, even when well intentioned, can increase feelings of insecurity and increase stress levels.

There are treatments available that can help to reduce the signs of aging and improve appearance. It is important that the practitioner carefully explains to the patient the expected results, possibility of surgery and the consequence of lasers. In these moments, the presence of family members or care providers are a great benefit in helping the elderly patient to understand any recommendations or instructions.

Table 4.1 Clinical skin signs of elderly

Wrinkles	Telangiectasia	Dry skin	Liver or age spots	Seborrheic keratoses
Cherry angiomas	Varicose veins/ ulcers	Bruising (purpura)	Itching	Skin cancers

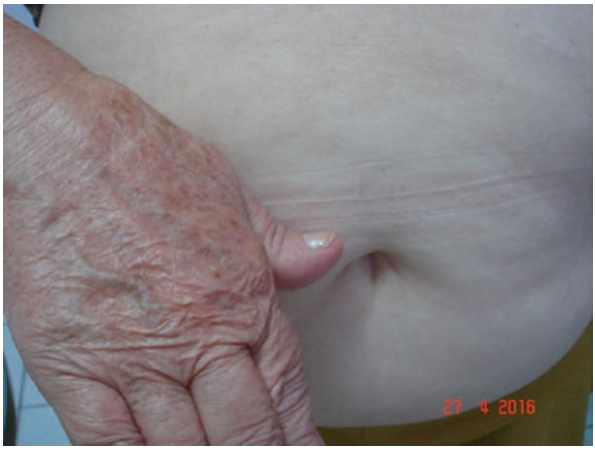


Fig. 4.1 Skin comparison: arms and hands showing aging skin from chronic sun exposition in contrast with skin without any evidence of actinesenescense

The Relationship Between Stress and Skin

Psychological stress is caused by a stimulus that induces the brain to react with different mechanisms of the endocrine, immunological and nervous systems [7].

The skin is constantly exposed to a wide range of stress agents that can cause signs of aging in the skin. It has long been acknowledged that some of these triggers come from the environment, UV radiation, chemical products, smoking and environmental changes. This may cause allergies, infections, the production of free radicals and metabolites [7].

The brain and skin share the same ectodermic origin and therefore have a close relationship [8]. Both the skin and nervous system resulted simultaneously during embryonic development from the same primary germ layer. It has also been shown that neuronal signaling pathways contain a protein that is also present in skin cells. This may explain how the activities in the central nervous system can also influence cellular function in the skin and the appearance of many inflammatory, autoimmune and allergic diseases that may be triggered during stressful periods [7].

Although there is limited evidence linking psychological stress to skin aging, there are an increasing number of publications that cite research showing the relationship between psychological stress to neurological, endocrine, and immune reactions that influence the mechanisms which are known to cause aging [9] (Fig. 4.2).

In response to acute stress a part of the brain called hypothalamic-pituitary-adrenal (HPA) is activated, triggering the production and release of glucocorticoids, such as cortisol and some neurotransmitters called cathecolamines, particularly dopamine, norepinephrine and epinephrine. Cathecolamines activates an area called amygdala, which appears to trigger an emotional response to a stressful event. The

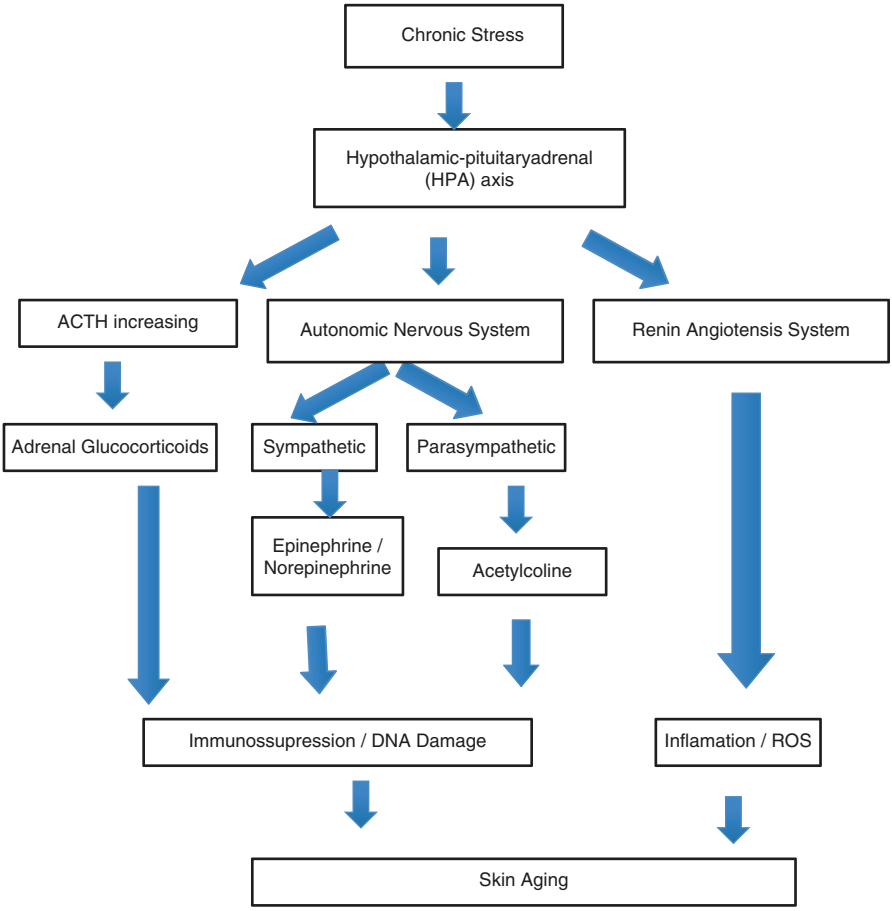


Fig. 4.2 Stress response and skin aging [7, 10]

brain releases neuropeptide S, a small protein that modulates stress by decreasing sleep and increasing alertness and a sense of anxiety. Cathecolamines also suppress areas at the front of the brain concerned with short-term memory, concentration, inhibition, and rational thought that allows a person to react quickly. At the same time, neurotransmitters signal the hippocampus to store the emotionally loaded experience in long-term memory. The stress response also affects the heart, lungs and circulation. The skin response to acute stress moves blood flow away to support the heart and muscle tissue. Once the threat has passed and the effect has not been harmful, the stress hormones return to normal. This is known as the relaxation response [9].

People respond to stress differently, depending on different factors such as: early nurturing, personality traits, genetic factors, immune regulated diseases and the length and quality of stressors. The longer the duration and the more intense the

stressors, the more harmful the effects. As people age, achieving a relaxation response after a stressful event becomes more difficult. Aging may simply wear out the systems in the brain that respond to stress, so that they become inefficient. The elderly, too, are very often exposed to major stressors such as medical problems, the loss of a spouse and friends, a change in a living situation, and financial worries. No one is immune to stress [9].

Although the relationships between the brain and skin have been studied, none demonstrated the exact mechanism by which chronic stress participates in skin aging. The study of Romana-Souza et al. investigates the effects of chronic psychological stress on mouse skin. Mice were submitted daily to rotational stress, for 28 days, until euthanasia. After 28 days, the mice were killed and normal skin was analyzed. Macroscopically, dorsum skin of chronically stressed mice presented more wrinkles when compared to that of non-stressed mice. In mouse skin, chronic stress increased lipid peroxidation, carbonyl protein content, nitrotyrosine levels, neutrophil infiltration, neutrophil elastase and tissue inhibitor of metalloproteinase-1 and metalloproteinase-8 levels. The authors concluded that stress might be an important extrinsic factor, which contributes to skin aging in mice [11].

Treatments Available

There are a number of cosmetic treatments available for daily use as well as a range of different chemical peels, fillers, botulinum toxins and various new technologies that will give the skin an improved appearance and even help it continue improving by stimulating the production of new collagen.

Photodamage caused by the accumulation of UV radiation leads to many undesired transformations on the epidermis and in the dermis. Treatment will depend on whether the degree of photodamage is considered mild, moderate or severe. Solar lentigines, roughness, color changes and wrinkles can be improved with chemicals peels, Intense Pulsed Light and Fractional ablative lasers.

Topical skincare products such as rejuvenating creams that increase the turnover of cells, retinoic acid, retinol and retinaldehyde are recommended for daily use. Others that fight against free radicals such as vitamin C, ferulic acid, resveratrol, coenzyme Q-10 idebenone, Lipoic acid and flavonoids are also very useful. There are a large number of moisturizers available for the treatment of dry skin such as vitamin E, urea, hialuronc acid, alpha-hydroxid acids, ceramides, among others [12].

The right product for each skin type and condition can be prescribed by a dermatologist.

Intense Pulsed Light (IPL) is used effectively for the treatment of common signs of aging including telangiectasias, age spots (melanosis) and cherry angiomas. Symptoms of Rosacea can worsen in the later years of life and IPL can be very useful in treating redness and small broken blood vessels [1].

For the more severe wrinkles, CO2 laser and Baker and Gordon Phenol Peel are highly effective. To guarantee the success of this deep peel procedure, a comprehensive explanation from the physician to the patient and family is required as recovery demands attention and dedication.

An obvious sign of chronological aging is skin laxity on the face and neck. The non-surgical technique called Radiofrequency or Microfocused Ultrasound (Ultherapy) is available and should be performed twice a year to obtain optimal results [1].

For dynamic wrinkles, the 'gold standard' treatment is botulin toxin type A. This treatment can be very useful for both the wrinkles on neck and the upper chest.

With time, facial fat compartments turn atrophic and facial volume changes. Better results can be achieved from volume replacement treatments when begun earlier in the aging process. There are also many products, such as Hialuronic acid volumizer, calcium hydroxyapatite and poly-L-lactic acid that will help replace volume by increasing collagen levels. The last two products are known as biostimulators of the dermis [1, 5].

To reduce stress and its consequences, three are many medications available that can only be prescribed by a psychiatrist. However, the benefits of non-pharmacological treatments to reduce stress hold great promise, such as yoga, relaxation, meditation, mindfulness, psychotherapy and hypnoses. The physical improvement that this relaxing exercises brings are the reduction of heart frequency, blood sugar level and the cortisol level in the saliva, among others. The psychological effects are the reduction of anxiety and the increase of emotional, social and spiritual well-being [13].

In addition to all these measures described above, the importance of good nutrition, regular habits of physical exercises, treatment of diseases, social interaction and love from the members of their families cannot be understated.

A healthy, active and positive lifestyle is fundamental in helping a person to better deal with the stress of aging in its multiple forms.

Conclusion

Psychological stress is considered to be a possible component of skin aging. Despite the limited evidence directly connecting the two, there are many known signs of mental tension that influence the normal function of the skin that might be explained by the close relationship between the brain and skin.

It is important to consider that not only can stress cause skin aging but skin aging itself can be a source of stress, particularly for the elderly. By understanding the relationship between stress and aging, the physician can provide the patient with ways of dealing with psychological stress and treatments for the signs of skin aging. Today there is a wide range of effective treatments that can deliver the desired outcomes. Attention and care from loved ones and family will improve self-esteem and restore the joy of living to this valuable, aging population.

References

1. Sandoval MHL. Cosmetic dermatology for the elderly. In: Jafferany M, França K, editors. Geriatric psychodermatology. 1st ed. New York: Nova; 2015. p. 227–35.
2. Peters EM. Stressed skin? – a molecular psychosomatic update on stress-causes and effects in dermatologic diseases. J Dtsch Dermatol Ges. 2016;14(3):233–52.
3. Hansen F. Stress and aging: the latest research. 2014. http://adrenalfadiguesolution.com/stress-and-aging/.
4. Sampaio SAP, Rivitti EA. Dermatologia. 2nd ed. Artes Médicas: São Paulo; 2000.
5. Sandoval MHL, Sandoval DL. Preenchedores Ácido Poli-L-Láctico. In: Steiner D, Addor F, editors. Envelhcimento Cutâneo. 1st ed. Rio de Janeiro: AC Farmacêutica; 2014. p. 250–5.
6. Mateus A. Clínica do Fotoenvelhecimento. In: Steiner D, Addor F, editors. Envelhecimento Cutâneo. 1st ed. Rio de Janeiro: AC Farmacêutica; 2014. p. 29–33.
7. Dunn JH, Koo J. Psychological stress and skin aging: a review of possible mechanisms and potential therapies. Dermatol Online J. 2013;19(6):1.
8. França K. Aspectos Psicodermatológicos nos Procedimentos Cosmiátricos. In: Ayres EL, Sandoval MHL, editors. Toxina Botulínica na Dermatologia. 1st ed. Rio de Janeiro: Guanabara Koogan; 2016. p. 9–16.
9. Stress – University of Maryland Medical Center in http://umm.edu/health/medical/reports/articles/stress#ixzz39LPAaPeN
10. Chen Y, Lyga J. Brain-skin connection: stress, inflammation and skin aging. Inflamm Allergy Drug Targets. 2014;13(3):177–90.
11. Romana-Souza B, Santos Lima-Cezar G, Monte-Alto-Costa A. Psychological stress-induced catecholamines accelerates cutaneous aging in mice. Mech Ageing Dev. 2015;152:63–73.
12. Ramos-e-Silva M, Carneiro SCS. Elderly skin and its rejuvenation: products and procedures for the aging skin. J Cosmet Dermatol. 2007;6:40–50.
13. Isaac AR. Estresse e pele. In: Azambuja RD, Rocha TN, Conrado LA, Senra MS, editors. Psicodermatologia pele, mente e emoções. 1st ed. São Paulo: AC Farmacêutica; 2014. p. 12–8.

Chapter 5
Environmental Psychodermatology: Stress, Environment and Skin

Katlein França, Aparecida Porto França, and Reginaldo de França

Introduction

The skin is the largest organ in the body. It has three main functions including protection, regulation and sensation. The skin is responsible for protecting internal organs from noxious substances, including toxic chemicals, ultraviolet radiation and repeated exposure to water [1]. It is an important interface between man and environment and is a portal of entry for different hazardous agents [2]. Environmental stressors refer to biological, physical and chemical constraints on the productivity of species and on the development of ecosystems. These stressors can be natural environmental factors or may result from human's actions. Ecosystems and different species have the ability to adapt and tolerate the changes of stressors with limitations. When the limits are exceeded by increases in the intensity of stressors, significant changes in the environment are caused [3]. Everyday life is full of environmental stressors that can cause skin diseases (Table 5.1). Environmental psychodermatology is a developing area that studies the interaction between stressors (that may affect the psychology and quality of life of patients), skin and the environment (Scheme 5.1).

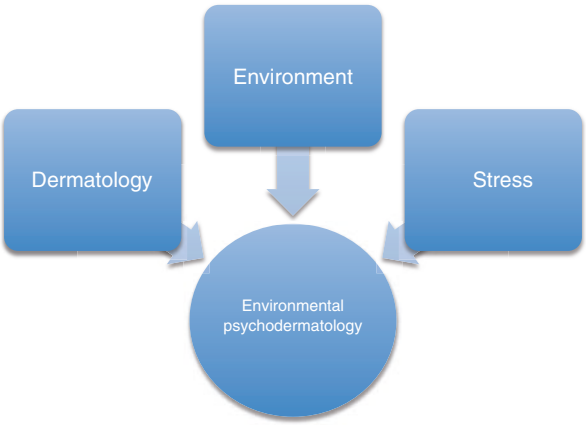
K. França, MD, PhD (✉)
Centro Studi per la Ricerca Multidisciplinare e Rigenerativa, Università Degli Studi "G. Marconi", Rome, Italy

Department of Dermatology and Cutaneous Surgery, Department of Psychiatry and Behavioral Sciences, Institute for Bioethics and Health Policy, University of Miami Miller School of Medicine, Miami, FL, USA
e-mail: k.franca@med.miami.edu

A.P. França, BS, PhD
Instituto Universitario Italiano de Rosario, Rosario, Argentina

R. de França, MSc
Universidad de Buenos Aires, Buenos Aires, Argentina

K. França, M. Jafferany (eds.), *Stress and Skin Disorders*,
DOI 10.1007/978-3-319-46352-0_5



Scheme 5.1 Environmental psychodermatology is a developing area that studies the interaction between stressors, skin and the environment

Ozone Layer Depletion and Skin Cancer

The ozone layer is an area of the stratosphere (upper atmosphere, 25–35 km altitude), which has a high concentration of ozone. It's a basic bio-protective filter that absorbs the solar radiation [6]. About 98 % of the ultraviolet radiation of high frequency emitted by the sun is absorbed. Without this layer of human life on our planet would be virtually impossible to achieve (Fig. 5.1).

There are many external (exogenous) factors that influence the health of the skin. These factors are determined by the environment that surrounds us, our overall health and lifestyle choices we make.

The ozone layer is a basic bio-protective filter that absorbs the solar ultraviolet radiation [6]. The ozone-layer depletion occurs when chemical substances containing chlorine and bromine are emitted to the atmosphere. Since 1980, a sustained depletion of stratospheric ozone levels is occurring. The depletion of this important

Table 5.1 Most common environmental stressors and definitions

Ultraviolet light	A form of radiation that is not visible to the human eye. It's in an invisible part of the "electromagnetic spectrum" that reaches the earth from the sun. It has the UVA, UVB and UVC wavelengths that are shorter than visible light and invisible to naked eye [4]
Biological	Diverse types of interactions between organisms. Biological stressors can result from parasitism, competition, herbivory or predation [4]
Pollution	Presence or introduction into the environment of substances with harmful effects. There are several types of environmental pollutions: air, water, land, light, and visual, among others [4, 5]
Climatic	These stressors are associated with excessive or reductions of temperature, solar radiation, moisture, among others [3]

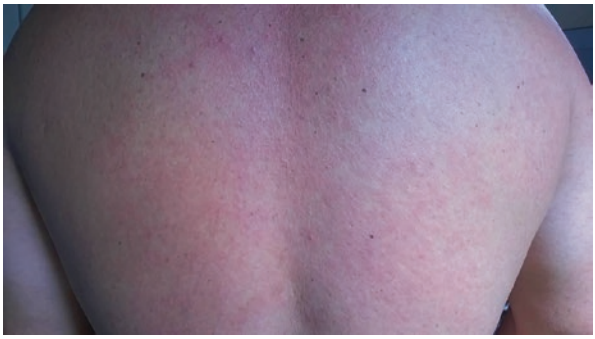


Fig. 5.1 Diffuse exanthema in a patient with Zika virus (Courtesy of Dr Renata P. N Módolo)

layer leads to increase of Ultraviolet levels in the environment, [7, 8] UV radiation causes deleterious effects on cells producing direct and indirect DNA damage, leading in mutagenesis in skin cells, leading to skin cancers [9]. Skin cancers can cause functional damage and disfigurement (For more information, see Chap. 10).

UV Radiation and Premature Biological Aging of the Skin

Skin is under daily UV explosion. UV radiation explosion can cause acute or chronic harmful effects on the skin [10]. Solar and UV radiation causes cellular and molecular damage that results in histopathologic and clinical degenerative changes that causes photosensitivity and photo-aging [11]. Sunburn and tanning are the acute and reversible effects of the UV radiation on skin. While the chronic effects include immunosuppression, skin cancer and premature aging of the skin [11, 12]. Skin aging is characterized by formation of wrinkles and lines, loss of firmness and elasticity, increased pigmentation, and dull skin [13]. Skin aging can cause significant psychological distress for many individuals leading to social anxiety and isolation (For more information, see Chap. 4).

Insects, Environment and Skin

Insects dominate all terrestrial environments [14]. They play a crucial role in functioning of natural ecosystems and biogeochemical cycling of nutrients [14, 15]. They are human's competitors for natural resources, food and fibers. Although insects are part of a natural system that provides environmental stability they can also transmit many diseases that affect plants, domestic animals and humans [14, 16]. They have the capacity of spreading diseases caused by different types of

Table 5.2 Most common diseases caused by insects and their cutaneous manifestations

Disease	Vector	Dermatologic manifestations
Dengue fever	*Aedes aegypti and Aedes albopictus* mosquitoes	Confluent erythema, morbilliform eruptions, and hemorrhagic lesions [17]
Zika virus	*Aedes aegypti*	Diffuse or localized Exanthema [18] (Fig. 5.1)
Chikungunya fever	*Aedes aegypti and Aedes albopictus*	Skin rash, apthae like ulcers, pigmentary changes, desquamation, exacerbation of the existing dermatoses [19]
Malaria	*Anopheles* mosquitoes	Urticaria, angioedema, reticulated blotchy erythema with petechiae [20]
West Nile virus	Genus *Culex mosquitoes (most common)*	Generalized, maculopapular rash, dysesthesias, pruritus [21]
Filariasis	*Culex, Anopheles and Aedes* mosquitos (most common vectors)	Edema with thickening of the skin and underlying tissues, rashes, urticarial papules, and arthritis, hyper- and hypopigmentation macules, chronic ulceration, epidermal and sub-epidermal nodules, and clinical intertrigo [22]
Cutaneous leishmaniasis	*Phlebotomine Sand flies*	Skin and mucosal ulcers [23]
Chagas disease	*Triatomines* mosquitoes	Swelling and/or redness at the skin infection site [24]

bacteria, protozoans and viruses. The most common diseases caused by insects and their cutaneous manifestations are presented in the Table 5.2.

Environmental Pollutants and the Skin

The skin acts as a barrier between the organism and environment and is constantly exposed to environmental pollution. Different types of pollutants can come into contact with skin through inhalation, ingestion or topically. Pollutants become toxic to vital organs after metabolization, accumulation or activation and are related to a genotoxic effect.

Ultraviolet radiation, described before, can be considered a “physical pollutant” and is responsible for skin cancers [25].

Volatile organic compounds such as benzene is another widely distributed environmental contaminant that has cutaneous absorption and is also present in the air, food. Intoxication by benzene can cause leukemia [25, 26]. Benzo[a]pyrene induces oxidative stress in the skin inducing skin cancer and inflammatory skin diseases [27]. Heavy metals, another common environmental pollutant, can also be absorbed

by skin and cause systemic diseases. These metals are more commonly found in petrol, soil and industrial effluents [28]. One example that has a correlation with skin diseases is the arsenic. Jarup explains that long-term exposure to arsenic in drinking water is related to hyperkeratosis, pigmentation changes as well increased risks of skin cancer [29]. In addition, environmental cigarette smoke, another oxidizing agent, is related with androgenetic alopecia [30].

Air Pollution is also responsible for skin aging. Research has shown that air pollution exposure can cause pigment spots and wrinkles. These pollutants break the collagen fibers in the skin and disrupt the lipid layer, impairing the skin barrier function and leading to aging. Some examples of air pollutants include smog, dust, cigarette smoke, and car exhaust. An anti-pollution daily skin care may be helpful to minimize the damage caused by air pollution exposure and should include regular wash of the face, use of oral and topical antioxidants and a balanced diet [31].

Climatic Stressors and Skin

Different types of contaminants circulating in the air are gradually changing the climate on Earth. Exposure to extreme temperatures have been linked to increased morbidity and mortality [32]. The normal ambient temperature for humans is 37 °C or 98.6 °F [33]. One main role of the skin thermoregulation. Exposure to cold temperature stimulates receptors of the skin that causes cold thermal sensations and stimulates of the sympathetic nervous system, causing vasoconstriction in the skin [34]. The most common diseases of the skin associate with cold weather are erythema, xerosis, urticaria, cold cryoglobulinemias, panniculitis and chilblains. Prolonged exposure to heat, insufficient to produce burns, can also cause urticaria, erythema, skin hyperpigmentation, transient acantholytic dermatosis, induce hyperhidrosis among other skin diseases [35, 36].

Conclusion

The skin is an important barrier and interface between man and environment and is constantly exposed to environmental stressors. It is a portal of entry for different hazardous agents. Human beings are in constant contact with different environmental stressors such as UV light, pollution, biological and climatic stressors. Environmental psychodermatology is an emerging subspecialty of psychodermatology that aims to study the complex and interesting connection between the skin, the environment, and stress, how these factors interact and their effect on a person's life.

References

1. English JS, Dawe RS, Ferguson J. Environmental effects and skin disease. Br Med Bull. 2003;68:129–42.
2. Suskind RR. Environment and the skin. Environ Health Perspect. 1977;20:27–37.
3. No author listed. Ecological stress – environmental, species, ecosystems, and stressors – JRank Articles. Available at: http://science.jrank.org/pages/6549/Stress-Ecological.html#ixzz3uF84sbo6. Accessed 13 Dec 2015.
4. No author listed. Understanding UVA and UVB. Available at: http://www.skincancer.org/prevention/uva-and-uvb/understanding-uva-and-uvb. Accessed 14 Dec 2015.
5. Ring J, Eberlein-Koenig B, Behrendt H. Environmental pollution and allergy. Ann Allergy Asthma Immunol. 2001;87(6 Suppl 3):2–6.
6. Cooney CM. Stress–pollution interactions: an emerging issue in children's health research. Environ Health Perspect. 2011;119(10):a431–5.
7. Jankowski J, Cader AB. The effect of depletion of the earth ozone layer on the human health condition. Int J Occup Med Environ Health. 1997;10(4):349–64.
8. Sánchez CF. The relationship between the ozone layer and skin cancer. Rev Med Chil. 2006;134(9):1185–90. Epub 2006 Dec 12.
9. Amaro-Ortiz A, Yan B, D'Orazio JA. Ultraviolet radiation, aging and the skin: prevention of damage by topical cAMP manipulation. Molecules (Basel, Switzerland). 2014;19(5):6202–19.
10. Ichihashi M, Ueda M, Budiyanto A, Bito T, Oka M, Fukunaga M, Tsuru K, Horikawa T. UV-induced skin damage. Toxicology. 2003;189(1–2):21–39.
11. Gonzaga ER. Role of UV light in photodamage, skin aging, and skin cancer: importance of photoprotection. Am J Clin Dermatol. 2009;10 Suppl 1:19–24.
12. D'Orazio J, Jarrett S, Amaro-Ortiz A, Scott T. UV Radiation and the skin. Int J Mol Sci. 2013;14(6):12222–48.
13. Chen Y, Lyga J. Brain-skin connection: stress, inflammation and skin aging. Inflamm Allergy Drug Targets. 2014;13(3):177–90.
14. Meyer J. A class of distinction. Available at: https://www.cals.ncsu.edu/course/ent425/text01/impact1.html. Accessed 01 May 2016.
15. Rosenberg DM, Danks HV, Lehmkuhl DM. Importance of insects in environmental impact assessments. Environ Manag. 1986;10:773–83.
16. Durvasula RV, Gumbs A, Panackal A, et al. Prevention of insect-borne disease: an approach using transgenic symbiotic bacteria. Proc Natl Acad Sci U S A. 1997;94(7):3274–8.
17. Thomas EA, John M, Kanish B. Mucocutaneous manifestations of dengue fever. Indian J Dermatol. 2010;55(1):79–85.
18. Barbaud A. What's new in clinical dermatology? Ann Dermatol Venereol. 2014;141 Suppl 4:S597–609.
19. Bhat RM, Rai Y, Ramesh A, et al. Mucocutaneous manifestations of chikungunya Fever: a study from an epidemic in Coastal Karnataka. Indian J Dermatol. 2011;56(3):290–4.
20. Vaishnani JB. Cutaneous findings in five cases of malaria. Indian J Dermatol Venereol Leprol [serial online]. 2011 [cited 6 Jan 2016];77:110. Available from: http://www.ijdvl.com/text.asp?2011/77/1/110/74985.
21. Ferguson DD, Gershman K, LeBailly A, Peterson LR. Characteristics of the rash associated with West Nile virus fever. Clin Infect Dis. 2005;41(8):1204–7.
22. Burri H, Loutan L, Kumaraswami V, Vijayasekaran V. Skin changes in chronic lymphatic filariasis. Trans R Soc Trop Med Hyg. 1996;90(6):671–4.
23. Goto H, Lindoso JA. Current diagnosis and treatment of cutaneous and mucocutaneous leishmaniasis. Expert Rev Anti Infect Ther. 2010;8(4):419–33.
24. Teixeira ARL, Nitz N, Guimaro MC, Gomes C. Chagas disease. Postgrad Med J. 2006;82(974):788–98.

25. Baudouin C, Charveron M, Tarroux R, Gall Y. Environmental pollutants and skin cancer. Cell Biol Toxicol. 2002;18(5):341–8.
26. Wester RC, Maibach HI. Benzene percutaneous absorption: dermal exposure relative to other benzene sources. Int J Occup Environ Health. 2000;6(2):122–6.
27. Costa C, Catania S, De Pasquale R, Stancanelli R, Scribano GM, Melchini A. Exposure of human skin to benzo[a]pyrene: role of CYP1A1 and aryl hydrocarbon receptor in oxidative stress generation. Toxicology. 2010;271(3):83–6.
28. Singh R, Gautam N, Mishra A, Gupta R. Heavy metals and living systems: an overview. Indian J Pharmacol. 2011;43(3):246–53.
29. Järup L. Hazards of heavy metal contamination. Br Med Bull. 2003;68:167–82.
30. Kim KE, Cho D, Park HJ. Air pollution and skin diseases: adverse effects of airborne particulate matter on various skin diseases. Life Sci. 2016;152:126–34. pii: S0024-3205(16)30188-6.
31. Draelos ZD. Aging in a polluted world. J Cosmet Dermatol. 2014;13(2):85.
32. Medina-Ramón M, Zanobetti A, Cavanagh DP, Schwartz J. Extreme temperatures and mortality: assessing effect modification by personal characteristics and specific cause of death in a multi-city case-only analysis. Environ Health Perspect. 2006;114(9):1331–6.
33. Lu SH, Leasure AR, Dai YT. A systematic review of body temperature variations in older people. J Clin Nurs. 2010;19(1–2):4–16.
34. Rintamäki H. Human responses to cold. Alaska Med. 2007;49(2 Suppl):29–31.
35. Kibbi AG, Tannous Z. Skin diseases caused by heat and cold. Clin Dermatol. 1998;16(1):91–8.
36. Hu CH, Michel B, Farber EM. Transient acantholytic dermatosis (Grover's disease). A skin disorder related to heat and sweating. Arch Dermatol. 1985;121(11):1439–41.

Chapter 6
Itch and Stress

Jacek C. Szepietowski and Radomir Reszke

Introduction

Stress is a multidimensional term used frequently in various contexts and situations. Numerous definitions of stress do exist, representing physical, medical or psychological approaches. In physics, stress refers to an external force that causes deformation when applied to the surface of a material [1]. Hans Selye [2], a famous endocrinologist, defined stress as "the nonspecific response of the body to any demand made upon it". Lazarus and Folkmann [3] referred to psychological stress as "a relationship with the environment that the person appraises as significant for his or her well-being and in which the demands tax or exceed available coping resources". Rees [1] described the term as an abstraction because it has no meaning without considering the reaction of the organism to the potentially damaging forces. Moreover, the term "stress" was derived from the fifteenth century word "distress" which is closely connected to "disease". The latter evolved from the term "disease". Therefore a certain initial connection is implied when considering an impact of stress on various ailments.

Itch, also referred to as pruritus, is an unpleasant cutaneous sensation which provokes the desire to scratch (reviewed by Twycross et al. [4]). This definition still remains valid today although its origins date back to seventeenth century. Itch is regarded as the most common symptom in dermatology and is also frequent in general medicine [5]. In a German study point prevalence of chronic pruritus reached 13.5 % in general adult population, 16.4 % during 12-month period and 22.6 % lifetime prevalence [6]. Later population-based study (n = 11730) by Stander et al. [7] reported 16.8 % prevalence of itch during previous 6 weeks.

J.C. Szepietowski, MD (✉) • R. Reszke, MD
Department of Dermatology, Venerology and Allergology, Wroclaw Medical University,
Ul. Chalubinskiego 1, 50-368 Wroclaw, Poland
e-mail: jacek.szepietowski@umed.wroc.pl

K. França, M. Jafferany (eds.), *Stress and Skin Disorders*,
DOI 10.1007/978-3-319-46352-0_6

Table 6.1 The aetiological classification of pruritus according to the International Forum for the Study of Itch (IFSI) [11]

Category	Examples of diseases
I – Dermatological	Atopic dermatitis, urticaria, eczematous disorders, psoriasis, scabies
II – Systemic	Chronic kidney disease, primary biliary cirrhosis, Hodgkin's disease, drug-induced itch
III – Neurological	Multiple sclerosis, brain tumours, stroke, notalgia paresthetia
IV – Psychogenic	Depression, schizophrenia, hallucinosis, delusional parasitosis, psychogenic pruritus
V – Mixed	Several disorders form different groups
VI – Other	Senile pruritus

Acute and chronic forms of pruritus are acknowledged, the latter being characterized by pruritus lasting for more than 6 weeks and usually associated with chronic entities [8]. Pruritus may be elicited both by cutaneous and extracutaneous causes. Dermatological disorders often manifest by the presence of pruritus; the most common include atopic dermatitis (AD), urticaria, eczematous disorders, lichen planus, psoriasis, mycosis fungoides or prurigo nodularis.

A wide spectrum of additional potential causes of itching encompass systemic (e.g. renal, hepatic, endocrine, hematologic, infectious) and neurological disorders. Another distinctive subtype is the somatoform pruritus (also called psychogenic itch) which is evoked due to psychiatric and psychosomatic factors. Reports have shown that pruritus is common (25.2 %) in subjects suffering from psychiatric disorders [9]. Over 70 % of dermatology inpatients complaining of pruritus were diagnosed with at least one psychiatric condition [10]. Depressive symptoms seemed to be associated with more pronounced pruritus.

The classification of pruritus based on its aetiology is presented in Table 6.1.

Skin disorders cause a significant burden for health systems worldwide, placing 4th in the ranking of years lost due to disability (YLD) in 2010 [12]. Higher burden was attributed to low back pain, major depressive disorder and iron-deficiency anaemia (placed 1st, 2nd and 3rd, respectively). Pruritus was regarded among 50 most prevalent diseases worldwide and was associated with higher YLD values especially in the elderly population. Recently it has been estimated that pruritus global therapeutics market will have exceeded 16 billion USD by 2025 [13].

The relation between itch and stress is highly complex. In general, stress may be regarded as a consequence of the underlying disease, including those accompanied by pruritus. Stress may coexist with pruritus, both stemming from the presence of the disease. Pruritus itself is so bothersome that it also increases stress levels. Researches investigating health related quality of life (HRQoL) have proven that stress is a major problem in numerous diseases, especially in dermatological disorders that manifest with pruritus [14–16]. On the other hand, high stress levels frequently contribute to the development and exacerbation of acute and chronic diseases. Analogically, these observations also hold true for dermatological conditions, especially those presenting with itch [17–20]. Therefore, a composite network of associations seems evident when analysing the causal link between stress and itch.

The Pathogenesis of Pruritus

The pathogenesis of pruritus is multifactorial. Currently this phenomenon is considered as a separate type of sensation, although for many years it has been perceived as sub-modality of pain [21]. Pruritus can be interpreted as a defence mechanism directed against dangerous organisms or stimuli [5]. These comprise parasites, insects, sharp objects, irritants and allergens [22]. Various stimuli are transmitted from skin through cutaneous sensory unmyelinated C-nerve fibres but also via thinly myelinated Aδ fibers [23–25]. The transmission proceeds through dorsal root ganglia into the spinal cord, then due to lamina I neurons through the spinothalamic tract, thalamus and eventually reaches cerebral cortex. Several areas of cortex are activated, both sensory and motoric [26–28]. Regarding the crucial role of central nervous system (CNS) in generating itch sensation validates the following statement: *it is the brain that itches*.

Numerous chemical substances contribute to pathogenesis of itch. No universal mediator exists, rather disease-specific sets of mediators [5]. Neurotransmitters in the skin are synthesized by nerve fibers and numerous cells including Merkel cells, Langerhans cells, keratinocytes, melanocytes, granulocytes, lymphocytes, monocytes-macrophages and mast cells [29]. Histamine is commonly regarded as a classic mediator of itch although over the years other substances have been investigated. In general, pruritus transmission is divided into histaminic and non-histaminic [30]. The latter is associated with mediators such as acetylcholine (Ach), α-melanocyte-stimulating hormone (α-MSH), beta-endorphine, catecholamines, calcitonin gene related protein (CGRP), endothelin 1 (ET-1), gastrin-releasing peptide (GRP), interleukin 31 (IL-31), nerve-growth factor (NGF), neurokinin A (NK-A), opioids, prostaglandins, proteases, substance P (SP) and vasoactive intestinal peptide (VIP) [31–60]. Growing evidence concerning the mediators of itch contributes to the continuous appearance of selective therapeutic approaches, for example nalfurafine (kappa opioid receptor agonist) or aprepitant (NKR1 antagonist). It must be noted that administration of various drugs may also elicit pruritus, especially antimalarials, opioids and hydroxyethylstarch (HES) [61]. Although selective serotonine reuptake inhibitors (SSRI) may be used as a treatment modality in several forms of pruritus [62–65], they may also elicit pruritus in certain situations [66, 67]. Iatrogenic types of pruritus may occasionally result from the dermatologic treatment itself, for example due to contact irritant reaction (high concentrations of topical modalities) or phototherapy.

Interestingly, pruritus may also be regarded as a “contagious” phenomenon. This hypothesis has been evaluated in recent studies performed by Papoiu et al. [68], van Laarhoven et al. [69] and Bartels et al. [70]. The contagious pruritus is an example of a “nocebo effect” in which a subject expects a certain form of reaction from the organism based solely on a suggestion. In contrast to “placebo effect”, the reaction is considered as unfavourable. Holle et al. [71] suggested that the social contagion of itch is a normative response, being experienced by most people. Functional magnetic resonance imaging (fMRI) revealed that key

areas of the brain responsible for experiencing and responding to itch were anterior insula, premotor cortex, primary somatosensory cortex and prefrontal cortex. Neuroticism as a personality trait was also postulated as factor influencing the itch contagion [71].

It is acknowledged that certain intrinsic personality factors combined with stressful life events make an individual more prone to develop pruritus [72]. Bandura [73] described the concept of perceived self-efficacy which is defined as people's beliefs about their capabilities. These beliefs determine feelings, thoughts, motivation and behaviour. In consequence, perceived self-efficacy may influence the way in which an individual copes with difficult situations and stress. Furthermore, a possible influence is implied regarding skin disorders and itch. Dalgard et al. [72] have proven that adolescent individuals with poor self-efficacy complained of itch twice as often in highly stressful situations as those with high self-efficacy (30 % vs. 15 %; $p = 0.072$). The authors suggested that itch may possibly be alleviated by psychotherapeutic interventions that strengthen the general coping mechanisms.

Itch inhibition has many aspects. Thermal and mechanical counterstimuli may inhibit histamine-associated pruritus in human subjects [74, 75]. Spinal interneurons releasing glycine and gamma-aminobutyric acid (GABA) contribute to this phenomenon, as demonstrated by Akiyama et al. [76]. Recently, the role of spinal B5-interneurons and kappa-opioid agonist dynorphin as an itch inhibiting neuromodulator has been reported in mice [77]. Glutamate release associated with VGLUT-2 transporter and TRPV-1 receptors generates pain and inhibits pruritus [78, 79]. Tropomyosin-receptor kinase A (TrkA) functioning as NGF receptor has recently been targeted by novel CT327 antagonist [80].

Itch and Stress: Wide Spectrum of Associations

Acute and chronic stressors trigger responses in skin as well. Stress exerts its influence on dermatological disorders and itch itself due to releasing neuropeptides and hormones [81]. Mediators released locally or systematically increase sensory innervation, promote the synthesis of pruritogenic substances, stimulate neurogenic inflammation and lower the threshold of itch [82]. An impaired parasympathetic response possibly links chronic stress and itch [83]. Stress influences itch whereas itch results in additional stress. Thus, vicious "itch-scratch-itch" cycle appears and perpetuates itself. The relationship between itch and stress has been evaluated directly in several researches, predominantly in those focusing on subjects suffering from atopic dermatitis or psoriasis.

Atopic Dermatitis

Atopic dermatitis (AD) is a common chronic or recurrent inflammatory skin disease affecting 15–20 % of children and 1–3 % of adults worldwide [84]. Pruritus is a key feature of AD included in the classic diagnostic criteria proposed by Hannifin and Rajka [85] and by UK Working Party [86]. The pathogenesis of itch in AD is multifactorial. Pruritus threshold is diminished and various factors trigger itch in lower concentrations than in healthy subjects [87, 88]. Epidermal barrier dysfunction measured by increase in transepidermal water loss (TEWL) was reported by several authors [89, 90]. Altered pattern of cutaneous innervation was observed in skin specimens. In animal models of AD as well as in human subjects the density of epidermal and dermal nerve fibres was higher [37, 91]. Plasma concentrations of SP, CGRP, NPY, beta-endorphine, NGF, brain-derived neurotrophic factor (BDNF) were altered in patients with AD [92–96]. Increased levels of histamine were reported in plasma and skin of patients suffering from AD [87, 97]. Rukwied et al. [98] observed that histamine induced extravasation of proteins was lower in atopic subjects, implying that other mediators may elicit pruritus in this group of patients. This issue was reflected by inconsistent effectiveness of antihistamines in reducing itch. Interleukines were also investigated in the context of itching, such as Il-2, Il-6, Il-13 or Il-31 [99–101].

Yosipovitch et al. [102] reported that 87 % subjects suffering from AD experienced pruritus on a daily basis. The worst itch intensity reached 9.0 ± 1.2 points (VAS). Similar results were published by Dawn et al. [103] – 91 % subjects experienced pruritus at least once every day, whereas mean itch intensity was 8.3/10 (Likert scale). Several studies have proven that stress is important factor influencing pruritus in AD. In a previously mentioned study the severity of itch increased due to stress in 71 % respondents; 22 % identified stress as the most common factor initiating the onset of pruritus [102].

Oh et al. [104] observed that pruritus intensity (VAS) was positively correlated with state-anxiety and trait-anxiety values ($r = 0.573$; $r = 0.525$; respectively). Subjects with anxiety and pruritus levels presented with more intense NPY and NGF immunohistochemical staining.

A study conducted by our group proved that the intensity of pruritus assessed with VAS (mean 7.9 ± 2.2) was related to the stress experienced by AD patients prior to disease exacerbation ($\rho = 0.37$, $p < 0.001$) [105]. Stress was evaluated utilising Social Readjustment Rating Scale and Stress Self-assessment Scale. Moreover, pruritus intensity was higher in subjects presenting with symptoms possibly associated with depression (VAS 9.1 ± 1.6 vs. 7.6 ± 2.2 points, $p = 0.004$; 4-Item Itch Questionnaire: 17.3 ± 2.5 vs. 13.1 ± 4.4 points, $p < 0.001$).

Peters et al. [106] observed significant positive correlation between itch and NGF+ neurofilaments in non-lesional skin (tau 0.466, p=0.028) and between itch and NF-mast cell contacts (tau 0.745, p=0.022) in lesional skin in subjects suffering from AD who had performed TSST. Tran et al. [107] focused on autonomic nervous system dysfunction in AD. Heart rate variability (HRV) was measured after eliciting histamine-induced itch, after artificial scratching the itchy area of the skin using cytology brush and after performing TSST. AD patients presented higher heart rates than healthy subjects, marked sympathetic response to itch and scratching (based on very low frequency and low frequency spectrum of HRV) and dysfunctional parasympathetic response to itch and scratching (based on high frequency spectrum of HRV).

Schut et al. [108] investigated the influence of personality traits and depression on itch. Pruritus was induced using an experimental video "Itch – what is behind it?", while a video "Skin – the communication organ" was used as a control. Predictor variables were assessed with The Neo Five-Factor Inventory (NEO-FFI; the questionnaire measures personality traits defined as neuroticism, extraversion, openness to experience, agreeableness and conscientiousness), The Hospital Anxiety and Depression Scale (HADS) and The Self-Consciousness Scale (SCS). The intensity of itch was measured using VAS and by observing the number of scratch movements. Unsurprisingly, AD subjects with high HADS scores were prone to experience more pronounced itch, whereas the increase in the number of scratch movements was associated with high public self-consciousness and low agreeableness (detailed results therein). A recent study attempted to determine the role of coping as a possible mediator influencing the relationship between stress and pruritus [109]. The instruments for assessing Itch intensity, perceived stress and disease specific coping included VAS, Recovery-Stress Questionnaire (REST-Q) along with postawakening cortisol levels in saliva, and Marburger Skin Questionnaire (MSQ), respectively. The latter focused on factors such as "social anxiety-avoidance", "itch scratch cycle", "helplessness" and "anxious depressive mood". Cortisol levels were not significantly correlated with itch intensity, contrarily to perceived stress and coping mechanisms (detailed results therein). The results supported the hypothesis that pruritus-related stress leads to unfavourable coping mechanisms which further perpetuate this bothersome phenomenon.

Psoriasis

Psoriasis is a chronic inflammatory disorder affecting approximately 0.73–2.9 % of European population [110]. Among adults aged 20–59 years in the US, the prevalence of psoriasis in Caucasians, African Americans and Hispanics was 3.6 %, 1.9 % and 1.6 %, respectively [111]. Frequency of pruritus in psoriasis patients ranges from 67 to 96.6 % [112–120].

The pathogenesis of pruritus in psoriatic subjects is associated, at least to some extent, with neurogenic inflammation. In a Japanese study an increased number of SP-positive nerves in the perivascular area, increased number of NGF-immunoreactive keratinocytes and increased NGF skin concentration was found [121]. High affinity receptor for NGF (TrkA) was observed in the epidermis and

dermal nerve fibers, while protein gene product 9 (PGP-9.5) immunoreactive nerve fibers were more prevalent in the epidermis and upper dermis. These aspects were correlated with itch intensity as well. Moreover, the authors established that E-selectin immunoreactive vessels as well as endothelial leucocyte adhesion molecule 1 (ELAM-1) density in venules contribute to the pathogenesis of itch. Madej et al. [122] emphasized the role vascular adhesion protein-1 (VAP-1). Wiśnicka et al. [123] and Reich et al. [124] observed that pruritus intensity may be correlated with high CGRP and low NPY plasma levels. Several authors investigated the role of semaphorine-3A (axon-guidance molecule) in association with pruritus [125, 126]. Decreased level of semaphorine-3A upregulates NGF expression, further resulting in hyperinnervation of C-fibers. Additionally, downregulation of kappa-opioid receptor in epidermis was also observed in psoriasis. Nigam et al. [127] reported that Gamma-aminobutyric acid (GABA) and its receptor ($GABA_A$) participate in pathogenesis of psoriasis and development of pruritus in these individuals.

Individuals suffering from psoriasis regard pruritus as the most bothersome symptom [128, 129]. The intensity of pruritus in psoriasis is regarded as moderate one. Reich et al. [115] reported mean VAS scores of 4.2 ± 2.4, while in a study conducted by Yosipovitch et al. [113] the worst VAS scores reached 6.4 ± 2.5.

Many researchers focused on the relationship between stress and pruritus in psoriasis. A Swedish study revealed that 67 % of respondents deemed stress as an aggravating factor of pruritus; pruritus intensity (verbal four-point rating scale and VAS) and stress were positively correlated ($r = 0.8$, $p < 0.05$) [118]. Pruritus negatively impacted QoL of participants: 60 % complained of mood disturbances, whereas problems concerning concentration, sleep, sexual desire and appetite were declared by 47 %, 35 %, 21 % and 11 % of participants, respectively. Reich et al. [115] reported that patients suffering from heavy or extremely heavy stress (as assessed by Social Readjustment Rating Scale and self-assessment method) were more susceptible to the occurrence of itch ($p < 0.05$). The severity of stress and the intensity of pruritus were positively correlated ($p = 0.015$). Zachariae et al. [18] reported moderate correlation between stress reactivity and the degree of itching in a large group of Nordic subjects comprising members of psoriasis associations ($n = 5795$) and psoriasis patients ($n = 702$). A later study emphasized a significant decrease in HRQoL in patients suffering from itch (DLQI 12.2 ± 7.0 vs. 6.8 ± 7.1; $p = 0.02$) [117]. Over 70 % of patients had experienced at least one stressful event within 1 month before exacerbation of the disease. Regarding stress levels, no differences were observed between patients experiencing pruritus and those who did not (72.8 % vs. 70.0 %, respectively; $p = 0.85$). Similar itch levels were present in patients who had experienced at least one stressful life event prior to exacerbation as in patients who had not. In the majority of subjects itch intensity was significantly correlated with stress degree.

In a study by Chang et al. [116] pruritus was exacerbated by emotional stress in over 49 % of Korean outpatients ($n = 152$). Additionally, the authors performed skin biopsies and histologic examination along with immunofluorescent staining. Specimens from lesional, itchy skin presented with more pronounced staining for TrkA particles (high affinity receptor for NGF), SP-receptors (SPR) and CGRP-receptors (CGRPR) when compared to healthy areas of skin and lesional, non-pruritic areas. These observations serve as a link between pathogenesis and clinical

symptomatology. However, in a study by Remrod et al. [130] pruritus intensity measured with VAS was not correlated neither with the number of SP positive fibers and SP positive cells, nor with salivary cortisol levels.

A recent study established that stress is the most important factor inducing and aggravating itch in psoriasis (49 % and 61 % of patients, respectively) [128].

Gupta et al. [131] reported that pruritus severity (10-point scale) was correlated with depression scores (Carroll rating scale for depression; CRSD) among outpatients suffering from psoriasis, atopic dermatitis and chronic idiopathic urticaria. The authors suggested that depressive symptoms may be regarded both as a primary feature of the skin disorder or as its consequence. Elevated levels of corticotropin-releasing factor associated with depression could intensify itch perception by increasing opiate levels in CNS.

Urticaria

Urticaria is a heterogenous group of disorders characterized by sudden appearance of urticarial wheals and/or angioedema. The prevalence rates vary according to different studies, ranging from 0.3 to 11.3 % of population [132]. Zuberbier et al. [133] conducted a study among German subjects reported lifetime prevalence of any urticarial lesions and chronic urticaria (CU) reaching 8.8 % and 1.8 %, respectively. Possibly up to 20 % of population will experience at least one episode of acute urticaria (AU) during their lifetime. In 40 % cases angioedema is also present [134]. Acute forms of urticaria subside within 6 weeks (most commonly within 24 h), whereas chronic forms last longer than 6 weeks. In chronic idiopathic urticaria (CIU) lesions appear spontaneously due to known or unknown causes [135]. Among chronic urticaria subtypes inducible urticaria is also mentioned along with its variants.

Itching in urticaria is almost invariable; some patients complain of more intense pruritus than the others [136]. Pruritus is described as pricking or burning in quality and exacerbates in the evening or during night. Although the lesions are itchy, patients tend to rub the skin rather than scratch it.

Quality of life is severely impaired in this group of patients, as reported in various studies [137–141]. Patients suffering from CIU present with impaired functioning in various daily activities and coexist with psychological co-morbidity. O'Donnell et al. [137] evaluated general health status of chronic urticaria patients (n = 142) utilizing the Nottingham health profile (NHP) questionnaire. The NHP scores obtained during the study were compared to NHP scores among patients suffering from ischemic heart disease. CU patients presented almost identical scores concerning energy, social isolation, emotional reactions and higher sleep disturbance.

Yosipovitch et al. [102] evaluated subjects suffering from CIU (n = 100). Pruritus intensity (VAS) at its worst state was more pronounced in patients that felt depressed (9.0 ± 1.6 vs. 7.7 ± 1.8, $p = 0.018$), agitated (8.4 ± 1.5 vs. 7.4 ± 2.1; $p = 0.006$) and

anxious (9.1 ± 1.2 vs. 7.7 ± 1.9; p = 0.016). Moreover, 25 % respondents claimed that stress increased the perceived pruritus intensity.

Conrad et al. [142] researched the relationship between pruritus and anger in patients suffering from chronic idiopathic urticaria (n = 41) and psoriasis (n = 44). Eighty-five percent of the urticaria group presented at least moderate pruritus and more than 20 wheals day, while 82 % of subjects with psoriasis had at least 10 % of affected body surface area. Mean VAS scores for pruritus were similar in both groups (2.6 ± 1.1 and 2.2 ± 1.2, respectively). The authors assessed psychological distress and psychopathological symptoms perceived by the subjects as well. Symptom Checklist 90-R (SCL-90-R) questionnaire was utilized to assess nine psychopathological symptoms (somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism) and provide three global distress indices. Additionally, state anger, trait anger and anger expression were evaluated with State Trait Anger Expression Inventory (STAXI). Compared to healthy subjects (n = 49), both groups were characterized by higher emotional distress, depression and anxiety. Anger trait and anger state values were also more pronounced in the latter groups. In terms of pruritus severity, state anger was a significant predictor accounting for 19 % of its variance among the urticaria group. Among subjects suffering from psoriasis depression was the only significant predictor responsible for 12 % variance in pruritus severity.

Miscellaneous Cutaneous Disorders

Among adolescents with acne vulgaris (n = 108), 36.1 % subjects complained of pruritus that had occurred within the acne lesions in the past, while 13.9 % participants reported that their acne lesions were pruritic at the time of examination [143]. The latter group experienced pruritus intensity reaching approximately 3.1 ± 2.9 points (VAS). The maximal intensity of pruritus within acne lesions in the past had reached 4.0 ± 2.5 points. Itch aggravation associated with stress was reported by 33.3 % of subjects. Corresponding results were obtained by Lim et al. [144].

Peyri et al. [145] evaluated patients with seborrheic dermatitis (n = 2159). Over 90 % subjects complained of pruritus. Although no direct statistical correlation between stress and pruritus was reported, 76.4 % respondents reported that disease outbreak was triggered by factors such as stress, depression or fatigue.

A study by Niemeier et al. [17] conducted on 101 patients with hand dermatoses (26 with psoriasis, 33 with vesicular hand eczema and 42 with contact dermatitis) revealed that high stress responders experienced more severe pruritus intensity than low stress responders (VAS = 5.4 ± 2.2 and 4.0 ± 2.6 points, respectively; $p \leq 0.01$). When evaluated with Coping with Chronic Skin Diseases Questionnaire (CSD), high stress responders were more likely to present social anxiety and avoidance (33.1 ± 10.0 points vs. 26.6 ± 9.8 points; $p \leq 0.001$), vicious circle of itching or scratching (23.2 ± 6.3 points vs. 18.2 ± 6.6; $p \leq 0.001$), helplessness (25.2 ± 7.9

Table 6.2 Diagnostic criteria for functional itch disorder [150]

3 compulsory criteria
Localized or generalized pruritus *sine materia* (without primary skin lesion)
Chronic pruritus (>6 weeks)
No somatic cause
3/7 optional criteria
A chronological relationship of pruritus with one or several life events that could have psychological repercussions
Variations in intensity associated with stress
Nocturnal variations
Predominance during rest or inaction
Associated psychological disorder
Pruritus that could be improved by psychotropic drugs
Pruritus that could be improved by psychotherapies

points vs. 20.9 ± 7.2 points; $p \leq 0.01$) and anxious-depressive mood (23.0 ± 5.9 points vs. 16.5 ± 6.2 points; $p \leq 0.001$).

Certain studies revealed that wound healing is impaired by psychological factors including stress [146–148]. On the other hand, pruritus is a serious issue in patients suffering from burn injuries. The problem was addressed by van Loey et al. [149]. At 3 months postburn, 87 % subjects suffered from mild to severe itching. At 1 and 2 years postburn the percentages dropped to 70 % and 67 %, respectively. Itch intensity decreased from 2.8 ± 1.8 at 3 months postburn, through 1.8 ± 1.8 at 1 year postburn and eventually 1.5 ± 1.6 points at 2 years postburn. Additionally, the itching complaints seemed to be related to early post-traumatic stress symptoms. It is possible that pruritus experienced by patients suffering from chronic wounds may not only stem from the underlying disease but also induce additional stress and therefore impair the healing process. These theoretical speculations further encourage the application of treatment modalities that both alleviate itch and are aimed at psychological well-being of an individual.

Psychogenic Pruritus

Psychogenic, somatoform or idiopathic pruritus is a somewhat mysterious clinical entity. Also referred to as functional itch disorder (FID), this entity was defined by French Psychodermatology Group (FPDG) as an “itch disorder, where itch is at the centre of the symptomatology, and where psychological factors play an evident role in the triggering intensity, aggravation or persistence of the pruritus” [150]. More precise and accurate criteria were also proposed (Table 6.2). All compulsory criteria and at least three optional criteria are to be met in order to establish the diagnosis.

It is evident that the diagnosis of FID is based on excluding other possible causes of pruritus, both cutaneous and extracutaneous. This process is time- and cost-consuming, occasionally requiring prolonged hospitalization. If established,

the diagnosis frequently remains unclear from patient's perspective. However, physicians should bear in mind that regardless of its aetiology chronic pruritus is a very bothersome symptom, deteriorating the quality of life and possibly facilitating secondary psychological or even psychiatric problems. Therefore abnormalities detected during psychiatric evaluation in a patient suffering from chronic pruritus do not necessarily imply psychogenic aetiology.

Although studies evaluating psychiatric problems in subjects suffering from skin disorders are profuse, few focused specifically on the subject of psychogenic pruritus. In a German study 195 dermatological outpatients were evaluated [151]. Somatoform pruritus was diagnosed in over 10 % subjects. An interesting study was conducted by Kretzmer et al. [152]. Among 100 psychiatric ward inpatients idiopathic pruritus was diagnosed in 42 % of the subjects, more frequently among females (58 % vs. 34 %; $p = 0.03$). The diagnosis seemed to be associated with psychosocial stress as it was established in 48.5 % and 29 % patients without and with adequate social support, respectively ($p = 0.02$). Idiopathic pruritus was diagnosed in 76 % of patients regularly receiving opioids. Additionally, the diagnosis was more frequent in patients with higher scores on the anger-trait measure ($p = 0.02$), angry temperament measure ($p = 0.02$) and ruminative catastrophization ($p = 0.04$).

Therapeutic Recommendations

Therapy of itch frequently poses significant challenge to physicians. Regardless of itch aetiology, certain recommendations are widely acknowledged. Factors that increase skin dryness should be avoided, especially in AD individuals. These include dry climate, heat, excessive washing and bathing [8]. Likewise, contact with irritants, allergens, hot and spicy meals, hot beverages, alcohol and stressful situations is unadvisable. Washing should be prompt, performed with mild, non-alcaline soaps or syndets and followed by emollient application. The latter need to be prescribed in adequate amounts (e.g. 250 g per week) and ideally administered liberally and frequently [153]. In general, treatment of an underlying dermatological or systemic condition is fundamental in alleviating itch. Depending on the disease, topical therapy, phototherapy and systemic therapy are recommended. Numerous treatment modalities have been evaluated, whereas several require further description. H_1 antihistamines have been deemed as a mainstay of pruritus therapy in AD for many years. First generation antihistamines (hydroxyzine, clemastine) may improve sleep due to their sedative properties [153]. According to randomized controlled trials second generation antihistamines proved somewhat disappointing in relieving pruritus intensity in AD patients. They are, however, utilized as a treatment of choice in chronic urticaria [154]. Novel therapeutic modalities in AD (dupilumab) or psoriasis patients (apremilast) also significantly reduce itch [155, 156]. As depression symptoms frequently accompany chronic pruritus individuals (10 %) [10], SSRI therapy seems advisable in selected cases. Paroxetine proved useful in patients with polycythaemia vera, paraneoplastic pruritus or pruritus associated with psychiatric diseases [62, 64,

157], while sertraline was effective in cholestatic pruritus [65, 158] and uremic pruritus [159, 160]. In order to cease vicious itch-scratch cycle psychosomatic methods may also be instigated. Multidisciplinary programmes support the development of itch coping mechanisms [161–163]. Concerning the role of stress in itch development patient education, stress management and relaxation techniques are beneficial. Habit reversal therapy (HRT) is a subtype of cognitive therapy encompassing awareness training, inducing responses replacing dysfunctional behaviour and increasing the motivation to control the habits. AD patients utilizing HRT experienced an improvement in skin status and reduction in scratch behaviour [164–166].

Conclusions

The associations between itch and stress in dermatologic disorders constitute current and relevant issues in clinical practice. Stress initiates the onset of pruritus and frequently contributes to its exacerbation. Additionally, itch itself is a stressful symptom, negatively affecting quality of life. Many aspects still lack comprehensive explanation, although the interactions between nervous system, endocrine system and skin seem evident. Growing number of researches regarding pathogenesis of itch may contribute to the development of novel therapeutic approaches which may further turn out to be effective in clinical practice. Decreasing the intensity of itch will possibly result in reducing the stress perceived by an afflicted individual as well. Holistic approach towards the patient warrants utilization of different therapeutic modalities, including those originating from psychology and psychiatry.

References

1. Rees WL. Stress, distress and disease. The Presidential Address at the annual meeting of the Royal College of Psychiatrists, held in London, 9th July, 1975. Br J Psychiatry. 1976;128:3–18.
2. Selye H. Stress without distress. In: Selye H, editor. Psychopathology of human adaptation. Boston: Springer; 1976. p. 137–46.
3. Lazarus RS, Folkman S. Cognitive theories of stress and the issue of circularity. In: Appley MH, Trumbull RA, editors. Dynamics of stress. New York: Springer; 1988. p. 63–80.
4. Twycross R, Greaves MW, Handwerker H, Jones EA, Libretto SE, Szepietowski JC, Zylicz Z. Itch: scratching more than the surface. QJM. 2003;96:7–26.
5. Steinhoff M, Bienenstock J, Schmelz M, Maurer M, Wei E, Bíró T. Neurophysiological, neuroimmunological, and neuroendocrine basis of pruritus. J Invest Dermatol. 2006;126:1705–18.
6. Matterne U, Strassner T, Apfelbacher CJ, Diepgen TL, Weisshaar E. Measuring the prevalence of chronic itch in the general population: development and validation of a questionnaire for use in large-scale studies. Acta Derm Venereol. 2009;89:250–6.
7. Ständer S, Schäfer I, Phan NQ, Blome C, Herberger K, Heigel H, Augustin M. Prevalence of chronic pruritus in Germany: results of a cross-sectional study in a sample working population of 11,730. Dermatology. 2010;221:229–35.

8. Weisshaar E, Szepietowski JC, Darsow U, Misery L, Wallengren J, Mettang T, Gieler U, Lotti T, Lambert J, Maisel P, Streit M, Greaves MW, Carmichael AJ, Tschachler E, Ring J, Ständer S. European guideline on chronic pruritus. Acta Derm Venereol. 2012;92:563–81.
9. Picardi A, Abeni D, Melchi CF, Puddu P, Pasquini P. Psychiatric morbidity in dermatological outpatients: an issue to be recognized. Br J Dermatol. 2000;143:983–91.
10. Schneider G, Driesch G, Heuft G, Evers S, Luger TA, Ständer S. Psychosomatic cofactors and psychiatric comorbidity in patients with chronic itch. Clin Exp Dermatol. 2006;31:762–7.
11. Ständer S, Weisshaar E, Mettang T, Szepietowski JC, Carstens E, Ikoma A, Bergasa NV, Gieler U, Misery L, Wallengren J, Darsow U, Streit M, Metze D, Luger TA, Greaves MW, Schmelz M, Yosipovitch G, Bernhard JD. Clinical classification of itch: a position paper of the International Forum for the Study of Itch. Acta Derm Venereol. 2007;87:291–4.
12. Hay RJ, Johns NE, Williams HC, Bolliger IW, Dellavalle RP, Margolis DJ, Marks R, Naldi L, Weinstock MA, Wulf SK, Michaud C, J L Murray C, Naghavi M. The global burden of skin disease in 2010: an analysis of the prevalence and impact of skin conditions. J Invest Dermatol. 2014;134:1527–34.
13. Grand View Research. Pruritus therapeutics market by product (corticosteroids, antihistamines, local anesthetics, counterirritants, immunosuppressant, calcineurin inhibitors, pipeline, unmet needs), by disease type is expected to reach USD 16.38 billion by 2025. Available at: http://www.grandviewresearch.com/press-release/global-pruritus-therapeutics-market. March 2015. Accessed 27 Jan 2016.
14. Fortune DG, Main CJ, O'Sullivan TM, Griffiths CE. Quality of life in patients with psoriasis: the contribution of clinical variables and psoriasis-specific stress. Br J Dermatol. 1997;137:755–60.
15. Bhosle MJ, Kulkarni A, Feldman SR, Balkrishnan R. Quality of life in patients with psoriasis. Health Qual Life Outcomes. 2006;4:35.
16. Finzi A, Colombo D, Caputo A, Andreassi L, Chimenti S, Vena G, Simoni L, Sgarbi S, Giannetti A, PSYCHAE Study Group. Psychological distress and coping strategies in patients with psoriasis: the PSYCHAE Study. J Eur Acad Dermatol Venereol. 2007;21:1161–9.
17. Niemeier V, Nippesen M, Kupfer J, Schill WB, Gieler U. Psychological factors associated with hand dermatoses: which subgroup needs additional psychological care? Br J Dermatol. 2002;146:1031–7.
18. Zachariae R, Zachariae H, Blomqvist K, Davidsson S, Molin L, Mørk C, Sigurgeirsson B. Self-reported stress reactivity and psoriasis-related stress of Nordic psoriasis sufferers. J Eur Acad Dermatol Venereol. 2004;18:27–36.
19. Verhoeven EW, Kraaimaat FW, de Jong EM, Schalkwijk J, van de Kerkhof PC, Evers AW. Individual differences in the effect of daily stressors on psoriasis: a prospective study. Br J Dermatol. 2009;161:295–9.
20. Balieva F, Lien L, Kupfer J, Halvorsen JA, Dalgard F. Are common skin diseases among Norwegian dermatological outpatients associated with psychological problems compared with controls? An observational study. Acta Derm Venereol. 2015;96(2):227–31. doi:10.2340/00015555-2200.
21. Sun YG, Zhao ZQ, Meng XL, Yin J, Liu XY, Chen ZF. Cellular basis of itch sensation. Science. 2009;325:1531–4.
22. Paus R, Schmelz M, Bíró T, Steinhoff M. Frontiers in pruritus research: scratching the brain for more effective itch therapy. J Clin Invest. 2006;116:1174–86.
23. Handwerker HO, Forster C, Kirchhoff C. Discharge patterns of human C-fibers induced by itching and burning stimuli. J Neurophysiol. 1991;66:307–15.
24. Andrew D, Craig AD. Spinothalamic lamina I neurons selectively sensitive to histamine: a central neural pathway for itch. Nat Neurosci. 2001;4:72–7.
25. Ringkamp M, Schepers RJ, Shimada SG, Johanek LM, Hartke TV, Borzan J, Shim B, LaMotte RH, Meyer RA. A role for nociceptive, myelinated nerve fibers in itch sensation. J Neurosci. 2011;31:14841–9.

26. Darsow U, Drzezga A, Frisch M, Munz F, Weilke F, Bartenstein P, Schwaiger M, Ring J. Processing of histamine-induced itch in the human cerebral cortex: a correlation analysis with dermal reactions. J Invest Dermatol. 2000;115:1029–33.
27. Drzezga A, Darsow U, Treede RD, Siebner H, Frisch M, Munz F, Weilke F, Ring J, Schwaiger M, Bartenstein P. Central activation by histamine-induced itch: analogies to pain processing: a correlational analysis of O-15 H2O positron emission tomography studies. Pain. 2001;92:295–305.
28. Mochizuki H, Sadato N, Saito DN, Toyoda H, Tashiro M, Okamura N, Yanai K. Neural correlates of perceptual difference between itching and pain: a human fMRI study. Neuroimage. 2007;36:706–17.
29. Misery L. Atopic dermatitis and the nervous system. Clin Rev Allergy Immunol. 2011;41:259–66.
30. Papoiu AD, Coghill RC, Kraft RA, Wang H, Yosipovitch G. A tale of two itches. Common features and notable differences in brain activation evoked by cowhage and histamine induced itch. Neuroimage. 2012;59:3611–23.
31. Heyer G, Vogelgsang M, Hornstein OP. Acetylcholine is an inducer of itching in patients with atopic eczema. J Dermatol. 1997;24:621–5.
32. Heyer G, Groene D, Martus P. Efficacy of naltrexone on acetylcholine-induced alloknesis in atopic eczema. Exp Dermatol. 2002;11:448–55.
33. Shimizu K, Andoh T, Yoshihisa Y, Shimizu T. Histamine released from epidermal keratinocytes plays a role in α-melanocyte-stimulating hormone-induced itching in mice. Am J Pathol. 2015;185:3003–10.
34. Lee CH, Hong CH, Yu WT, Chuang HY, Huang SK, Chen GS, Yoshioka T, Sakata M, Liao WT, Ko YC, Yu HS. Mechanistic correlations between two itch biomarkers, cytokine interleukin-31 and neuropeptide β-endorphin, via STAT3/calcium axis in atopic dermatitis. Br J Dermatol. 2012;167:794–803.
35. Haustein UF. Adrenergic urticaria and adrenergic pruritus. Acta Derm Venereol. 1990;70:82–4.
36. Hundley JL, Yosipovitch G. Mirtazapine for reducing nocturnal itch in patients with chronic pruritus: a pilot study. J Am Acad Dermatol. 2004;50:889–91.
37. Tobin D, Nabarro G, Baart de la Faille H, van Vloten WA, van der Putte SC, Schuurman HJ. Increased number of immunoreactive nerve fibers in atopic dermatitis. J Allergy Clin Immunol. 1992;90:613–22.
38. McCoy ES, Taylor-Blake B, Zylka MJ. CGRPα-expressing sensory neurons respond to stimuli that evoke sensations of pain and itch. PLoS One. 2012;7:e36355. doi:10.1371/journal.pone.0036355.
39. Rogoz K, Andersen HH, Lagerström MC, Kullander K. Multimodal use of calcitonin gene-related peptide and substance P in itch and acute pain uncovered by the elimination of vesicular glutamate transporter 2 from transient receptor potential cation channel subfamily V member 1 neurons. J Neurosci. 2014;34:14055–68.
40. Gomes LO, Hara DB, Rae GA. En dothelin-1 induces itch and pain in the mouse cheek model. Life Sci. 2012;91:628–33.
41. Kido-Nakahara M, Buddenkotte J, Kempkes C, Ikoma A, Cevikbas F, Akiyama T, Nunes F, Seeliger S, Hasdemir B, Mess C, Buhl T, Sulk M, Müller FU, Metze D, Bunnett NW, Bhargava A, Carstens E, Furue M, Steinhoff M. Neural peptidase endothelin-converting enzyme 1 regulates endothelin 1-induced pruritus. J Clin Invest. 2014;124:2683–95.
42. Sun YG, Chen ZF. A gastrin-releasing peptide receptor mediates the itch sensation in the spinal cord. Nature. 2007;448:700–3.
43. Andoh T, Kuwazono T, Lee JB, Kuraishi Y. Gastrin-releasing peptide induces itch-related responses through mast cell degranulation in mice. Peptides. 2011;32:2098–103.
44. Nattkemper LA, Zhao ZQ, Nichols AJ, Papoiu AD, Shively CA, Chen ZF, Yosipovitch G. Overexpression of the gastrin-releasing peptide in cutaneous nerve fibers and its receptor in the spinal cord in primates with chronic itch. J Invest Dermatol. 2013;133:2489–92.
45. Sonkoly E, Muller A, Lauerma AI, Pivarcsi A, Soto H, Kemeny L, Alenius H, Dieu-Nosjean MC, Meller S, Rieker J, Steinhoff M, Hoffmann TK, Ruzicka T, Zlotnik A, Homey B. IL-31:

a new link between T cells and pruritus in atopic skin inflammation. J Allergy Clin Immunol. 2006;117:411–7.
46. Raap U, Wichmann K, Bruder M, Ständer S, Wedi B, Kapp A, Werfel T. Correlation of IL-31 serum levels with severity of atopic dermatitis. J Allergy Clin Immunol. 2008;122:421–3.
47. Tanaka A, Matsuda H. Expression of nerve growth factor in itchy skins of atopic NC/NgaTnd mice. J Vet Med Sci. 2005;67:915–9.
48. Suga H, Sugaya M, Miyagaki T, Ohmatsu H, Fujita H, Kagami S, Asano Y, Tada Y, Kadono T, Sato S. Association of nerve growth factor, chemokine (C-C motif) ligands and immunoglobulin E with pruritus in cutaneous T-cell lymphoma. Acta Derm Venereol. 2013;93:144–9.
49. Akiyama T, Nguyen T, Curtis E, Nishida K, Devireddy J, Delahanty J, Carstens MI, Carstens E. A central role for spinal dorsal horn neurons that express neurokinin-1 receptors in chronic itch. Pain. 2015;156:1240–6.
50. Ko MC, Song MS, Edwards T, Lee H, Naughton NN. The role of central mu opioid receptors in opioid-induced itch in primates. J Pharmacol Exp Ther. 2004;310:169–76.
51. Phan NQ, Lotts T, Antal A, Bernhard JD, Ständer S. Systemic kappa opioid receptor agonists in the treatment of chronic pruritus: a literature review. Acta Derm Venereol. 2012;92(5):555–60.
52. Jannuzzi RG. Nalbuphine for treatment of opioidinduced pruritus: a systematic review of literature. Clin J Pain. 2016;32:87–93.
53. Neisius U, Olsson R, Rukwied R, Lischetzki G, Schmelz M. Prostaglandin E2 induces vasodilation and pruritus, but no protein extravasation in atopic dermatitis and controls. J Am Acad Dermatol. 2002;47:28–32.
54. Yosipovitch G. The pruritus receptor unit: a target for novel therapies. J Invest Dermatol. 2007;127:1857–9.
55. Reddy VB, Lerner EA. Plant cysteine proteases that evoke itch activate protease-activated receptors. Br J Dermatol. 2010;163:532–5.
56. Akiyama T, Lerner EA, Carstens E. Protease-activated receptors and itch. Handb Exp Pharmacol. 2015;226:219–35.
57. Ostlere LS, Cowen T, Rustin MH. Neuropeptides in the skin of patients with atopic dermatitis. Clin Exp Dermatol. 1995;20:462–7.
58. Ständer S, Luger TA. Itch in atopic dermatitis – pathophysiology and treatment. Acta Dermatovenerol Croat. 2010;18:289–96.
59. Rukwied R, Heyer G. Cutaneous reactions and sensations after intracutaneous injection of vasoactive intestinal polypeptide and acetylcholine in atopic eczema patients and healthy controls. Arch Dermatol Res. 1998;290:198–204.
60. Rukwied R, Heyer G. Administration of acetylcholine and vasoactive intestinal polypeptide to atopic eczema patients. Exp Dermatol. 1999;8:39–45.
61. Reich A, Ständer S, Szepietowski JC. Drug-induced pruritus: a review. Acta Derm Venereol. 2009;89:236–44.
62. Zylicz Z, Smits C, Krajnik M. Paroxetine for pruritus in advanced cancer. J Pain Symptom Manage. 1998;16:121–4.
63. Biondi M, Arcangeli T, Petrucci RM. Paroxetine in a case of psychogenic pruritus and neurotic excoriations. Psychother Psychosom. 2000;69:165–6.
64. Tefferi A, Fonseca R. Selective serotonin reuptake inhibitors are effective in the treatment of polycythemia vera-associated pruritus. Blood. 2002;99:2627.
65. Browning J, Combes B, Mayo MJ. Long-term efficacy of sertraline as a treatment for cholestatic pruritus in patients with primary biliary cirrhosis. Am J Gastroenterol. 2003;98:2736–41.
66. Cederberg J, Knight S, Svenson S, Melhus H. Itch and skin rash from chocolate during fluoxetine and sertraline treatment: case report. BMC Psychiatry. 2004;4:36.
67. Mazzatenta C, Peonia G, Martini P. Pruritus induced by interruption of paroxetine therapy. Br J Dermatol. 2004;150:787–8.

68. Papoiu AD, Wang H, Coghill RC, Chan YH, Yosipovitch G. Contagious itch in humans: a study of visual 'transmission' of itch in atopic dermatitis and healthy subjects. Br J Dermatol. 2011;164:1299–303.
69. van Laarhoven AI, Vogelaar ML, Wilder-Smith OH, van Riel PL, van de Kerkhof PC, Kraaimaat FW, Evers AW. Induction of nocebo and placebo effects on itch and pain by verbal suggestions. Pain. 2011;152:1486–94.
70. Bartels DJ, van Laarhoven AI, Haverkamp EA, Wilder-Smith OH, Donders AR, van Middendorp H, van de Kerkhof PC, Evers AW. Role of conditioning and verbal suggestion in placebo and nocebo effects on itch. PLoS One. 2014;9:e91727. doi:10.1371/journal.pone.0091727.
71. Holle H, Warne K, Seth AK, Critchley HD, Ward J. Neural basis of contagious itch and why some people are more prone to it. Proc Natl Acad Sci U S A. 2012;109:19816–21.
72. Dalgard F, Stern R, Lien L, Hauser S. Itch, stress and self-efficacy among 18-year-old boys and girls: a Norwegian population-based cross-sectional study. Acta Derm Venereol. 2012;92:547–52.
73. Bandura A. Self-efficacy. In: Ramachaudran VS, editor. Encyclopedia of human behaviour, vol. 4. New York: Academic Press; 1994. p. 71–81.
74. Ward L, Wright E, McMahon SB. A comparison of the effects of noxious and innocuous counterstimuli on experimentally induced itch and pain. Pain. 1996;64:129–38.
75. Yosipovitch G, Duque MI, Fast K, Dawn AG, Coghill RC. Scratching and noxious heat stimuli inhibit itch in humans: a psychophysical study. Br J Dermatol. 2007;156:629–34.
76. Akiyama T, Iodi Carstens M, Carstens E. Transmitters and pathways mediating inhibition of spinal itch-signaling neurons by scratching and other counterstimuli. PLoS One. 2011;6:e22665. doi:10.1371/journal.pone.0022665.
77. Kardon AP, Polgár E, Hachisuka J, Snyder LM, Cameron D, Savage S, Cai X, Karnup S, Fan CR, Hemenway GM, Bernard CS, Schwartz ES, Nagase H, Schwarzer C, Watanabe M, Furuta T, Kaneko T, Koerber HR, Todd AJ, Ross SE. Dynorphin acts as a neuromodulator to inhibit itch in the dorsal horn of the spinal cord. Neuron. 2014;82:573–86.
78. Liu Y, Abdel Samad O, Zhang L, Duan B, Tong Q, Lopes C, Ji RR, Lowell BB, Ma Q. VGLUT2-dependent glutamate release from nociceptors is required to sense pain and suppress itch. Neuron. 2010;68:543–56.
79. Lagerström MC, Rogoz K, Abrahamsen B, Persson E, Reinius B, Nordenankar K, Olund C, Smith C, Mendez JA, Chen ZF, Wood JN, Wallén-Mackenzie A, Kullander K. VGLUT2-dependent sensory neurons in the TRPV1 population regulate pain and itch. Neuron. 2010;68:529–42.
80. Roblin D, Yosipovitch G, Boyce B, Robinson J, Sandy J, Mainero V, Wickramasinghe R, Anand U, Anand P. Topical TrkA kinase inhibitor CT327 is an effective, novel therapy for the treatment of pruritus due to psoriasis: results from experimental studies, and efficacy and safety of CT327 in a phase 2b clinical trial in patients with psoriasis. Acta Derm Venereol. 2015;95:542–8.
81. Grandgeorge M, Misery L. Mediators of the relationship between stress and itch. Exp Dermatol. 2015;24:334–5.
82. Arck P, Paus R. From the brain-skin connection: the neuroendocrine-immune misalliance of stress and itch. Neuroimmunomodulation. 2006;13:347–56.
83. Kim HS, Yosipovitch G. An aberrant parasympathetic response: a new perspective linking chronic stress and itch. Exp Dermatol. 2013;22:239–44.
84. Nutten S. Atopic dermatitis: global epidemiology and risk factors. Ann Nutr Metab. 2015;66:8–16.
85. Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. Acta Derm Venereol (Stockh). 1980;92(Suppl):44–7.
86. Williams HC, Burney PG, Hay RJ, Archer CB, Shipley MJ, Hunter JJ, Bingham EA, Finlay AY, Pembroke AC, Graham-Brown RA. The U.K. Working Party's Diagnostic Criteria for Atopic Dermatitis. I. Derivation of a minimum set of discriminators for atopic dermatitis. Br J Dermatol. 1994;131:383–96.

87. Hanifin JM. Pharmacophysiology of atopic dermatitis. Clin Rev Allergy. 1986;4:43–65.
88. Morren MA, Przybilla B, Bamelis M, Heykants B, Reynaers A, Degreef H. Atopic dermatitis: triggering factors. J Am Acad Dermatol. 1994;31:467–73.
89. Lee CH, Chuang HY, Shih CC, Jong SB, Chang CH, Yu HS. Transepidermal water loss, serum IgE and beta-endorphin as important and independent biological markers for development of itch intensity in atopic dermatitis. Br J Dermatol. 2006;154:1100–7.
90. Polańska A, Dańczak-Pazdrowska A, Silny W, Jenerowicz D, Osmola-Mańkowska A, Olek-Hrab K. Evaluation of selected skin barrier functions in atopic dermatitis in relation to the disease severity and pruritus. Postep Derm Alergol. 2012;29:373–7.
91. Tominaga M, Takamori K. Itch and nerve fibers with special reference to atopic dermatitis: therapeutic implications. J Dermatol. 2014;41:205–12.
92. Glinski W, Brodecka H, Glinska-Ferenz M, Kowalski D. Increased concentration of beta-endorphin in the sera of patients with severe atopic dermatitis. Acta Derm Venereol. 1995;75:9–11.
93. Toyoda M, Nakamura M, Makino T, Hino T, Kagoura M, Morohashi M. Nerve growth factor and substance P are useful plasma markers of disease activity in atopic dermatitis. Br J Dermatol. 2002;147:71–9.
94. Hon KL, Lam MC, Wong KY, Leung TF, Ng PC. Pathophysiology of nocturnal scratching in childhood atopic dermatitis: the role of brain-derived neurotrophic factor and substance P. Br J Dermatol. 2007;157:922–5.
95. Salomon J, Baran E. The role of selected neuropeptides in pathogenesis of atopic dermatitis. J Eur Acad Dermatol Venereol. 2008;22:223–8.
96. Teresiak-Mikołajczak E, Czarnecka-Operacz M, Jenerowicz D, Silny W. Neurogenic markers of the inflammatory process in atopic dermatitis: relation to the severity and pruritus. Postepy Dermatol Alergol. 2013;30:286–92.
97. Imaizumi A, Kawakami T, Murakami F, Soma Y, Mizoguchi M. Effective treatment of pruritus in atopic dermatitis using H1 antihistamines (second-generation antihistamines): changes in blood histamine and tryptase levels. J Dermatol Sci. 2003;33:23–9.
98. Rukwied R, Lischetzki G, McGlone F, Heyer G, Schmelz M. Mast cell mediators other than histamine induce pruritus in atopic dermatitis patients: a dermal microdialysis study. Br J Dermatol. 2000;142:1114–20.
99. Lippert U, Hoer A, Möller A, Ramboer I, Cremer B, Henz BM. Role of antigen-induced cytokine release in atopic pruritus. Int Arch Allergy Immunol. 1998;116:36–9.
100. Takaoka A, Arai I, Sugimoto M, Honma Y, Futaki N, Nakamura A, Nakaike S. Involvement of IL-31 on scratching behavior in NC/Nga mice with atopic-like dermatitis. Exp Dermatol. 2006;15:161–7.
101. Oh MH, Oh SY, Lu J, Lou H, Myers AC, Zhu Z, Zheng T. TRPA1-dependent pruritus in IL-13-induced chronic atopic dermatitis. J Immunol. 2013;191:5371–82.
102. Yosipovitch G, Goon AT, Wee J, Chan YH, Zucker I, Goh CL. Itch characteristics in Chinese patients with atopic dermatitis using a new questionnaire for the assessment of pruritus. Int J Dermatol. 2002;41:212–6.
103. Dawn A, Papoiu AD, Chan YH, Rapp SR, Rassette N, Yosipovitch G. Itch characteristics in atopic dermatitis: results of a web-based questionnaire. Br J Dermatol. 2009;160:642–4.
104. Oh SH, Bae BG, Park CO, Noh JY, Park IH, Wu WH, Lee KH. Association of stress with symptoms of atopic dermatitis. Acta Derm Venereol. 2010;90:582–8.
105. Chrostowska-Plak D, Reich A, Szepietowski JC. Relationship between itch and psychological status of patients with atopic dermatitis. J Eur Acad Dermatol Venereol. 2013;27:e239–42.
106. Peters EM, Michenko A, Kupfer J, Kummer W, Wiegand S, Niemeier V, Potekaev N, Lvov A, Gieler U. Mental stress in atopic dermatitis – neuronal plasticity and the cholinergic system are affected in atopic dermatitis and in response to acute experimental mental stress in a randomized controlled pilot study. PLoS One. 2012;9:e113552. doi:10.1371/journal.pone.0113552.

107. Tran BW, Papoiu AD, Russoniello CV, Wang H, Patel TS, Chan YH, Yosipovitch G. Effect of itch, scratching and mental stress on autonomic nervous system function in atopic dermatitis. Acta Derm Venereol. 2010;90:354–61.
108. Schut C, Bosbach S, Gieler U, Kupfer J. Personality traits, depression and itch in patients with atopic dermatitis in an experimental setting: a regression analysis. Acta Derm Venereol. 2014;94:20–5.
109. Schut C, Weik U, Tews N, Gieler U, Deinzer R, Kupfer J. Coping as mediator of the relationship between stress and itch in patients with atopic dermatitis: a regression and mediation analysis. Exp Dermatol. 2015;24:148–50.
110. Parisi R, Symmons DP, Griffiths CE, Ashcroft DM. Global epidemiology of psoriasis: a systematic review of incidence and prevalence. J Invest Dermatol. 2013;133:377–85.
111. Rachakonda TD, Schupp CW, Armstrong AW. Psoriasis prevalence among adults in the United States. J Am Acad Dermatol. 2014;70:512–6.
112. Gupta MA, Gupta AK, Kirkby S, Weiner HK, Mace TM, Schork NJ, Johnson EH, Ellis CN, Voorhees JJ. Pruritus in psoriasis. A prospective study of some psychiatric and dermatologic correlates. Arch Dermatol. 1988;124(7):1052–7.
113. Yosipovitch G, Goon A, Wee J, Chan YH, Goh CL. The prevalence and clinical characteristics of pruritus among patients with extensive psoriasis. Br J Dermatol. 2000;143:969–73.
114. Szepietowski JC, Reich A, Wiśnicka B. Itching in patients suffering from psoriasis. Acta Dermatovenerol Croat. 2002;10:221–6.
115. Reich A, Szepietowski JC, Wiśnicka B, Pacan P. Does stress influence itching in psoriatic patients? Dermatol Psychosom. 2003;4:151–5.
116. Chang SE, Han SS, Jung HJ, Choi JH. Neuropeptides and their receptors in psoriatic skin in relation to pruritus. Br J Dermatol. 2007;156:1272–7.
117. Reich A, Hrehorów E, Szepietowski JC. Pruritus is an important factor negatively influencing the well-being of psoriatic patients. Acta Derm Venereol. 2010;90:257–63.
118. Amatya B, Wennersten G, Nordlind K. Patients' perspective of pruritus in chronic plaque psoriasis: a questionnaire-based study. J Eur Acad Dermatol Venereol. 2008;22:822–6.
119. Prignano F, Ricceri F, Pescitelli L, Lotti T. Itch in psoriasis: epidemiology, clinical aspects and treatment options. Clin Cosmet Investig Dermatol. 2009;2:9–13.
120. Bilac C, Ermertcan AT, Bilac DB, Deveci A, Horasan GD. The relationship between symptoms and patient characteristics among psoriasis patients. Indian J Dermatol Venereol Leprol. 2009;75:551.
121. Nakamura M, Toyoda M, Morohashi M. Pruritogenic mediators in psoriasis vulgaris: comparative evaluation of itch-associated cutaneous factors. Br J Dermatol. 2003;149:718–30.
122. Madej A, Reich A, Orda A, Szepietowski JC. Vascular adhesion protein-1 (VAP-1) is overexpressed in psoriatic patients. J Eur Acad Dermatol Venereol. 2007;21:72–8.
123. Wiśnicka B, Szepietowski JC, Reich A, Orda A. Histamine, substance P and calcitonin gene-related peptide plasma concentration and pruritus in patients suffering from psoriasis. Dermatol Psychosom. 2004;5:73–8.
124. Reich A, Orda A, Wiśnicka B, Szepietowski JC. Plasma concentration of selected neuropeptides in patients suffering from psoriasis. Exp Dermatol. 2007;16:421–8.
125. Taneda K, Tominaga M, Negi O, Tengara S, Kamo A, Ogawa H, Takamori K. Evaluation of epidermal nerve density and opioid receptor levels in psoriatic itch. Br J Dermatol. 2011;165:277–84.
126. Kou K, Nakamura F, Aihara M, Chen H, Seto K, Komori-Yamaguchi J, Kambara T, Nagashima Y, Goshima Y, Ikezawa Z. Decreased expression of semaphorin-3A, a neurite-collapsing factor, is associated with itch in psoriatic skin. Acta Derm Venereol. 2012;92:521–8.
127. Nigam R, El-Nour H, Amatya B, Nordlind K. GABA and GABA(A) receptor expression on immune cells in psoriasis: a pathophysiological role. Arch Dermatol Res. 2010;302:507–15.
128. Reich A, Welz-Kubiak K, Rams L. Apprehension of the disease by patients suffering from psoriasis. Postepy Dermatol Alergol. 2014;31:289–93.

129. Lebwohl MG, Bachelez H, Barker J, Girolomoni G, Kavanaugh A, Langley RG, Paul CF, Puig L, Reich K, van de Kerkhof PC. Patient perspectives in the management of psoriasis: results from the population-based Multinational Assessment of Psoriasis and Psoriatic Arthritis Survey. J Am Acad Dermatol. 2014;70:871–81.
130. Remröd C, Lonne-Rahm S, Nordlind K. Study of substance P and its receptor neurokinin-1 in psoriasis and their relation to chronic stress and pruritus. Arch Dermatol Res. 2007;299:85–91.
131. Gupta MA, Gupta AK. Stressful major life events are associated with a higher frequency of cutaneous sensory symptoms: an empirical study of non-clinical subjects. J Eur Acad Dermatol Venereol. 2004;18:560–5.
132. Sánchez-Borges M, Asero R, Ansotegui IJ, Baiardini I, Bernstein JA, Canonica GW, Gower R, Kahn DA, Kaplan AP, Katelaris C, Maurer M, Park HS, Potter P, Saini S, Tassinari P, Tedeschi A, Ye YM, Zuberbier T. Diagnosis and treatment of urticaria and angioedema: a worldwide perspective. World Allergy Organ J. 2012;5:125–47.
133. Zuberbier T, Balke M, Worm M, Edenharter G, Maurer M. Epidemiology of urticaria: a representative cross-sectional population survey. Clin Exp Dermatol. 2010;35:869–73.
134. Kaplan AP. Clinical practice. Chronic urticaria and angioedema. N Engl J Med. 2002;346:175–9.
135. Zuberbier T, Aberer W, Asero R, Bindslev-Jensen C, Brzoza Z, Canonica GW, Church MK, Ensina LF, Giménez-Arnau A, Godse K, Gonçalo M, Grattan C, Hebert J, Hide M, Kaplan A, Kapp A, Abdul Latiff AH, Mathelier-Fusade P, Metz M, Nast A, Saini SS, Sánchez-Borges M, Schmid-Grendelmeier P, Simons FE, Staubach P, Sussman G, Toubi E, Vena GA, Wedi B, Zhu XJ, Maurer M. The EAACI/GA(2) LEN/EDF/WAO guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. Allergy. 2014;69:868–87.
136. Greaves M. Chronic urticaria. J Allergy Clin Immunol. 2000;105:664–72.
137. O'Donnell BF, Lawlor F, Simpson J, Morgan M, Greaves MW. The impact of chronic urticaria on the quality of life. Br J Dermatol. 1997;136:197–201.
138. Baiardini I, Giardini A, Pasquali M, Dignetti P, Guerra L, Specchia C, Braido F, Majani G, Canonica GW. Quality of life and patients' satisfaction in chronic urticaria and respiratory allergy. Allergy. 2003;58:621–3.
139. Grob JJ, Revuz J, Ortonne JP, Auquier P, Lorette G. Comparative study of the impact of chronic urticaria, psoriasis and atopic dermatitis on the quality of life. Br J Dermatol. 2005;152:289–95.
140. Poon E, Seed PT, Greaves MW, Kobza-Black A. The extent and nature of disability in different urticarial conditions. Br J Dermatol. 1999;140:667–71.
141. Maurer M, Ortonne JP, Zuberbier T. Chronic urticaria: a patient survey on quality-of-life, treatment usage and doctor-patient relation. Allergy. 2009;64:581–8.
142. Conrad R, Geiser F, Haidl G, Hutmacher M, Liedtke R, Wermter F. Relationship between anger and pruritus perception in patients with chronic idiopathic urticaria and psoriasis. J Eur Acad Dermatol Venereol. 2008;22:1062–9.
143. Reich A, Trybucka K, Tracinska A, Samotij D, Jasiuk B, Srama M, Szepietowski JC. Acne itch: do acne patients suffer from itching? Acta Derm Venereol. 2008;88:38–42.
144. Lim YL, Chan YH, Yosipovitch G, Greaves MW. Pruritus is a common and significant symptom of acne. J Eur Acad Dermatol Venereol. 2008;22:1332–6.
145. Peyrí J, Lleonart M. Clinical and therapeutic profile and quality of life of patients with seborrheic dermatitis. Actas Dermosifiliogr. 2007;98:476–82 [article in Spanish].
146. Kiecolt-Glaser JK, Marucha PT, Malarkey WB, Mercado AM, Glaser R. Slowing of wound healing by psychological stress. Lancet. 1995;346:1194–6.
147. Cole-King A, Harding KG. Psychological factors and delayed healing in chronic wounds. Psychosom Med. 2001;63:216–20.
148. Gouin JP, Kiecolt-Glaser JK. The impact of psychological stress on wound healing: methods and mechanisms. Immunol Allergy Clin North Am. 2011;31:81–93.

149. Van Loey NE, Bremer M, Faber AW, Middelkoop E, Nieuwenhuis MK. Itching following burns: epidemiology and predictors. Br J Dermatol. 2008;158:95–100.
150. Misery L, Alexandre S, Dutray S, Chastaing M, Consoli SG, Audra H, Bauer D, Bertolus S, Callot V, Cardinaud F, Corrin E, Feton-Danou N, Malet R, Touboul S, Consoli SM. Functional itch disorder or psychogenic pruritus: suggested diagnosis criteria from the French psychodermatology group. Acta Derm Venereol. 2007;87:341–4.
151. Stangier U, Köhnlein B, Gieler U. Somatoforme Störungen bei ambulanten dermatologischen Patienten. Psychotherapeut. 2003;48:321–8 [article in German].
152. Kretzmer GE, Gelkopf M, Kretzmer G, Melamed Y. Idiopathic pruritus in psychiatric inpatients: an explorative study. Gen Hosp Psychiatry. 2008;30:344–8.
153. Ring J, Alomar A, Bieber T, Deleuran M, Fink-Wagner A, Gelmetti C, Gieler U, Lipozencic J, Luger T, Oranje AP, Schäfer T, Schwennesen T, Seidenari S, Simon D, Ständer S, Stingl G, Szalai S, Szepietowski JC, Taïeb A, Werfel T, Wollenberg A, Darsow U. Guidelines for treatment of atopic eczema (atopic dermatitis) part I. J Eur Acad Dermatol Venereol. 2012;26:1045–60.
154. Simons FE, Simons KJ. H1 antihistamines: current status and future directions. World Allergy Organ J. 2008;1:145–55.
155. Beck LA, Thaçi D, Hamilton JD, Graham NM, Bieber T, Rocklin R, Ming JE, Ren H, Kao R, Simpson E, Ardeleanu M, Weinstein SP, Pirozzi G, Guttman-Yassky E, Suárez-Fariñas M, Hager MD, Stahl N, Yancopoulos GD, Radin AR. Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. N Engl J Med. 2014;371:130–9.
156. Paul C, Cather J, Gooderham M, Poulin Y, Mrowietz U, Ferrandiz C, Crowley J, Hu C, Stevens RM, Shah K, Day RM, Girolomoni G, Gottlieb AB. Efficacy and safety of apremilast, an oral phosphodiesterase 4 inhibitor, in patients with moderate-to-severe plaque psoriasis over 52 weeks: a phase III, randomized controlled trial (ESTEEM 2). Br J Dermatol. 2015;173:1387–99.
157. Zylicz Z, Krajnik M, Sorge AA, Costantini M. Paroxetine in the treatment of severe non-dermatological pruritus: a randomized, controlled trial. J Pain Symptom Manage. 2003;26:1105–12.
158. Mayo MJ, Handem I, Saldana S, Jacobe H, Getachew Y, Rush AJ. Sertraline as a first-line treatment for cholestatic pruritus. Hepatology. 2007;45:666–74.
159. Shakiba M, Sanadgol H, Azmoude HR, et al. Effect of sertraline on uremic pruritus improvement in ESRD patients. Int J Nephrol. 2012;2012:363901.
160. Chan KY, Li CW, Wong H, Yip T, Chan ML, Cheng HW, Sham MK. Use of sertraline for antihistamine-refractory uremic pruritus in renal palliative care patients. J Palliat Med. 2013;16:966–70.
161. van Os-Medendorp H, Ros WJ, Eland-de Kok PC, Kennedy C, Thio BH, van der Schuur-van der Zande A, Grypdonck MH, Bruijnzeel-Koomen CA. Effectiveness of the nursing programme 'Coping with itch': a randomized controlled study in adults with chronic pruritic skin disease. Br J Dermatol. 2007;156:1235–44.
162. Evers AW, Duller P, de Jong EM, Otero ME, Verhaak CM, van der Valk PG, van de Kerkhof PC, Kraaimaat FW. Effectiveness of a multidisciplinary itch-coping training programme in adults with atopic dermatitis. Acta Derm Venereol. 2009;89:57–63.
163. Bathe A, Matterne U, Dewald M, Grande T, Weisshaar E. Educational multidisciplinary training programme for patients with chronic pruritus. Acta Derm Venereol. 2009;89:498–501.
164. Rosenbaum MS, Ayllon T. The behavioral treatment of neurodermatitis through habit-reversal. Behav Res Ther. 1981;19:313–8.
165. Melin L, Frederiksen T, Noren P, Swebilius BG. Behavioural treatment of scratching in patients with atopic dermatitis. Br J Dermatol. 1986;115:467–74.
166. Norén P, Melin L. The effect of combined topical steroids and habit-reversal treatment in patients with atopic dermatitis. Br J Dermatol. 1989;121:359–66.

Chapter 7
Scars and Stress

Annelyse Cristine Ballin, Bettina Carvalho, Katlein França, and Flavia Lira Diniz

Introduction

Scars are the result of the wound healing process in the skin and other body tissues. Although scars constitute a natural part of the healing process, sometimes they can deviate from the normal process, developing into problematic scars [25].

When the scar results from augmented production of collagen and hyperproliferation of fibroblasts, due to an imbalance of the natural process of healing (production and degradation of collagen), they can develop into hypertrophic scars or keloids. The difference between them is that hypertrophic scars are elevated scars that remain within the limits of the original lesion, but tends to regression over time; while keloids extend outside the borders of the original incision (Fig. 7.1). In addition, there is usually no significant regression of keloids over time, because the healing process continues for an indefinite period, and it is marked by recurrence

A.C. Ballin, MD (✉)
CEFOR (Center of the Face and Otolaryngology),
369 Bruno Filgueira Street, Curitiba, PR, Brazil 80240-220

Faculty of Medicine of Santa Casa of São Paulo, São Paulo, SP, Brazil
e-mail: annelysecb@gmail.com

B. Carvalho, MD
Otolaryngology Department, Federal University of Parana, Curitiba, PR, Brazil

K. França, MD, PhD
Centro Studi per la Ricerca Multidisciplinare e Rigenerativa, Università Degli Studi "G. Marconi", Rome, Italy

Department of Dermatology and Cutaneous Surgery, Department of Psychiatry and Behavioral Sciences, Institute for Bioethics and Health Policy, University of Miami Miller School of Medicine, Miami, FL, USA

F.L. Diniz, MD
Department of Otolaryngology, University of São Paulo, São Paulo, SP, Brazil

K. França, M. Jafferany (eds.), *Stress and Skin Disorders*,
DOI 10.1007/978-3-319-46352-0_7

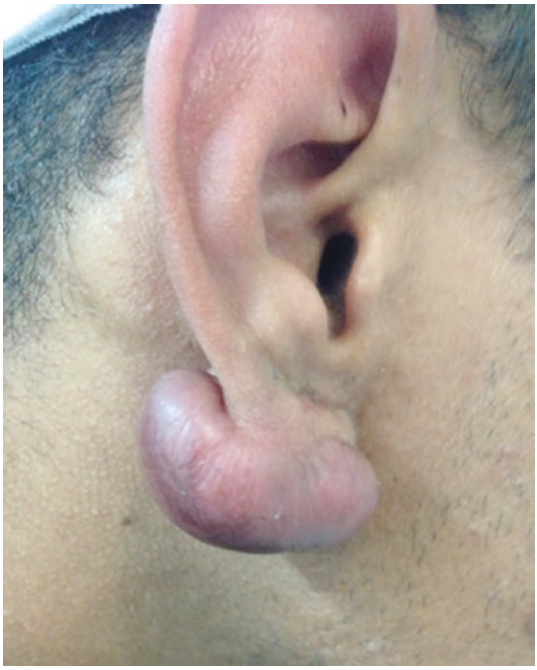


Fig. 7.1 Ear keloid in an Afro-American patient

after resection [4, 14, 15]. The majority of patients who seek treatment for scars have either keloids or a mix of keloids and hypertrophic scars [12].

In this chapter we aim to show evidence that stress can affect wound healing producing unaesthetic scars, such as keloids, and suggest possible solutions.

Importance of Scars

Impact of Inadequate Skin Scars

Inadequate scars can lead to loss of function, restriction of growth, restriction of movement (particularly because of contractures over joints), poor aesthetics, and adverse psychological effects.

Increase in Surgical Procedures

The USA population is becoming older. It is estimated that people aged 65 and over will almost double its population of 2012 in 2050 [24]. Consequently, there is an increased chance that people may require an operative procedure in some point of life and therefore may be susceptible to development of scars.

The numbers of plastic surgeries are also increasing due a change in the mentality and awareness about the benefits of this type of surgery. There are also many new products and devices available. Non-invasive or minimally invasive procedures can also cause scars [22].

Any surgery, even endoscopic surgeries in which very small incisions are made, will always produce a scar. These scars can be a small yet permanent reminder of the disease that was treated by surgery or they can become a problem itself.

The goal of the surgeon, especially if the surgery is performed in the face and/or for cosmetic purpose, is to achieve a non-visible scar (or at least minimally visible scar). Many patients do not want other people to know they went through a surgery, especially if it was a plastic surgery. A bad scar can be a major problem for these patients.

In order to obtain a pleasant scar, the surgeon must be aware of the factors that should either be avoided or performed during surgical procedures, as well as the patient's habits and characteristics. For example, the habit of smoking is known to interfere with all scarring stages. This habit should ideally be discontinued before any surgery, especially before certain cosmetic surgeries, such as facelifts that can produce visible scars [23]. On the other hand, patients' ethnical background or skin types (precisely IV or V) may impact negatively on the scar [12], but this cannot be changed. The surgeon's obligation is to recognize and when possible, change the factors that can impact in the scar healing.

Recent studies have been shown the impact of an interesting modifying factor in the healing process: the stress.

Stress can be modified or managed with innumerous anxiety-decreasing techniques, such as exercising, relaxation techniques, and medications, which goes beyond the scope of this chapter. It is recommended that elective surgeries should be avoided during stressful periods, such as school testing period.

Wound Healing

The process of wound healing can be divided into three main processes: inflammation, proliferation, and remodeling.

Inflammation starts when disruptions of capillary blood vessels start the induction of the hemostatic cascade. The leaked intra- vascular contents form fibrin clots. Platelets degranulation releases enzymes and cytokines that recruit cells such as fibroblasts.

The second stage in wound healing is proliferation, which begins around day 4 or 5 with the migration of fibroblasts into the wound matrix. The fibroblasts synthetize extracellular matrix (ECM), which paves the way for migration of various cells that collaborate in the wound healing process.

Wound contraction usually begins around day 10 to 12. Myofibroblasts, which contain actin filaments, help to initiate wound contraction.

By 2–4 weeks, the fibroblasts replace the fibrin with a more robust matrix of collagen fibers. In the mature wound, the initial elastic fiber network is no longer observed and explains the firmness and absence of elasticity of scars.

The third and last stage in wound healing is the remodeling phase, which usually begins 3 weeks after tissue injury. Microscopic findings of this stage include decreases in fibroblast count, occlusion of blood vessels, and hardening of collagen fibers (transformation from collagen type III to type I).

Continuous collagen production and degradation has an effect of remodeling the mature wound matrix for approximately 6 months post injury. At this point, production and degradation balances each other, and no significant change in collagen amount is observed. The remodeling phase is the most responsible for intra and interpersonal variations in scar qualities. A wound can become an unsightly scar during this period.

These phases are not distinct, but intertwined. The whole healing process is a continuum of this three processes occurring at the same time [10, 21].

Measuring Stress

There are different types of stress. Stress can be chronic, acute, sequenced, distant, actual or perceived.

Actual stress involves things that have a direct effect on the subject, which includes environmental stress (air, water and noise pollution), harming behaviors (smoking, drinking, diets, lack of sleep) and even psychological stress (issues related to relationships, job, financial, and others). On the other hand, perceived stress are the feelings or thoughts that an individual has about how much stress they are under at a given point in time or over a given time period. It is result of the interaction between the individual and his or her environment, and this assessment is influenced by traits such as personality, coping resources, and social support [19].

In addition, the question is: Would there be a difference in the healing process and therefore formation of unaesthetic scars or keloids if the person were experiencing actual stress or perceived stress? To correctly answer this question is important to keep in mind that actual and perceived stress are not directly proportional. Sometimes, people with high perceived stress have low actual stress levels. But perceived stress raises cortisol levels just as the actual stress does.

Burns et al. [3] evaluated the immune response to a vaccine, and found that high perceived stress, but not life events stress (actual stress), was associated with low antibody titers (low immunity) [3].

In addition to directly modulating physiological responses to skin damage, stress can also indirectly influence wound repair by promoting the adoption of health-damaging behaviors. Individuals who experience greater levels of stress are more likely to increase their alcohol and tobacco use, decrease their participation in physical activity, experience sleep disturbances, and make poorer diet choices, compared to

Table 7.1 Hormones and signals produced by the skin relating the skin to the Neuro-Endorine-Immune system

Hormones	**Cells**
CRH (corticotropin-releasing hormone)	Keratinocytes, melanocytes, pilosebaceous units
ACTH (adrenocorticotropic hormone) and α-MSH (α-melanocyte stimulating hormone)	Keratiinocytes, melanocytes, pilosebaceous units, fibroblasts, endothelial cells
Cortisol	Keratinocytes, pilosebaceous units
Cytokines and growth factors	**Cells**
IL-1 (inteleukin 1)	Keratinocytes, melanocytes, fibroblasts, endothelial cells
IL-6	Keratinocytes, fibroblasts, pilosebaceous units, endothelial cells
TNF-α (Tumor necrosis factor-α)	Keratinocytes, melanocytes
Interferon-γ	Keratinocytes, fibroblasts

individuals reporting less distress. These negative health behavior practices can then compound the detrimental impact of stress on physiological healing processes [11].

The Patophisiology of the Stress on Scars

The skin is actually considered part of the **Neuro-Immune-Endocrine System**, establishing a bidirectional communication: from periphery (skin) to central (central nervous system) and vice-versa (Table 7.1).

There are two important axis: (1) the skin has an equivalent to the **Hypothalamus-pituitary-adrenal (HPA) axis**, which coordinates stress responses with the central HPA axis. The activity of the HPA axis is governed by the production of Corticotrophin releasing hormone (CRH) by the Hypothalamus, which on your turn activate the secretion of Adrenocorticotropic hormone (ACTH) by the Pituitary gland. The ACTH stimulates the secretion of steroids by the Adrenal cortex. (2) Since the skin is highly innervated with sensory nerves derived from the dorsal root ganglion, it forms a direct path between skin and the adrenal glands, the (**Sympathetic-Adrenal-Medullary axis**). This system mediates the main adaptive response to systemic stress, either external or internal. In the skin, it protects against stressors such as the UV radiation and pathogens.

Skin reactions to stress can range from itching and pain (which are well known as psychodermatosis, induced by neurotrophins and neuropeptides) sweating (that can cause alteration of skin conductance and impedance, which alters patterns of migration of cells to injured areas), and affected barrier function by alteration of permeability homeostasis and can facilitate infection (induced by increased levels of glucocorticoids which inhibit epidermal lipid synthesis). All these factors can alter the process of wound healing [1, 7, 13, 20].

Stress X Scars: Human Studies

Many studies show that psychological stress can affect the skin, for example in diseases such as psoriasis, atopic dermatitis and urticaria. Studies performed in animal models showed that psychological stress induced by insomnia, over-crowding, and noise affect the wound healing process [1, 5]. A few prospective studies were conducted in humans to evaluate the effect of the stress in the wound healing (Table 7.2).

The effects of stress in the recurrence of keloids were studied by Furtado et al. The perceived stress, anxiety and depression, evaluated through the Hospital Anxiety and Depression Scale (HADS), showed no difference in the recurrence and no recurrence of keloids groups. Also, no difference was found in itching and pain (symptoms of stress) between groups. Although cortisol levels were elevated in both groups, there was no difference between groups either. The recurrence group had greater instability to an acute stressor stimulus with a lower threshold for sympathetic nervous system release, as measured by galvanic skin responses. Thus the conclusion was that stress was correlated to recurrence of keloids, even though it was difficult to measure [7].

Prevention of Unesthetic Scars

Like in any subject in Medicine, prevention is always better than treatment for any disease. Correct surgery technique is the most important way of preventing surgical scars and includes asepsis, correct direction of incisions (according to Langer's lines of skin tension to avoid tension), atraumatic tissue handling, the avoidance of raw surfaces, and accurate approximation (the 5 A's).

In the surgical field, other than proper use of surgical techniques and materials, the prevention of scars and keloids can benefit from the use of certain procedures. Liu et al reviewed prophylactic treatments to either prevent or minimize postsurgical scars, performed around the time of surgery. These procedures included botulinum toxin, laser and intradermal injectable products and have shown effectiveness in minimizing eventual scar appearance [17].

To which extent such treatments should be applied on patients is the question. Which patient would qualify for a preventive scar treatment? Maybe patients with a history of bad healing in previous surgeries or with genetic factors that would make them prone to bad healing. These ones should definitely receive preventive treatment for scar formation.

Patients, who are prone to keloid formation, either with personal or family history, should also be informed before any surgical procedures about the likelihood of recurrence and the need for continued management.

Certain over the counter treatments such as ointments and silicone sheeting are non invasive, and could be suggested to all patients.

Table 7.2 Human based studies comparing skin healing and stress

Authors	Year	n	Control group	Skin injury	Stress condition	Skin evaluation after the injury	Stress evaluation	Results and conclusions
Furtado et al.[7]		25 patients with keloid	Nonrecurrence of keloid group	Keloid excision	Presence of keloid	Keloid recurrence Galvanic skin response	PSS HADS Salivary cortisol	Psychological stress influenced the recurrence of keloids in the post-operative period, which was demonstrated by the increase in the minimum and maximum galvanic skin responses during stress situations
Muizzuddin et al. [18]	2003	28 females	Yes	Removing stratum corneum layers with tape strippings	Process of marital separation X perceived "happy" controls	Trans-epidermal water loss before and after injury	PSS	Psychological stress of marital dissolution does not appear to change skin barrier strength but has negative impact on skin barrier recovery
Garg et al. [9]	2001	27 students	Same patients in different period of time	Barrier disruption by cellophane tape stripping	During final examinations (presumed higher stress) Before winter vacations and after spring break (assumed lower stress occasions)	Permeability barrier kinetics after barrier disruption	PSS Profile of MoodStates	Decline in permeability barrier recovery kinetics after disruption in parallel with increase in perceived psychological stress

(continued)

Table 7.2 (continued)

Authors	Year	n	Control group	Skin injury	Stress condition	Skin evaluation after the injury	Stress evaluation	Results and conclusions
Altemus et al. [2]	2001	25 women interview, 11 sleep deprivation, 10 exercise	No	Tape stripping	After a stressful situation: interview, sleep deprivation or exercise	Transepidermal water loss Recovery of skin barrier function Stratum corneum water content (skin conductance)	Plasma levels of: several stress-response hormones and cytokines, natural killer cell activity, absolute numbers of peripheral blood leukocytes	Acute psychosocial and sleep deprivation stress disrupts skin barrier function homeostasis in women, and this disruption may be related to stress-induced changes in cytokine secretion
Cole-king and Harding [6]	2001	53 (31 women, 22 men)	No	Chronic leg ulcers	Anxiety and depression	Wound healing (likert scale)	HADS (hospital anxiety and depression scale)	Relationship between healing of wounds and HADS was statistically significant: Delayed healing was associated with a higher mean HAD score Higher HAD scores (indicating "caseness") were also associated with delayed healing
Kiecolt-glaser et al. [16]	1995	13 women (age 62.3 [se 2.3])	13 controls matched for age (60.4 [2.8] years) and family income	Punch biopsy	Women caring for demented relatives x controls	Wound healing Production of IL-1	Stress caused by caring of a relative with Alzheimer's disease	Caregivers group: Wound healing took longer Peripheral blood leucocytes produced less IL-1

Note: HADS= Hospital Anxiety and Depression Scale; PSS= Perceived Stress Scale

It is always important to remember that the surgeon's responsibility does not end with the removal of the stitches, as the healing process will continue for months, so hypertrophic scars or keloids formation may occur belatedly. Therefore, it is important to keep a close follow-up during the year after surgery.

After surgery, the management of the scar involves minimizing tension (using adhesive paper tape for example), maintenance of moisture (using ointments or silicone sheeting), avoidance of inflammation (sunscreen and anti-oxidants), and optimization of the molecular environment (massage and pressure forces induce changes in enzymatic expression that are thought to decrease collagen synthesis). All these should be carried on for 12 months after surgery.

Psychological Evaluation

It is highly recommended that patients seeking plastic surgery should be psychologically evaluated before surgery as part of a routine consultation. This evaluation should include an assessment of, body image and self-esteem and the patients' expectations of the outcomes of the surgery.

While the surgery itself may be justified and can even show perfect results, it will not resolve the initial dissatisfaction, because this is based on the body perception and not its physical appearance. Many psychological tools have been developed and are still under development to address these issues.

A patient with lower self-esteem may find a scar more unaesthetic than a person with good self-esteem, or a non-visible scar can have the same impact as a visible scar in the patient's quality of life depending on the patient's perspective [8].

Another question raised is whether a stress level evaluation would be important as well, considering that stress levels could be related to bad wound healing after surgery.

Even patients who seek plastic surgery to correct scars, burns, or other injuries that can be accidental have to pass these evaluations to show that they understand realistically the possible results of the surgery. For example, a patient with PTSD (post traumatic stress disorder) will not be able to recover from their psychological trauma by eliminating the scar; however, if they have realistic expectations and proper psychiatric treatment, these patients may be good candidates for a corrective cosmetic surgery.

The approach to these patients should be multidisciplinary and include dermatologists, plastic surgeons, psychologists, psychiatrists, and physiotherapists.

Conclusions

Psychological evaluations are important before any cosmetic surgery to survey patient expectations; a stress evaluation would be interesting as well.

More researches are necessary to draw conclusions, but there is a possibility that keloids formation and recurrence are related to stress. On the other hand, the relation between stress and wound healing is already proved.

Until more good quality studies are conducted we cannot confirm that either actual or perceived stress causes scars or keloid formation, but it is always a good idea to offer counseling and recommend stress management techniques to all patients.

References

1. Aberg KM, Radek KA, Choi EH, Kim DK, Demerjian M, Hupe M, Kerbleski J, Gallo RL, Ganz T, Mauro T, Feingold KR, Elias PM. Psychological stress downregulates epidermal antimicrobial peptide expression and increases severity of cutaneous infections in mice. J Clin Invest. 2007;117(11):3339–49.
2. Altemus M, Rao B, Dhabhar FS, Ding W, Granstein RD. Stress-induced changes in skin barrier function in healthy women. J Invest Dermatol. 2001;117(2):309–17.
3. Burns V, Drayson M, Ring C, Carroll D. Perceived stress and psychological well-being are associated with antibody status after meningitis C conjugate vaccination. Psychosom Med. 2002;64(6):963–70.
4. Carvalho B, Ballin AC, Berger R, Ribeiro TB, Cavichiolo J, Ballin CR, Mocellin M. Treatment of retroauricular keloids: revision of cases treated at the ENT Service of HC/UFPR. Intl Arch Otorhinolaryngol. 2012;16(2):195–200.
5. Chen Y, Lyga J. Brain-skin connections: stress, inflammation and skin aging. Inflamm Allergy Drug Targets. 2014;13(3):177–90.
6. Cole-King A, Harding KG. Psychological factors and delayed healing in chronic wounds. Psychosom Med. 2001;63(2):216–20.
7. Furtado F, Hochman B, Farber PL, Muller MC, Hayashi LF, Ferreira LM. Psychological stress as a risk factor for postoperative keloid recurrence. J Pshychosom Res. 2012;72:282–7.
8. Furtado F, Hochman B, Ferrara SF, Dini GM, Nunes JM, Juliano Y, Ferreira LM. What factors affect the quality of life of patients with keloid? Rev Assoc Med Bras. 2009;55(6):700–4.
9. Garg A, Chren MM, Sands LP, Matsui MS, Marenus KD, Feingold KR, Elias PM. Psychological stress perturbs epidermal permeability barrier homeostasis: implications for the pathogenesis of stress-associated skin disorders. Arch Dermatol. 2001;137(1):53–9.
10. Gauglitz GG, Korting HC, Pavicic T, Ruzicka T, Jeschke M. Hypertrophic scarring and keloids: pathomechanisms and current and emerging treatment strategies. Mol Med. 2011;17(1–2):113–25.
11. Gouin J-P, Kiecolt-Glaser JK. The impact of psychological stress on wound healing: methods and mechanisms. Immunol Allergy Clin North Am. 2011;31(1):81–93.
12. Hochman B, Farkas CB, Isoldi FC, Ferrara SF, Furtado F, Ferreira LM. Distribuição de queloide e cicatriz hipertrofica Segundo fototipos de pele de Fitzpatrick. Rev Bras Cir Plast. 2012;27(2):185–9.
13. Hochman B, Furtado F, Isoldi FC, Nishioka MA, Ferreira LM. Psychological stress and skin wound healing: new highlights. In: Psychology of stress. New York: Nova Science Publishers, Inc; 2013.
14. Hochman B, Ishizuka CK, Ferreira LM, Oliveira LQ, Locali RF. Disfunções cicatriciais hiperproliferativas: Cicatrizes hipertróficas. Estima. 2004;2(3):32–9.
15. Hochman B, Locali RF, Oliveira LQR, Ferreira LM. Disfunções cicatriciais hiperproliferativas: Quelóide. Estima. 2004;2(4):33–9.

16. Kiecolt-Glaser JK, Marucha PT, Malarkey WB, Mercado AM, Glaser R. Slowing of wound healing by psychological stress. Lancet. 1995;346(8984):1194–6.
17. Liu A, Moy RL, Ozog DM. Current methods employed in the prevention and minimization of surgical scars. Dermatol Surg. 2011;37(12):1740–6.
18. Muizuddin N, Matsui MS, Marenus KD, Maes DH. Impact of stress of marital dissolution on skin barrier recovery: tape stripping and measurement of trans-epidermal water loss (TEWL). Skin Res Technol. 2003;9(1):34–8.
19. Phillips AC. Perceived stress. In: Encyclopedia of behavioral medicine. New York: Springer; 2007. p. 1453–4.
20. Slominski A. A nervous breakdown in the skin: stress and the epidermal barrier. J Clin Invest. 2007;117:3166–9.
21. Son D, Harijan A. Overview of surgical scar prevention and management. J Korean Med Sci. 2014;29:751–7.
22. The American Society for Aesthetic Plastic Surgery. Statistics released by The American Society for Aesthetic Plastic Surgery, Issued 2015. Available at: www.surgery.org/media/statistics Accessed 11 May 2016.
23. Thomas JR, Dizon TK. Preoperative evaluation of the aging neck patient. Facial Plast Surg Clin North Am. 2014;22(2):171–6.
24. U.S Census Bureau. An aging nation: the older population in the United States. Issued May 2014. Available at: http://www.census.gov/prod/2014pubs/p25-1140.pdf. Accessed 11 May 2016.
25. Vieira MH, Amini S, Valins W, Berman B. Innovative therapies in the treatment of keloids and hypertrophic scars. J Clin Aesthet Dermatol. 2010;3(5):20–6.

Chapter 8
Skin Picking and the Role of Stress

Madhulika A. Gupta and Aditya K. Gupta

Introduction

The evolution of stress as a medical and psychosomatic construct is largely based upon the works of Claude Bernard, Walter Cannon and Hans Selye [1]. Bernard discussed the concept of an organism's ability to maintain the '*milieu intérieur*' or a constant fluid environment bathing the cells of the body, and Cannon used the term 'homeostasis' to describe the maintenance of several physiological variables such as blood glucose and core body temperature within acceptable ranges [1]. When faced with a threat to homeostasis, Cannon described negative and positive feedback systems that regulate physiological mechanisms and correct the discrepancies between sensed and acceptable values. For example, when faced with a cold stressor and drop in core temperature, the body diminishes heat loss by cutaneous vasoconstriction and diversion of blood to internal organs, and shivering increases heat production; alternately when faced with a heat stressor and an increase in core body temperature, there is diversion of blood flow from the viscera to the skin and sweating enhances heat loss so that core body temperature returns to acceptable levels [1]. Cannon included the concept of psychosocial stressors as threats to homeostasis and in the early 1900s described the 'fight or flight' response and the associated acute changes in adrenal gland secretion and sympathetic nervous system [1]. In the mid-1900s Hans Selye defined stress as 'the nonspecific response of the body to any demand upon it' and it was later demonstrated that some of these changes are

M.A. Gupta, MD, FRCPC (✉)
Department of Psychiatry, Schulich School of Medicine and Dentistry, University of Western Ontario, 585 Springbank Drive, Suite 101, London, ON, Canada, N6J 1H3
e-mail: magupta@uwo.ca

A.K. Gupta, MD, PhD, FRCPC
Department of Medicine, University of Toronto, Toronto, ON, Canada

Mediprobe Research, London, ON, Canada

K. França, M. Jafferany (eds.), *Stress and Skin Disorders*,
DOI 10.1007/978-3-319-46352-0_8

associated with the activation of the hypothalamic-pituitary-adrenal (HPA) axis. In addition to the non-specific stress response, Selye acknowledged that responses to stressors have specific components that tend to reverse the effects of the stressor [1].

The current concept of stress views the stress response as having a degree of specificity depending upon the particular challenge to homeostasis, the organism's conscious and subconscious perception of the stressor, and the organism's perceived ability to cope with the stressor [1]. The earlier concept of homeostasis suggested the constancy of values for certain physiological variables; at present ranges of acceptable values are recognized and these ranges may vary, for example, there is a diurnal variation in body temperature and cutaneous blood flow. The term 'allostasis', first used by Sterling and Eyer in 1988 [2] is used to describe the fact that adaptation to different stressors includes alterations in the acceptable levels of the physiological variable being monitored. Adaptations involving allostasis are determined by genetic, developmental and previous experiential factors and the brain is the site where the effects of the stressors are processed and the appropriate neuroendocrine and behavioral responses initiated [1]. While the adaptive response may be effective when carried out over a short period, over time the cumulative effect of the response may have an adverse effect. For example, scratching or skin picking in response to a stressor (dermatological or psychological) that causes an itch or other dysesthesia is usually initially adaptive, but when scratching or skin picking becomes chronic it might lead to skin ulcers or trigger the 'itch-scratch cycle'. The risk of developing such adverse effects is termed 'allostatic load' [1–3]. 'Allostatic load' [1, 3] refers to the effects of prolonged activation of the effectors involved in allostasis, or the cost of adaptation, and provides a conceptual model for studying the effects of stress on the body, including the skin, in both health and disease. In this chapter, skin picking is considered to be initially an adaptive response to stress which may become severe or prolonged in certain psycho-dermatological situations and lead to pathological outcomes. Skin picking (SP) is a body-focused repetitive behavior that becomes a clinically significant symptom when recurrent skin picking results in skin lesions and causes significant impairment or distress in social, occupational or other important areas of functioning [4]. In the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) [4], clinically significant skin picking is classified as Excoriation or Skin Picking Disorder.

Biopsychosocial Approach to Stress and Skin-Picking

The skin serves as both (i) an immune organ and metabolically active interface between the individual and the outside world during sleep and wakefulness, (ii) an organ of communication throughout the life span- at neurobiological, psychological and social levels [5]. Due to its strategic location, the skin plays a critical role in preserving homeostasis [6], as it is regularly exposed to potentially dysregulating stimuli, both physical and psychosocial. The skin has the capacity to mount an allostatic response by recognizing, discriminating, and integrating various

physiological and psychosocial stimuli in a complex environment [6]. Rubbing and picking of the skin can often be a feature of this response. Assessment of the role of stress in SP involves the consideration of neurobiological, psychiatric, psychosocial and dermatologic factors as stress can have varying effects in any particular patient. When assessing the role of stress in SP, it is also important to consider the mediating effect of sleep, as SP and pruritus tend be worse during the evening and at bedtime or may occur during sleep.

There is an emerging literature on psychological stress, the cutaneous stress response and skin homeostasis [7]. In a non-clinical sample, the number of stressful major life events experienced over the previous 6 months was associated with an increased frequency and severity of a range of cutaneous sensory symptoms (such as sensations of moderate to severe itching, crawling, tingling, pricking, 'pins and needles', burning, pain, skin tenderness, easy bruising and numbness) during the previous month [8]; most of these cutaneous sensory symptoms could lead to scratching and SP. The most frequently reported body region affected was the scalp (59.5 %) and the most frequently affected symptom was itching (69.3 %). The total number of major life events experienced over the previous 6 months correlated with the severity of the individual cutaneous symptoms ($0.22 \leq$ Pearson $r \leq 0.41$, $p < 0.001$) and the total symptoms severity score (sum of all cutaneous ratings) (Pearson $r = 0.40$, $p < 0.001$) [8]. This correlation between stressful major life events and cutaneous sensory symptoms remained significant after the possible confounding effect of psychological factors was partialled out statistically (partial $r = 0.19$, $p = 0.001$). Disruption of cutaneous homeostasis by stress may lead to cutaneous sensory disturbances which can trigger SP.

Neurobiological Factors

In reaction to stress, the skin produces rapid neural responses and slower humoral or immune responses, at both local and systemic levels [6] and plays a central role in homeostasis. The co-ordination between the local and systemic responses is mediated by the skin's extensive neuroendocrine systems and immune responses [6, 9]. As a large sensory organ, the skin has afferent sensory nerves conveying sensations of touch, itch, pain, temperature and other stimuli to the central nervous system (CNS) and efferent autonomic, mainly sympathetic nerves that play a role in cutaneous homeostasis by regulating vasomotor and pilomotor functions and the activity of the eccrine and apocrine sweat glands [5, 6, 10]. The efferent autonomic nerves release the classic neurotransmitters such as serotonin, acetylcholine and noradrenalin, in addition to neuropeptides (such as β-endorphin, neuropeptide Y, galanin, and vasoactive intestinal peptide) and other biologically active substances such as nitric oxide [6], which act as co-transmitters and result in the activation of physiological responses such as pruritus, erythema, edema and hyperthermia [6], which could lead to rubbing and picking of the skin. An in-depth discussion of the skin's immune/neuroendocrine responses to stress is outside the scope of this chapter.

Role of Sleep and Circadian Physiology

Sleep plays a primary role in cutaneous homeostasis, and can play an important mediating role in the relation between SP and stress. Sleep and circadian disruption are core features of psychological stress and are encountered in a wide range of psychiatric disorders that are stress-related or exacerbated by stress and can be comorbid with dermatologic disorders [11] such as mood disorders, anxiety disorders, obsessive-compulsive disorder and posttraumatic stress disorder [12, 13]. These disorders may also be associated with SP (discussed below). Sleep deprivation and/or restriction and circadian rhythm disruption can cause a heightened pro-inflammatory state and are important mediating factors in pruritic inflammatory dermatoses [14] and could lead to sensory reactions in non-diseased skin that can induce skin-picking and scratching [10].

Various aspects of skin physiology show circadian rhythmicity including the generation of the stratum corneum barrier of the human skin [15]. There is circadian rhythmicity in trans-epidermal water loss (TEWL) with skin permeability being higher in the evening and night than in the morning [16]. Higher TEWL in the evening suggests that the epidermal barrier function is not optimal at this time. Itch intensity and tendency to pick the skin both tend to be higher during the evening and especially before bedtime, and may be related to higher TEWL and increased skin temperature during this time. Upto 65 % of pruritic dermatoses such as atopic dermatitis, psoriasis and chronic idiopathic urticaria tend to be associated with a lower pruritus threshold during the evening and night [14]. The diurnal pattern of pruritus and SP wherein their threshold is lower during the night, is most likely a reflection of complex circadian-mediated factors [5] such as lower cortisol levels, decreased epidermal barrier function, and increased skin temperature. Circadian disruption e.g., from rotating shift-work has been associated with an increased risk of pruritic inflammatory dermatoses such as psoriasis [5]. Circadian disruption is a feature of many psychiatric disorders [17]. There is an extensive emerging literature on the role of the circadian clock on metabolism, inflammation and other immune responses, and disruption of homeostasis due to circadian disruption is likely to reduce the threshold for pruritus and SP. Scratching and SP during sleep often significantly contributes to the overall morbidity associated with SP. Patients may pick their skin during sleep, resulting in bleeding and excoriations and may report that they have no control over their SP during their sleep. Scratching during sleep appears to be proportional to the overall sympathetic tone (a high sympathetic tone is typically a feature of stress and allostatic load) during a particular sleep stage, and usually occurs most frequently during non-rapid eye movement (NREM) stages 1 and 2 (or stages N1 and N2 as per the current nosology) versus the deep sleep stages 3 and 4 (or stage N3) when the sympathetic tone is the lowest. In rapid eye movement sleep (REM sleep or stage R) the severity of scratching is similar to stage 2 where the sympathetic tone is at an intermediate level [5, 14].

Cutaneous Sensory Innervation

In most instances SP is preceded by a disagreeable cutaneous sensation [10]. Stress can modulate subjective cutaneous sensations [8]. The cutaneous sensory neurons convey modality-specific information to the CNS and have specialized receptors (chemoreceptors, thermoreceptors, mechanoreceptors) and transducers for highly specific sensory functions [18]. These receptors are distributed throughout the skin and vary in density depending upon the skin region [18]. The sensory signals from the skin undergo modulation and integration in the CNS, and the nature of the stimulus and its location are encoded by the somatotopic organization of the neurons and synapses between the skin and the somatosensory cortex [18]. Regions with a high density of nerve endings include the regions of the face innervated by the three branches (V1, V2, V3) of the trigeminal nerve, lips, finger pads and genitalia [19]. Generally the density of epidermal innervation on the trunk and limbs is greater proximally than distally [20]. In the facial skin, the density of the epidermal fibers decreases and the density of myelinated dermal fibers increases as one moves from the supraorbital to the perioral region [19]. Skin with a greater density of epidermal innervation is more likely to develop unexplained dysesthesias which often precede SP [10], for example, the face and scalp are often sites of SP. The epidermis is innervated with thin axonal nerve endings or neurites that make up most of the pain sensing or nociceptive and autonomic fibers [18]. Over 90 % of the epidermal neurites consist of the small-diameter C-fibers (unmyelinated) and/or A-δ fibers (an intermediate thinly myelinated class) that transduce and transmit pain [18]. Myelination increases the diameter and conduction velocity of the axons. The sensation of pruritus is carried to the CNS by a subgroup of unmyelinated C-fibers [21]; these fibers are anatomically the same but functionally different from the C-fibers associated with pain transmission. The input from the itch-related afferent C-fibers project to higher CNS structures including the anterior cingulate cortex and the insula, via the spinothalamic tract and thalamus [22]. These brain regions play a role in emotional regulation and psychiatric disorders, and may explain the role of psychiatric factors in cutaneous sensory disorders. The insula contains interoceptive representation that provides the basis for all subjective feelings from the body. Some of the interoceptive stimuli that originate from the skin and are associated with activation of the insula include itch, burning, pricking sensations and vasomotor flush [23]. The epidermal small fibers that transmit pain and itch to the CNS also have important efferent and trophic effects [10]; the small fiber mediated vasomotor and efferent functions contribute to itch by antidromic release of peptides such as substance P and calcitonin-gene related peptide [18, 21]. The itch and other sensations lead to scratching and SP. Most of the efferent autonomic fibers in the skin are sympathetic and therefore these cutaneous reactions are most likely to be exacerbated during sympathetic arousal associated with stressful situations.

Psychiatric and Psychosocial Factors

SP can be a feature of (i) a primary psychiatric disorder where stress plays a role as precipitating or perpetuating factor. The SP may be a feature of cutaneous dysesthesias arising from autonomic nervous system arousal such as in PTSD [13]; (ii) the SP can be a feature of a conditioned response e.g., tendency to pick the skin when watching television or before bedtime when the threshold for experiencing cutaneous sensory symptoms is also low, or SP may be part of a compulsive trait or ritual [24]; (iii) SP may represent underlying difficulties with body image and interoceptive awareness, and poor self-concept [25] e.g., in Eating Disorders and Body Dysmorphic Disorder. SP can represent the patient's attempt to achieve a perfect appearance especially during times of stress (e.g., acne excoriée in the adolescent with acne); and (iv) SP serves to regulate emotions (Fig. 8.1) [26–28], especially during states of

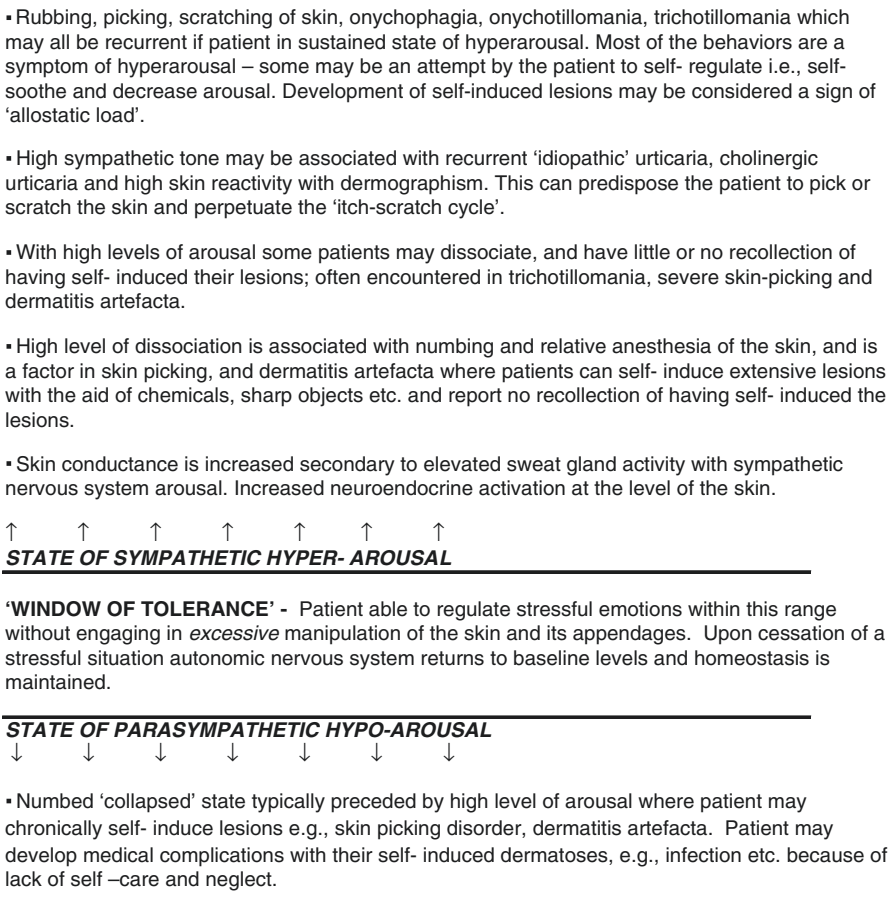


Fig. 8.1 Emotional dysregulation, autonomic nervous system reactivity and cutaneous self-manipulation (including skin picking) (Adapted from Gupta [28])

heightened sympathetic arousal, where the SP can result in self-induced lesions. High levels of stress and dissociation can be associated with SP (Fig. 8.1). Dissociation typically occurs within the context of severe stress, when the emotions are at their extreme and outside the range of the patient's usual coping capacity or 'window of tolerance' (Fig. 8.1) [28]. Dissociation, which is typically a feature of stress syndromes such as PTSD, is associated with an increased threshold for pain perception and skin numbness [29], which can be key factors in SP and the self-induced dermatoses [30]. Like anxiety, dissociation scores can be mild and in the non-clinical range (such as in occasional absent-mindedness) to severe (such as in Dissociative Identity Disorder). In a non-dermatologic sample (consisting of psychiatric patients and community based non-clinical participants) severity of cutaneous sensory symptoms correlated directly (Pearson $r=0.56$, $p<0.001$) with dissociation scores; numbness, pain and itching were the best predictors of the dissociation scores (adjusted $R^2=0.34$, $p<0.001$) [31]. The four major mechanisms discussed above are not mutually exclusive and often coexist depending upon the underlying psychiatric pathology. Difficulties with emotional regulation (Fig. 8.1) and dissociation, which both typically occur in the context of moderate to high levels of stress, are possibly the most important psychosomatic factors in the pathogenesis of SP in clinical settings.

Skin Picking Disorder (Excoriation Disorder)

In the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) [4] recurrent SP, most commonly affecting the face, arms and hands, that results in skin lesions and significant distress and impairment in the occupational, social or other areas of functioning, is classified as Skin-Picking Disorder (SPD) or Excoriation Disorder, under the section on Obsessive- Compulsive and Related Disorders (OCRD) [4]. SPD [4] often begins in adolescence in association with the onset of acne and picking of the acne lesion (*acne excoriée*), however the picking may involve clinically healthy skin, minor skin irregularities, other pimples, calluses or scabs resulting from self-excoriation [4]. SPD can occur in all age groups, and may have first onset in a previously active person who loses mobility e.g., due to accident or illness [32]. The skin picking may be accompanied by a range of rituals or behaviors involving the skin or scabs, and some individuals engage in skin picking that is more focused, with preceding tension and subsequent relief, features that are consistent with obsessive-compulsive symptoms [4]. Some individuals may engage in more automatic skin picking with the picking seeming to occur without full awareness and without preceding tension, symptoms that are consistent with dissociation [5]. The DSM-5 mentions that many patients have a mix of both (i.e., obsessive-compulsive and dissociative) behavioral styles. In patients where SP occurs without preceding tension or full awareness, there typically tends to be much higher levels of stress and dissociation, and such patients require stabilization and assessment for suicide risk [5]. Stressful life events are known to be associated with the onset of obsessive-compulsive symptoms [33]. Psychological trauma and traumatic stress are well recognized precursors of dissociation [34]. Stress may therefore precede and be the result of SPD.

Body Dysmorphic Disorder

SP involving acne or other skin lesions, may be a feature of excessive grooming in Body Dysmorphic Disorder (BDD) (DSM-5) [4], also classified under OCRD, where the patient is preoccupied with a perceived defect in their physical appearance. The compulsive SP which is intended to improve the perceived defects in the skin can cause skin damage and infections [4]. The individual feels driven to perform the SP, which may not be pleasurable and may increase the anxiety and dysphoria, and cause clinically significant distress or impairment in social, occupational and other areas of functioning [4].

Other Psychiatric Disorders

SP may be encountered in a wide range of other psychiatric disorders where stress can play a role in the onset or exacerbation of the disorder [4].

Major Depressive Disorder (MDD)

MDD is the most common psychiatric comorbidity in dermatologic disease. MDD is associated with a decrease in the threshold for pruritus perception [35]. MDD may be associated with amplification of a wide range of cutaneous dysesthesias which can all lead to SP [10].

Posttraumatic Stress Disorder (PTSD)

In PTSD the traumatic event may be re-experienced in many ways including dissociative flashbacks including cutaneous sensory flashbacks that represent the cutaneous sensory component of the traumatic experience. The autonomic arousal can also result in heightened cutaneous sympathetic reactivity which can present as cutaneous sensory complaints [10]. These symptoms can lead to SP.

Dissociative Disorders (DD)

DD typically occur during states of extreme stress, which are associated with marked hyper- or hypo-arousal. The skin can be a focus of tension-reducing behaviors which can manifest as excessive manipulation of the skin and its appendages, including SP.

Schizophrenia Spectrum and Other Psychotic Disorders

Somatic delusions and tactile hallucinations may be associated with SP, including delusions of infestation or parasitosis or other sensory delusions involving the skin.

Dermatologic Disorders

Psychological stress and psychiatric factors are important in one-third of dermatology patients [36]. A large number of dermatologic disorders that are exacerbated by psychological stress have an immune basis and are associated with pruritus e.g. psoriasis, atopic dermatitis and chronic idiopathic urticaria. Stress can precipitate SP in these patients. A blunted HPA-axis cortisol response and heightened sympathetic response to stressors have been observed in psoriasis [37–39], factors that can decrease the threshold for pruritus perception and predispose the patient to SP.

References

1. Goldstein DS, Kopin IJ. Evolution of concepts of stress. Stress. 2007;10(2):109–20.
2. McEwen BS. Stress, adaptation, and disease. Allostasis and allostatic load. Ann N Y Acad Sci. 1998;840:33–44.
3. McEwen BS, Stellar E. Stress and the individual. Mechanisms leading to disease. Arch Intern Med. 1993;153(18):2093–101.
4. American Psychiatric Association. Obsessive-compulsive and related disorders. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington, VA: American Psychiatric Association; 2013. p. 235–64.
5. Gupta MA, Gupta AK. Current concepts in psychodermatology. Curr Psychiatry Rep. 2014;16(6):449.
6. Slominski AT, Zmijewski MA, Skobowiat C, Zbytek B, Slominski RM, Steketee JD. Sensing the environment: regulation of local and global homeostasis by the skin's neuroendocrine system. Adv Anat Embryol Cell Biol. 2012;212:V, vii, 1–115.
7. Hunter HJ, Momen SE, Kleyn CE. The impact of psychosocial stress on healthy skin. Clin Exp Dermatol. 2015;40(5):540–6.
8. Gupta MA, Gupta AK. Stressful major life events are associated with a higher frequency of cutaneous sensory symptoms: an empirical study of non-clinical subjects. J Eur Acad Dermatol Venereol. 2004;18(5):560–5.
9. Arck PC, Slominski A, Theoharides TC, Peters EM, Paus R. Neuroimmunology of stress: skin takes center stage. J Invest Dermatol. 2006;126(8):1697–704.
10. Gupta MA, Gupta AK. Cutaneous sensory disorder. Semin Cutan Med Surg. 2013;32(2):110–8.
11. Gupta MA, Levenson JL. Dermatology. In: Levenson JL, editor. The American Psychiatric Publishing textbook of psychosomatic medicine: psychiatric care of the medically ill. 2nd ed. Washington, DC: American Psychiatric Association; 2011. p. 667–90.
12. Boland EM, Ross RJ. Recent advances in the study of sleep in the anxiety disorders, obsessive-compulsive disorder, and posttraumatic stress disorder. Psychiatr Clin North Am. 2015;38(4):761–76.

13. Gupta MA. Review of somatic symptoms in post-traumatic stress disorder. Int Rev Psychiatry. 2013;25(1):86–99.
14. Gupta MA, Gupta AK. Sleep-wake disorders and dermatology. Clin Dermatol. 2013; 31(1):118–26.
15. Yosipovitch G, Xiong GL, Haus E, Sackett-Lundeen L, Ashkenazi I, Maibach HI. Time-dependent variations of the skin barrier function in humans: transepidermal water loss, stratum corneum hydration, skin surface pH, and skin temperature. J Invest Dermatol. 1998; 110(1):20–3.
16. Yosipovitch G, Sackett-Lundeen L, Goon A, Yiong Huak C, Leok Goh C, Haus E. Circadian and ultradian (12 h) variations of skin blood flow and barrier function in non-irritated and irritated skin-effect of topical corticosteroids. J Invest Dermatol. 2004;122(3):824–9.
17. Jones SG, Benca RM. Circadian disruption in psychiatric disorders. Sleep Med Clin. 2015;10(4):481–93.
18. Oaklander AL, Siegel SM. Cutaneous innervation: form and function. J Am Acad Dermatol. 2005;53(6):1027–37.
19. Nolano M, Provitera V, Caporaso G, Stancanelli A, Leandri M, Biasiotta A, et al. Cutaneous innervation of the human face as assessed by skin biopsy. J Anat. 2013;222(2):161–9.
20. Lauria G, Holland N, Hauer P, Cornblath DR, Griffin JW, McArthur JC. Epidermal innervation: changes with aging, topographic location, and in sensory neuropathy. J Neurol Sci. 1999;164(2):172–8.
21. Oaklander AL. Common neuropathic itch syndromes. Acta Derm Venereol. 2012;92(2):1 18–25.
22. Patel TS, Yosipovitch G. Central transmission: from skin to brain. In: Misery L, Stander S, editors. Pruritus. London: Springer; 2010. p. 23–6.
23. Craig AD. The sentient self. Brain Struct Funct. 2010;214(5–6):563–77.
24. Gupta MA, Gupta AK, Schork NJ. Psychosomatic study of self-excoriative behavior among male acne patients: preliminary observations. Int J Dermatol. 1994;33(12):846–8. 25.
25. Gupta MA, Gupta AK, Schork NJ. Psychological factors affecting self-excoriative behavior in women with mild-to-moderate facial acne vulgaris. Psychosomatics. 1996;37(2): 127–30.
26. Roberts S, O'Connor K, Belanger C. Emotion regulation and other psychological models for body-focused repetitive behaviors. Clin Psychol Rev. 2013;33(6):745–62.
27. Roberts S, O'Connor K, Aardema F, Belanger C. The impact of emotions on body-focused repetitive behaviors: evidence from a non-treatment-seeking sample. J Behav Ther Exp Psychiatry. 2015;46:189–97.
28. Gupta MA. Emotional regulation, dissociation, and the self-induced dermatoses: clinical features and implications for treatment with mood stabilizers. Clin Dermatol. 2013;31(1): 110–7.
29. van der Kolk BA, Greenberg MS, Orr SP, Pitman RK. Endogenous opioids, stress induced analgesia, and posttraumatic stress disorder. Psychopharmacol Bull. 1989;25(3):417–21.
30. Gupta MA, Gupta AK, Vujcic B. Body-focused repetitive behaviors (hair-pulling, skin-picking, onychophagia) and dissociation: an under-recognized association. Biol Psychiatry. 2015;77(9):48S.
31. Gupta MA, Gupta AK. Medically unexplained cutaneous sensory symptoms may represent somatoform dissociation: an empirical study. J Psychosom Res. 2006;60(2):131–6.
32. Gupta MA, Gupta AK, Haberman HF. Neurotic excoriations: a review and some new perspectives. Compr Psychiatry. 1986;27(4):381–6.
33. Goldberg X, Soriano-Mas C, Alonso P, Segalas C, Real E, Lopez-Sola C, et al. Predictive value of familiality, stressful life events and gender on the course of obsessive-compulsive disorder. J Affect Disord. 2015;185:129–34.
34. Ford JD, Gomez JM. The relationship of psychological trauma and dissociative and posttraumatic stress disorders to nonsuicidal self-injury and suicidality: a review. J Trauma Dissociation. 2015;16(3):232–71.

35. Gupta MA, Gupta AK, Schork NJ, Ellis CN. Depression modulates pruritus perception: a study of pruritus in psoriasis, atopic dermatitis, and chronic idiopathic urticaria. Psychosom Med. 1994;56(1):36–40.
36. Gupta MA, Gupta AK. Psychodermatology: an update. J Am Acad Dermatol. 1996;34(6):1030–46.
37. Arnetz BB, Fjellner B, Eneroth P, Kallner A. Stress and psoriasis: psychoendocrine and metabolic reactions in psoriatic patients during standardized stressor exposure. Psychosom Med. 1985;47(6):528–41.
38. Richards HL, Ray DW, Kirby B, Mason D, Plant D, Main CJ, et al. Response of the hypothalamic-pituitary-adrenal axis to psychological stress in patients with psoriasis. Br J Dermatol. 2005;153(6):1114–20.
39. Evers AW, Verhoeven EW, Kraaimaat FW, de Jong EM, de Brouwer SJ, Schalkwijk J, et al. How stress gets under the skin: cortisol and stress reactivity in psoriasis. Br J Dermatol. 2010;163(5):986–91.

Chapter 9
The Role of Stress in Dermatitis Artefacta

Zeba Hasan Hafeez

Dermatitis Artefacta (Factitious Dermatitis) is a primary psychiatric disorder with secondary skin manifestations. The term, 'primary psychiatric disorder,' implies that a primary skin condition does not exist [1], and that skin lesions are produced by self-inflicted trauma which patients typically deny [2, 3]. Cutaneous lesions are produced in order to satisfy a subconscious psychological need which is that of being cared for, nurtured, by assuming the sick role [4, 5]. The Diagnostic and statistical manual of mental disorders, fifth edition (DSM-5), has categorized it in the somatic symptom and related disorders section [6].

Epidemiology

The incidence of dermatitis artefacta (DA) among dermatologic patients has been reported to be 0.3 % [3]. The skin lesions are known as a 'defense' in that they distract the patient from the underlying psychiatric problem [7]. It has been observed that either the patient or a close relative has been associated with some aspect of healthcare [8].

The age at onset of symptoms can broadly range from 9 to 73 years [2], with the highest prevalence being in adolescents and adults under the age of 30 [9]. Females are predominantly affected; the ratio of female to male varies from 20:1 to 4:1 [9]. Self-mutilating behavior has been observed in 10–15 % of healthy children, especially between the ages of 9 and 18 months. These self-mutilations are considered pathological after the age of 3. DA has been noted to develop among psychiatric inpatients [10], and in older males [8, 11–13]. The male to female ratio is 2:1 in the latter category of the population, and patients are more likely to produce subtle

Z.H. Hafeez, MD
Touro University College of Osteopathic Medicine, Vallejo, CA, USA
e-mail: zebahafeez@hotmail.com

K. França, M. Jafferany (eds.), *Stress and Skin Disorders*,
DOI 10.1007/978-3-319-46352-0_9

cutaneous lesions, and often have a past history of somatizing illnesses (pseudoseizures, abdominal pain, syncope, chronic fatigue, backache) [9]. In a follow up study of 43 patients, an 81 year old female (diagnosed with senile dementia) had a forgotten rubber band around her leg, and an 80 year old female had a rubber band under her wedding ring [14].

Clinical Features

The lesions have wide-ranging, morphologic features that are often bizarre with sharp, distinct, geometric margins surrounded by normal skin. Weeping, crusted, or scarred lesions, with post inflammatory hypopigmentation or hyperpigmentation can be seen. The lesions may range in number from single or a few to several hundred, and in chronic cases, scarring may be the only sign. The lesions are distributed in areas that the patient can easily access (e.g. the face, extensor surfaces of extremities, and upper back). Repetitive self-excoriation can also exacerbate a preexisting dermatosis [2]. The morphology of individual lesions is determined by the manner in which they are created, do not conform to the pattern of any known dermatoses and are non-healing. Blisters, purpura, ulcers, erythema, edema, sinuses, or nodules, deep excoriation by fingernails or other sharp object, chemical and thermal burns, occlusion of circulation around the limbs or digits [2, 8] can be seen. Thus factitial lesions may be very destructive.

A "hollow history" is a part of the clinical presentation. The patients usually insist that the lesions appeared mysteriously, even overnight, or over a short period of time [8, 15]. The patient typically appears unconcerned, while family members are very disturbed, often angry and confronting. Generally, patients and their family members have consulted multiple physicians of various specialties, with numerous tests [8].

Differential Diagnosis of Cutaneous Factitial Disease

Weber-Christian syndrome, bullous pemphigoid, cellulitis, vasculitis, pyoderma gangrenosum, deep fungal infection, arthropod bites and collagen vascular disease [2, 8].

The Role of Stress and Psychiatric Comorbidity

Psychological stress has been associated with the onset or exacerbation of a wide range of cutaneous disorders [16, 17]. In the literature, the term, 'stress,' is used to address the sequel of major catastrophes in the lives of individuals. These include

natural or accidental events such as major earthquakes or life threatening accidents. Psychological stress, which focuses on patients' subjective evaluations of their capacity to cope with life circumstances (e.g. the stress induced by the social stigma of having a skin disorder or the unexpected death of a loved one) [17]. Physical trauma represents a more severe form of stress. Such events include war, torture, concentration camp experiences, severe accidents or illness, child abuse, rape, violence in the family, personal assault/physical abuse [17].

Biological factors, such as stress-induced activation of the hypothalamic-pituitary-adrenal axis [17] commonly found in depression, likely has an important role given that skin disorders are more prevalent in depressed individuals. Due to difficulties in insight and body-image, DA has been compared with anorexia nervosa as it often coexists with this condition [10]. DA patients tend to have introverted personalities, self-centered attitudes and emotional immaturity. Subsequently, adults may respond to stressful circumstances in an impulsive manner [11], due to an immature personality style [2]. These patients experience difficulty when stressed and their discomfort is further aggravated because of poor communication skills [7, 18]. A background of emotional disturbance has been noted to be present during formative years, leading to feelings of insecurity and isolation in later life. The onset of DA has been closely associated with the psychological stress of a major life event. The visible lesions represent an attempt at nonverbal communication which is similar to an appeal [7].

Patients with factitious disorder usually have an affinity with the medical system, and have maladaptive coping skills. This behavior often occurs in the setting of a loss such as the death of a relative or an occupational loss. Securing the attention of family, friends, medical professionals is likely a way of obtaining emotional solace. There is a motivation to assume the sick role, which initially evolves within the family and then with health care providers. Behavioral theories postulate that in early life these individuals received reinforcement of the sick role. Patients can have self-hate and guilt, and an illness which allows inappropriate regression and avoidance of adult responsibilities [9]. The psychological trauma of sexual abuse has been reported to precipitate DA [9, 10, 19]. Factitious illness can also symbolize anger and conflict with authority figures (school phobia being a case in point). They usually experience emotional deprivation during childhood, resulting in an unstable body image, and a need to be cared for [7]. Children and adolescents often develop anxiety and immaturity of coping styles in response to a dysfunctional parent-child relationship (e.g. rejecting mother, absent father), bullying, physical changes in the body and substance use [9]. The sensation of self-induced pain and physical lesions may relieve their isolation and distress, and even help them establish a sense of identity [1]. Chronically affected patients generally have comorbid personality disorders, especially borderline and hysterical in women and paranoid personality disorder in men [7, 9].

In an observational study of 30 inpatients (29 females and one male), with the mean age of 18, 30 % of cases had single parent families. Another 30 % of the patients had been physically or sexually abused during childhood. A large majority of the patients, a whopping 73 %, had a previous suicide attempt and 63 % had been

hospitalized previously. Each patient had had at least two sets of experience with self-infliction, with the various body parts targeted as in parentheses (forearms 90 %, thighs 26.7 %, legs 16.7 %, chest 10 %, belly 10 %, hands and face 6.9 %, arms 6.7 %, and feet 3.3 %). Substance use disorders, such as the ones in parentheses (tobacco 46.7 %, alcohol 23.3 %, illicit drugs 16.7 %), and eating disorders (with a 50 % incidence of affliction with restrictive anorexia nervosa) were also presented. Psychiatric diagnoses included depressive disorder in 36 % of the cases, followed with personality disorder at 20 %, psychosis at 10 % and depressive disorder associated with personality disorder in 33.3 % [10].

Psychogenic purpura, also known as Gardner-Diamond syndrome or autoerythrocyte sensitization syndrome, is a rare condition characterized by the spontaneous, unexplained, painful bruising mainly seen on the extremities and trunk but can occur anywhere on the body. Severe stress and emotional trauma usually precedes the skin lesions. Women are commonly affected, but isolated cases have been reported in adolescents and in males [20].

Patients with DA have generally been noted to have a low incidence of suicide [2]. However, this has been documented to predispose individuals, especially habitual self-mutilating females, to suicide [21]. DA was observed to provide temporary relief from symptoms such as racing thoughts, depersonalization, and marked anxiety. Association with an eating disorder and substance abuse was noted in this series as well [21]. DA has been associated with dissociative identity disorder [22, 23].

Treatment

Psychocutaneous disorders are optimally managed when the dermatologist and psychiatrist collaborate in the patient's management, although treatment can be very challenging. Referral to either psychiatry or a multi-specialty clinic would be appropriate [11, 13]. These patients are often very reluctant to accept a referral to psychiatry. The treatment of DA consists of the doctor-patient relationship, topical and systemic treatments. A supportive, trusting, nonjudgmental relationship is needed for any type of treatment to succeed. This can be established with empathy, expressed commitment [15] and careful review of any papers that the patient brings and documenting what has been done to date [11, 14]. The clinician should avoid confronting the patient regarding the behavior or how the lesions were physically produced, as this would likely be counter- productive. However, when discussing cutaneous lesions, it may be helpful to emphasize on stress or depression as possible mediators, and this could facilitate the discussion of possibly consulting with a psychiatrist [1].

A detailed assessment of the patient's history for chronic dermatoses, chronic medical conditions, psychiatric illnesses, and psychosocial problems is necessary. Hospitalization may be required for some patients, depending upon the severity of the skin lesions and risk of suicide. General dermatologic care measures include baths, debridement, emollients, and topical antimicrobials. The use of occlusive dressings can permit healing [11, 13]. Analgesics should be avoided because of the

high probability of dependence. Systemic treatment can be dermatologic and psychiatric. Oral antibiotics and anti-fungal agents are prescribed as needed based on culture and laboratory findings, as are antihistamines (for pruritus) and appropriate supplements (i.e., iron or B-12) [11]. Anxiety is common and can be addressed with one of the selective serotonin reuptake inhibitors (SSRIs), or with anxiolytics such as buspirone or benzodiazepines [1]. SSRIs are considered first-line therapy for depression, and are usually prescribed in higher doses for compulsive and self-injurious behaviors [1]. Recently, a 15-year-old girl with psychogenic purpura was treated with intensive supportive therapy in combination with escitalopram 10 mg to address her depression. Follow-up after 3 and 6 months showed complete resolution of symptoms and improvement in mood symptoms [20].

A tricyclic antidepressant (TCA) with antihistamine, antipruritic, and antidepressant properties (e.g. doxepin) is recommended for depression with or without agitation and with pruritus as the primary symptom. A TCA with analgesic properties (e.g. amitriptyline) is appropriate for depression with pain sensations (e.g. burning, or stinging) as the primary symptom [24]. Low dose typical (e.g. pimozide) and atypical antipsychotics (e.g. olanzapine [25], aripiprazole [8], risperidone, quetiapine) may be considered for short-term use, particularly if skin lesions are associated with psychotic or delusional symptoms.

Nonpharmacologic, complementary adjuvant therapies can be considered. These may include acupuncture, cognitive-behavioral therapy (e.g. aversion therapy, systemic desensitization, or operant conditioning), biofeedback, aromatherapy and hypnosis [26].

Course and Prognosis

This varies, and is most likely related to the nature of the underlying psychiatric disorder. In some instances, recovery occurs after the initial psychiatric treatment, whereas in other cases, the disorder may persist for decades [7]. In a follow up study of 43 patients over a period of 22 years [14], it was observed that 30% of these patients continued to produce lesions 12.4 years after onset of symptoms. However, except in childhood, where the condition may be a transient response to a current psychosocial stress, most observers report a poor prognosis for cure, suggesting that the condition appears to wax and wane with the circumstances of the patient's life [8, 11, 13, 14].

References

1. Wong JW, Nguyen Tien V, Koo JYM. Primary psychiatric conditions: dermatitis artefacta, trichotillomania and neurotic excoriations. Indian J Dermatol. 2013;58(1):44–8.
2. Gupta MA, Gupta AK, Haberman HF. The self-inflicted dermatoses: a critical review. Gen Hosp Psychiatry. 1987;9:45–52.

3. Griesemer RD, Nadelson T. Emotional aspects of cutaneous disease. In: Fitzpatrick TB, Eisen HZ, Wolff K, Freedberg IM, Austen KF, editors. Dermatology in general medicine. New York: McGraw-Hill; 1979. p. 1353–13632.
4. Koblenzer CS. Neurotic excoriations and dermatitis artefacta. Dermatol Clin. 1996;14:447–55.
5. Taylor S, Hyler SE. Update on factitious disorders. Int J Psychiatry Med. 1993;23:81–94.
6. Reynolds CF. Somatic symptom disorders. Diagnostic and statistical manual of mental disorders. In: American Psychiatric Association. fifthth ed. Arlington VA: American Psychiatric Publishing; 2013.
7. Fabisch W. Psychiatric aspects of dermatitis artefacta. Br J Dermatol. 1980;102(1):29–34.
8. Koblenzer CS, Gupta R. Neurotic excoriations and dermatitis artefacta. Semin Cutan Med Surg. 2013;32:95–100.
9. Millard LG, Millard J. Psychocutaneous disorders. In: Burns T, Creathnach S, Cox N, Griffiths C, editors. Rook's textbook of dermatology, vol. 3. 8th ed. Oxford: Wiley-Blackwell; 2010. p. 64.35.
10. Baguelin-Pinaud A, Seguy C, Thibaut F. Self-mutilating behaviour: a study on 30 inpatients. Encéphale. 2009;35(6):538–43.
11. Koblenzer CS. Dermatitis artefacta. Clinical features and approaches to treatment. Am J Clin Dermatol. 2000;1(1):47–55.
12. Meadow SR. Who's to blame–mothers, Munchausen or medicine? J R Coll Physicians Lond. 1994;28(4):332–7.
13. Gattu S, Rashid RM, Khachemoune A. Self-induced skin lesions: a review of dermatitis artefacta. Cutis. 2009;84(5):247–51.
14. Sneddon I, Sneddon J. Self-inflicted injury: a follow-up study of 43 patients. Br Med J. 1975;1:527–30.
15. Van Moffaert M. The spectrum of dermatological self-mutilation and self-destruction including dermatitis artefacta and neurotic excoriations. In: Koo JYM, Lee CS, editors. Psychocutaneous medicine. New York: Marcel Decker; 2003. p. 169–89.
16. Gupta MA, Gupta AK. Psychodermatology: an update. J Am Acad Dermatol. 1996;34:1030–46.
17. Gupta MA, Lanius RA, Van der Kolk BA. Psychologic trauma, posttraumatic stress disorder, and dermatology. Dermatol Clin. 2005;23(4):649–56.
18. Doran AR, Roy A, Wolkowitz OM. Self-destructive dermatoses. Psychiatr Clin North Am. 1985;8(2):291–8.
19. Gupta MA, Gupta AK. Dermatitis artefacta and sexual abuse. Int J Dermatol. 1993;32(11):825–6.
20. Jafferany M, Bhattacharya G. Psychogenic Purpura (Gardner-Diamond Syndrome). Prim Care Companion CNS Disord. 2015;17(1). doi:10.4088/PCC.14br01697.
21. Favazza AR, Conterio K. Female habitual self-mutilators. Acta Psychiatr Scand. 1989;79(3):283–9.
22. Saxe GN, Chawla N, Van der Kolk B. Self-destructive behavior in patients with dissociative disorders. Suicide Life Threat Behav. 2002;32(3):313–20.
23. Shelley WB. Dermatitis artefacta induced in a patient by one of her multiple personalities. Br J Dermatol. 1981;105(5):587–9.
24. Lee CS, Koo J. Psychopharmacologic therapies in dermatology: an update. Dermatol Clin. 2005;23(4):735–44.
25. Lowry CL, Bewley A, Taylor R. Facial ulcer treated with olanzapine. Clin Exp Dermatol. 2013;38(5):504–6.
26. Shenefelt PD. Complementary psychocutaneous therapies in dermatology. Dermatol Clin. 2005;23(4):723–34.

Chapter 10
Psychodermato-Oncology and Stress

Katlein França and Torello Lotti

Introduction

Skin cancer is the most common type of cancer around the world affecting specially fair-skinned populations. Skin cancers pose a threat to public health due an increasing incidence and mortality rates [1]. Risk factors of skin cancer include ultraviolet light exposure, age, genetic susceptibility, male gender, and constitutional factors, for instance hair color, number of moles, skin color, and skin reaction to sun exposures [2, 3]. Ultraviolet radiation is the most important cause of skin cancer. Excessive exposure and sunburns cause cumulative damage, which induces immunosuppression and skin cancers [1].

There are three types of skin cancer: basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and melanoma, originating from three major types of cells in the epidermis [3]. The most common types are basal cell carcinoma followed by the squamous cell carcinoma, which are nonmelanoma skin cancers. Basal cell carcinoma accounts for 75 % of cases of NMSC, and squamous cell carcinoma (SCC) accounts for the remaining majority of NMSC cases [4]. These types of cancer rarely invade other parts of the body. Melanoma is the less prevalent type and it can cause metastasis [5].

Stress can affect, reveal or even exacerbate a number of skin disorders. Stress suppresses immune function and increases susceptibility to infections and skin dis-

K. França, MD, PhD (✉)
Centro Studi per la Ricerca Multidisciplinare e Rigenerativa, Università Degli Studi "G. Marconi", Rome, Italy

Department of Dermatology and Cutaneous Surgery, Department of Psychiatry and Behavioral Sciences, Institute for Bioethics and Health Policy, University of Miami Miller School of Medicine, Miami, FL, USA
e-mail: k.franca@med.miami.edu

T. Lotti, MD
Centro Studi per la Ricerca Multidisciplinare e Rigenerativa, Università degli Studi Guglielmo Marconi, Rome, Italy

K. França, M. Jafferany (eds.), *Stress and Skin Disorders*,
DOI 10.1007/978-3-319-46352-0_10

eases [6]. In the other hand, skin disorders can cause emotional stress in different levels [7, 8]. Receiving the diagnosis of skin cancer can be a stressful event and patients may go through an array of emotional reactions including anxiety and depression. Patients may fear scars and disfigurement caused by the treatment. Patients undergoing to multiple surgeries and skin grafts to correct the defect caused by skin cancer are especially vulnerable to emotional stress and depression [9, 10].

Chronic Stress, Short Term Stress and Skin Cancer

Stress denotes a real or perceived perturbation to an organism's physiological homeostasis or psychological well-being [11]. The American Psychological Association states some stress can be beneficial at times, producing a boost that provides the drive and energy to help people get through situations like exams or work deadlines. However, they emphasize that an extreme amount of stress can have health consequences and adversely affect the cardiovascular, immune, neuroendocrine and central nervous systems [12]. So stress can lead to psychological and physical health issues.

Chronic stress is defined as stress that persists for several hours, days, weeks, months or years and it has been shown to have immunosuppressive effects that causes suppression of skin cell mediated immunity [13].

Ultraviolet radiation is considered a "complete carcinogen" due its mutagen and non-specific damaging agent properties. It is a tumor initiator and tumor promoter [14]. The ultraviolet B radiation causes DNA damage, epidermal hyperplasia, inflammation, and subsequent tumor development [15].

Saul et al. performed a study to test the hypothesis that chronic stress could accelerates the emergence and progression of UVB induced squamous cell carcinoma and as well that it could inhibit the regression of this type of cancer. The researchers examined the effects of chronic stress on the emergence, progression, and regression of squamous cell carcinoma induced by low level exposure to UVB radiation in a mouse model and they found that chronic stress suppresses Type 1 cytokines and protective T cells and increases regulatory/suppressor T cell numbers. These events increased susceptibility to UV-induced squamous cell carcinoma in this mouse model. They also explained that because squamous cell carcinoma and basal cell carcinoma are immunogenic non-melanoma skin cancers, these findings could also be applicable to basal cell carcinoma [13].

In contrast to chronic stress that suppresses immunological function, acute or short-term fight-or-flight stress response experienced during immune activation can enhance innate and adaptive immunity. Dhabhar and colleagues performed a study to evaluate effects of short-term stress on cellular immunity and resistance to squamous cell carcinoma. The authors compared a control group and a short-term stress group of mice's. They were treated identically except that the short-term stress group was restrained (2.5 h) before each of nine UV-exposure sessions during weeks 4–6 of the 10-week UV-exposure protocol. Tumors were measured weekly, and tissue collected at weeks 7, 20 and 32. Compared to controls, the short-term stress group showed that activation of short-term stress physiology increased chemokine

expression and T cell trafficking and/or function during/following UV exposure, and enhanced Type 1 cytokine-driven cell-mediated immunity that is crucial for resistance to SCC. This research suggests that short-term stress has adjuvant-like immuno-enhancing effects that may provide a novel mechanism for enhancing immune system mediated tumor-detection and elimination [16].

Higher levels of anxiety can also increase the progression of squamous cell carcinoma. Another study performed by Dhabhar and colleagues found that high-anxious, stress-prone behavioral phenotype resulted in a higher chronic stress burden, lower protective-immunity, and increased progression of this immuno-responsive type of skin cancer. These researchers found that the deleterious effects of high trait anxiety could be: exacerbated by life-stressors, accentuated by the stress of cancer diagnosis/treatment, and also mediate increased tumor progression and/or metastasis. The use of anxiolytic medications after the diagnosis and during the treatment could improve the disease outcome [17].

Stressful events during childhood may predispose an individual to developing basal cell carcinoma. Child emotional maltreatment can result in lasting immune dysregulation that may be heightened in the context of more recent life stress. Fagundes et al. investigated 91 patients with diagnosis of BCC and found that maternal and paternal emotional maltreatment during childhood interacted with the occurrence of severe life events and predicted the local immune response to the tumor. The authors also found that the immunoreactivity observed in BCCs and the surrounding stroma reflected an anti–tumor-specific immune response that can be altered by stress [18].

Oxidative Stress and Skin Cancer

Oxidative stress is defined as a disturbance in the balance between the production of reactive oxygen species (free radicals) and antioxidant defenses [19]. Normal cell function includes the free radical production that occurs in all cells of the body. Excess free radical production originating from exogenous or endogenous sources contributes to development of many diseases including skin cancers [20]. An increased amount of oxidants causes chronic inflammation, collagen fragmentation and disruption in skin cell functions causing skin cancer. Oxidative stress also participates of carcinogenesis process [21]. Sander and colleagues explains that melanoma cells presents increased oxidative stress. This could cause tissue damage and lead to metastasis. While in non-melanoma skin cancer, the reduction of the antioxidants defense caused by chronic UV exposure contributes to the complex and multistep carcinogenesis [22].

Antioxidants functions include lowering oxidative stress, DNA damage, and malignant transformation. They attenuate the damaging effects of ROS and impair and/or reverse many of the events that contribute to epidermal toxicity and disease and can lower the incidence of certain types of cancer such as skin cancers [23, 24]. Different types of oral or topical exogenous antioxidants have been studied as adjuvants to skin cancer prevention [25]. Some examples include β-carotene, vitamin C, vitamin E, caffeine, retinoids, green tea, glutathione and silymarin [24, 25].

Psychological Stress and Distress as Consequence of Skin Cancer

The emotional stress of receiving the diagnosis of skin cancer, the fear of recurrence and treatment implications can create new or worsen preexisting psychological stress [26].

Melanoma is the leading cause of death from skin diseases. França et al. explains that the possibility of recurrence, metastasis, and mortality levels related to this type of skin cancer is responsible for psychological distress [27]. Approximately 30 % of all patients diagnosed with this type of cancer report levels of psychological distress indicative of the need for clinical intervention. Risk factors for distress include younger age, female sex, lower education, visibility of affected body site, lack of social support, and negative appraisal of melanoma [28].

The emotional impact of melanoma can be profound and long lasting and severely impact patients and family members quality of life [29]. Baesley et al. performed a study with 386 patients and found that 32 % had anxiety and 15 % had depression. Forty-six percent of patients reported unmet needs. The three highest needs were for help with fears about cancer spreading (17 %), information about risk of recurrence (17 %) and outcomes when spread occurred (16 %). These authors emphasize the need to provide further melanoma specific information and better support with psychological concerns [30]. Erim et al. investigated anxiety, posttraumatic stress, and fear of cancer progression in a group of 70 patients with malignant melanoma who attended cancer aftercare. These patients were surveyed using the psychometric instruments Hospital Anxiety and Depression Scale (HADS), Posttraumatic Symptom Scale (PTSS-10), and Fear of Progression Questionnaire (FoP-Q). The researchers reported that the scores for the three anxiety parameters were low, but 7 % of the patients presented an increased HADS score, and 17 % an increased PTSS-10 value. These patients should receive the support indicated for their specific distress. Another finding in this study was that patients feared physical disabilities more than mental distress or lack of social support [31].

Dermatologists must be trained to identify patient's needs and to screen the one's that need further psychological support [32]. Patients who are younger, with lower educational levels, distressed and socially isolated are part of group risk for developing more psychological problems [33]. Anxiety and depression symptoms may persist many years after the treatment of melanoma. According to Beutel et al. patients may continue experiencing distress and reduced quality of life predicted by fear of recurrence, lack of social support, pessimism and self- blame [34].

There are fewer studies on the psychological impact of non-melanoma skin cancer. Non-melanoma skin cancers are less aggressive than melanoma and have a higher cure rate. Although these types of cancers rarely result in death, they may cause psychological stress due disfigurement and scarring. Patients may have a late diagnosis for not visiting doctors when the first signs of cancer appear. One of the most common causes of delay in patient's visiting doctors is the fear of the surgical treatment [35]. Increased delay is associated with increased tumor growth. Many patients also deny the presence of the tumor. According to Alam et al. patients with

skin cancer history, younger than 65 years, with major life problems, and with a history of any type of cancer are most likely to wait to seek medical treatment [36].

Hextall and colleagues performed a qualitative and quantitative study with 76 patients with non melanoma skin cancer. Body image, psychological morbidity and Quality of Life (QOL) were assessed. These researchers found that patients were anxious about the diagnosis of skin cancer, however they were no more depressed or anxious than the general population. The quality of life index improved with time, but the patient's knowledge of NMSC that was poor during diagnosis did not improved after the treatment. Most patients were aware of the importance of checking their skin regularly for suspicious lesions but were not sure what to look for [37].

It is important to screen and identify patients at risk for depression and anxiety. A psychodermatologist inserted in the cutaneous oncology team could better assist these patients and offer them appropriate psychological support during the diagnosis, treatment and post-treatment time.

Conclusion

Skin cancer is the most common of all cancers. Risk factors of skin cancer include ultraviolet light exposure, age, genetic susceptibility, male gender, and constitutional factors, for instance hair color, number of moles, skin color, and skin reaction to sun exposures. Stress plays different roles in skin cancer pathogenesis. Chronic stress has been shown to have immunosuppressive effects that cause suppression of skin cell mediated immunity leading to skin cancers. Oxidative stress is defined as a disturbance in the balance between the production of reactive oxygen species (free radicals) and antioxidant defenses. Oxidants in excess cause chronic inflammation, collagen fragmentation and disruption in skin cell functions causing skin cancer. Oral and topical antioxidants such as β-carotene, vitamin C, vitamin E, caffeine, retinoids, green tea, glutathione and silymarin have been studied as adjuvants to skin cancer prevention. Further studies are needed to elucidate their efficacy on skin cancer prevention. Receiving the diagnosis of any type of skin cancer can cause psychological stress. The emotional impact of melanoma can be profound and long lasting and severely impact patients and family members quality of life. The possibility of recurrence, metastasis, and mortality levels related to this type of skin cancer can cause distress, depression and anxiety. Although non melanoma skin cancers rarely result in death, these types of cancers may cause psychological stress due disfigurement, scarring and fear of developing new lesions. Sun protection is essential for skin cancer prevention. Patients may also feel guilty for not preventing their skin cancer. It is important to screen patients at risk for depression and anxiety. Dermatologists should give patients adequate information about the diagnosis, treatment options and prognosis and encourage shared decision-making. Dermato oncology patients may benefit from psychological or psychiatric counseling.

References

1. Saladi RN, Persaud AN. The causes of skin cancer: a comprehensive review. Drugs Today (Barc). 2005;41(1):37–53.
2. Naldi L, Altieri A, Imberti GL, Giordano L, Gallus S, et al. Cutaneous malignant melanoma in women. Phenotypic characteristics, Sun exposure, and hormonal factors: a case–control study from Italy. Ann Epidemiol. 2005;15:545–50.
3. Xie J, Qureshi AA, Li Y, Han J. ABO blood group and incidence of skin cancer. Chan A-W, ed. PLoS One. 2010;5(8):e11972. doi:10.1371/journal.pone.0011972.
4. Samarasinghe V, Madan V. Nonmelanoma skin cancer. J Cutan Aesthet Surg. 2012;5(1):3–10. doi:10.4103/0974-2077.94323.
5. National Cancer Institute: PDQ® Skin cancer treatment. Bethesda: National Cancer Institute. Date last modified 20 Nov 2015. Available at: http://www.cancer.gov/types/skin/patient/skin-treatment-pdq. Accessed 20 Nov 2015.
6. Dhabhar FS. Psychological stress and immunoprotection versus immunopathology in the skin. Clin Dermatol. 2013;31(1):18–30. doi:10.1016/j.clindermatol.2011.11.003.
7. Reich A, Wójcik-Maciejewicz A, Slominski AT. Stress and the skin. G Ital Dermatol Venereol. 2010;145(2):213–9.
8. França K, Chacon A, Ledon J, Savas J, Nouri K. Pyschodermatology: a trip through history. An Bras Dermatol. 2013;88(5):842–3. doi:10.1590/abd1806-4841.20132059.
9. Winterbottom A, Harcourt D. Patients' experience of the diagnosis and treatment of skin cancer. J Adv Nurs. 2004;48(3):226–33.
10. Me Marely. Skin cancer. Available at: http://www.healthcentral.com/skin-cancer/c/640929/116000/depression/#sthash.rU8UVqwi.dpuf. Accessed 11 Nov 2015.
11. National Research Council (US). Committee on recognition and alleviation of distress in laboratory animals. Recognition and alleviation of distress in laboratory animals. Washington (DC): National Academies Press (US); 2008. 2. Stress and Distress: Definitions. Available from: http://www.ncbi.nlm.nih.gov/books/NBK4027/.
12. No author listed. Understanding chronic stress. Available at: http://www.apa.org/helpcenter/understanding-chronic-stress.aspx. Accessed 11 Nov 2015.
13. Saul AN, Oberyszyn TM, Daugherty C, et al. Chronic stress and susceptibility to skin cancer. J Natl Cancer Inst. 2005;97(23):1760–7. doi:10.1093/jnci/dji401.
14. D'Orazio J, Jarrett S, Amaro-Ortiz A, Scott T. UV radiation and the skin. Int J Mol Sci. 2013;14(6):12222–48. doi:10.3390/ijms140612222.
15. Berton TR, Pavone A, Fischer SM. Ultraviolet-B irradiation alters the cell cycle machinery in murine epidermis in vivo. J Invest Dermatol. 2001;117(5):1171–8.
16. Dhabhar FS, Saul AN, Daugherty C, Holmes TH, Bouley DM, Oberyszyn TM. Short-term stress enhances cellular immunity and increases early resistance to squamous cell carcinoma. Brain Behav Immun. 2010;24(1):127–37. doi:10.1016/j.bbi.2009.09.004.
17. Dhabhar FS, Saul AN, Holmes TH, et al. High-anxious individuals show increased chronic stress burden, decreased protective immunity, and increased cancer progression in a mouse model of squamous cell carcinoma. Rameshwar P, ed. PLoS One. 2012;7(4):e33069. doi:10.1371/journal.pone.0033069.
18. Fagundes CP, Glaser R, Johnson SL, et al. Basal cell carcinoma: stressful life events and the tumor environment. Arch Gen Psychiatry. 2012;69(6):618–26. doi:10.1001/archgenpsychiatry.2011.1535.
19. Betteridge DJ. What is oxidative stress? Metabolism. 2000;49(2 Suppl 1):3–8.
20. Young I, Woodside J. Antioxidants in health and disease. J Clin Pathol. 2001;54(3):176–86. doi:10.1136/jcp.54.3.176.
21. Kruk J, Duchnik E. Oxidative stress and skin diseases: possible role of physical activity. Asian Pac J Cancer Prev. 2014;15(2):561–8.
22. Sander CS, Hamm F, Elsner P, Thiele JJ. Oxidative stress in malignant melanoma and non-melanoma skin cancer. Br J Dermatol. 2003;148(5):913–22.

23. Trouba KJ, Hamadeh HK, Amin RP, Germolec DR. Oxidative stress and its role in skin disease. Antioxid Redox Signal. 2002;4(4):665–73.
24. Godic A, Poljšak B, Adamic M, Dahmane R. The role of antioxidants in skin cancer prevention and treatment. Oxid Med Cell Longev. 2014;2014:860479. doi:10.1155/2014/860479.
25. França K, Cohen JL, Grunebaum L. Cosmeceuticals for recurrence prevention after prior skin cancer: an overview. J Drugs Dermatol. 2013;12(5):516–8.
26. Institute of Medicine (US). Committee on psychosocial services to cancer patients/families in a community setting: Adler NE, Page AEK, editors. Cancer care for the whole patient: meeting psychosocial health needs. Washington (DC): National Academies Press (US); 2008. 1, The psychosocial needs of cancer patients. Available from: http://www.ncbi.nlm.nih.gov/books/NBK4011/.
27. França K, Nouri K. Psychodermato-oncology: skin cancers in the elderly. NovaSci Publ. 2015;1:187–93.
28. Kasparian NA. Psychological stress and melanoma: are we meeting our patients' psychological needs? Clin Dermatol. 2013;31(1):41–6. doi:10.1016/j.clindermatol.2011.11.005.
29. Vurnek Zivković M, Buljan M, Blajić I, Situm M. Psychological status and illness perceptions in patients with melanoma. Coll Antropol. 2008;32 Suppl 2:75–8.
30. Beesley VL, et al. Supportive care needs, anxiety, depression and quality of life amongst newly diagnosed patients with localised invasive cutaneous melanoma in Queensland, Australia. Psychooncology. 2015;24(7):763–70. doi:10.1002/pon.3718. Epub 2014 Oct 29.
31. Erim Y, Loquai C, Schultheis U, Lindner M, Beckmann M, Schadendorf C, Senf W. Anxiety, posttraumatic stress, and fear of cancer progression in patients with melanoma in cancer aftercare. Onkologie. 2013;36:540–4.
32. Körner A, Fritzsche K. Psychosomatic services for melanoma patients in tertiary care. Int J Dermatol. 2012;51(9):1060–7. doi:10.1111/j.1365-4632.2011.05228.x.
33. Molassiotis A, Brunton L, Hodgetts J, Green AC, Beesley VL, Mulatero C, Newton-Bishop JA, Lorigan P. Prevalence and correlates of unmet supportive care needs in patients with resected invasive cutaneous melanoma. Ann Oncol. 2014;25(10):2052–8. doi:10.1093/annonc/mdu366. Epub 2014 Jul 31.
34. Beutel ME, Fischbeck S, Binder H, Blettner M, Brähler E, Emrich K, Friedrich-Mai P, Imruck BH, Weyer V, Zeissig SR. Depression, anxiety and quality of life in long-term survivors of malignant melanoma: a register-based cohort study. PLoS One. 2015;10(1):e0116440.
35. Antoszewski B, Kasielska A, Fijałkowska M. Face skin neoplasms--reasons for delayed treatment. Pol Przegl Chir. 2011;83(7):361–6. doi:10.2478/v10035-011-0057-x.
36. Alam M, Goldberg LH, Silapunt S, Gardner ES, Strom SS, Rademaker AW, Margolis DJ. Delayed treatment and continued growth of nonmelanoma skin cancer. J Am Acad Dermatol. 2011;64(5):839–48. doi:10.1016/j.jaad.2010.06.028. Epub 2010 Nov 5.
37. Bath-Hextall F, Jenkinson C, Kumar A, Leonardi-Bee J, Perkins W, Cox K, Glazebrook C. Longitudinal, mixed method study to look at the experiences and knowledge of non melanoma skin cancer from diagnosis to one year. BMC Dermatol. 2013;13:13. doi:10.1186/1471-5945-13-13.

Chapter 11
The Role of Stress in Body Dysmorphic Disorder

Sarah H. Hsu and Neelam A. Vashi

Body dysmorphic disorder (BDD), originally termed dysmorphophobia by Enrico Morselli in 1981, was derived from the Greek work dysmorphia, meaning ugliness, specifically of the face. While most would admit to having something they do not like about their appearance, those with BDD develop a persistent, intrusive preoccupation with an imagined or slight defect. They are compelled to perform repetitive and compulsive behaviors in response to concerns regarding their appearance. These compulsions can be behavioral, such as excessive mirror checking, or mental acts, such as comparing one's appearance with that of other people. Many times, they are consumed by these preoccupations and compulsions, to the extent that it interferes with their daily functioning. Ninety-nine percent of subjects with BDD report that their symptoms interfere moderately or severely with social functioning, and 80 % report that they interfere with their occupational or academic functioning [1]. Furthermore, approximately 30 % of patients with this disorder have been reported to be completely housebound for at least a week because of their symptoms [1, 2].

Despite reports of significant impairment in psychosocial functioning, there are a relatively small number of studies examining the impact of BDD on the quality of life. The first study evaluating quality of life in patients with BDD was published in 2000 [3]. In this report, those with BDD were found to have notably poorer mental

S.H. Hsu, MD
Boston University School of Medicine, Boston Medical Center,
609 Albany St, Boston, MA 02118, USA
e-mail: sarhahn@gmail.com

N.A. Vashi, MD (✉)
Boston University Center for Ethnic Skin, Cosmetic and Laser Medicine, Department of Dermatology, Boston University School of Medicine, Boston Medical Center,
609 Albany St, J602, Boston, MA 02118, USA
e-mail: nvashi@bu.edu

K. França, M. Jafferany (eds.), *Stress and Skin Disorders*,
DOI 10.1007/978-3-319-46352-0_11

health-related quality of life when compared to the general population, as well as when compared to those with depression, acute medical conditions (recent myocardial infarction), and chronic medical conditions (type II diabetes mellitus). The outcomes of this study were not explained by concomitant depressive symptoms in those with BDD.

These findings were confirmed in a subsequent, larger sample study, evaluating similar quality of life measures, in addition to psychosocial functioning [4]. Those with BDD had very poor scores across all functioning and mental health domains, including psychological distress, emotional well-being, work, school, role activities, leisure activities, household functioning, all components of social functioning (friends, extended family, parental, family unit, and primary relationship), and life satisfaction. A remarkably high proportion of subjects were unemployed (36 %), and 79 % considered BDD as their most problematic disorder. Likewise, another study demonstrated that those with BDD had lower income, less likelihood of living with a partner, and higher unemployment rate than the general population [5, 6].

On comparison to those with other body-image disorders such as anorexia nervosa (AN) and bulimia nervosa (BN), BDD was still found to have a more negative impact on quality of life, as measured using the body image quality of life inventory [6, 7]. Similarly, an evaluation of admitted adolescent inpatients at a psychiatric hospital demonstrated that one-third had a body image disorder, and these patients had significantly higher levels of depressive and anxiety symptoms compared to adolescents with other psychiatric disorders [8]. Not surprisingly, individuals with BDD have been shown to have high levels of perceived stress, with perceived stress scores 2.3 SD units higher (i.e. worse) than a large national probability sample [9].

The reported poor quality of life and high perceived stress have translated to devastating statistics. These patients have been found to have high rates of psychiatric hospitalization (48 %), suicidal ideation (45–82 %), and suicide attempts (22–24 %) [1, 10]. Another study also found that those with BDD have higher rates of suicidal ideation and suicide attempts when compared to the general population (31 % vs. 3.5 % and 22 % vs. 2 %, respectively) [7].

Association Between Early Stress and the Development of BDD

Despite the strong association between BDD and impaired psychosocial functioning, greater perceived stress, and reduced quality of life, a question arises as to whether these individuals also have greater underlying stressors or traumatic experiences that may contribute to the development of BDD.

A semi-structured interview was conducted on 18 patients with BDD and 18 normal controls, between the ages 17 and 49 years [11]. It was found that those with

BDD tended to have significantly more spontaneously occurring images that were negative, recurrent, and viewed from the observer perspective than the normal participants. That is, they were more likely to report distressing images related to being bullied or teased because of their appearance. This suggests that negative self-images may have developed early on in these individuals, thereby contributing to the development of BDD symptoms.

Beyond childhood events related specifically to appearance, early traumatic or stressful experiences in general, have been also shown to serve as risk factors in the development of BDD. The majority of those with BDD reported a history of childhood mistreatment (79 %), which included emotional neglect (68 %), emotional abuse (56 %), physical abuse (35 %), physical neglect (33 %), and sexual abuse (28 %) [12]. Further, all patients suggested that their traumatic experience preceded their BDD symptoms.

Another study also showed that on comparison with normal controls, individuals with BDD were more likely to experience traumatic events in childhood or adolescence. They reported significantly more physical and sexual abuse and a trend towards a higher rate of emotional abuse compared to controls [13]. A possible explanation for the association between early-life traumatic experiences and the development of BDD may be extrapolated from the experiences of survivors of sexual abuse. Survivors of sexual abuse have been shown to have a distorted view of their body, especially the body part that they associate with the abuse and often develop general dissatisfaction, shame, and hatred towards that body part [13–15]. As such, it can be hypothesized that early-life traumatic experiences may shape a person's negative core belief, instilling feelings of inferiority and deficiency, and thereby contributing to a negative perception of their appearance. This may in part explain the high rate of suicide attempts among those with BDD. In addition to the distress of the BDD symptoms themselves, it is recognized that individuals with a traumatic history are also more likely to have attempted suicide [12].

Among the various environmental influences, the family arguably has the most profound impact on a child's development. One review specifically examined the family environment in pediatric populations with obsessive-compulsive and related disorders [16]. Disorders considered to be in the obsessive-compulsive spectrum include BDD, trichotillomania (hair pulling disorder), skin picking disorder, and hoarding. A strong relationship was demonstrated between obsessive-compulsive disorders (OCD) and poor parental mental health, with greater symptoms of anxiety, stress, and depression in parents of those with OCD. In addition, parenting styles tended to induce conflicting control beliefs in children (i.e. perceived low levels of control over one's life coupled with a desire for increased control). Further, there was a correlation between OCD and family dynamics (low family cohesion, family violence, and distress), familial emotional climate (higher levels of parental guilt, worry, and anger), and low levels of parental warmth. Again, these findings suggest that early-life experiences, especially within the family unit, are extremely important in a child's cognitive and behavioral development. Further, negative or

stress-inducing environments seem to increase the likelihood of developing obsessive-compulsive and related disorders.

Interestingly, a study comparing patients with BDD and OCD specifically reported an even higher rate of reported abuse in BDD, with 38 % of those with BDD reporting a history of childhood abuse relative to 14 % of individuals with OCD [17]. Further, those with BDD reported experiencing significantly greater emotional and sexual abuse than those with OCD (28 % vs. 2 % and 22 % vs. 6 %, respectively). Still, for either disorder, the rates of abuse were substantially higher than national averages.

Body dysmorphic disorder is a complex disease with multifactorial etiology. The exact sequence of events, including what risk factors are crucial in the development of BDD, is still unknown. However, each study discussed here highlights the correlation between early-life stressors and traumatic events in the development of BDD. While it may not be possible to make the definitive conclusion that traumatic experiences lead to the development of BDD, understanding this association offers a place for potential targets in considering treatment options for this challenging disorder.

Stress/Anxiety Reduction and Mindfulness in the Treatment of BDD

The first-line treatment modalities for BDD include psychotropic medications, specifically selective serotonin reuptake inhibitors, and cognitive behavioral therapy (CBT). However, this section will focus on the role of anxiety management and mindfulness in the treatment of BDD, in the context of dealing with the distress that accompanies this disorder.

It has been shown that there is a significant correlation between anxiety disorders, especially social anxiety disorder (SAD) and BDD. Twelve percent of those with SAD meet criteria for BDD, and 12–69 % of those with BDD meet criteria for SAD [18, 19]. Further, among all individuals with co-morbid SAD and BDD, onset of SAD preceded that of BDD [18, 20]. With the understanding that SAD may be a risk factor for the development of BDD, it was investigated whether psychological treatment for SAD in those with a primary diagnosis of SAD would improve BDD symptoms. In a series of two studies, it was found that both CBT and an attention retraining intervention for SAD resulted in reduction in body dysmorphic concerns [18].

Another study examined CBT that is targeted at BDD as compared to anxiety management. Anxiety management consisted of practicing progressive muscle relaxation and breathing exercises daily, identifying triggers associated with appearance related-anxiety, and utilizing brief muscle relaxation and breathing techniques during trigger situations [21]. As for the CBT, it consisted of several components, including engagement in a developmental understanding of the problem and setting up an alternative view, as well as the use of imagery rescripting for past aversive memories that were associated with the onset of BDD symptoms. Both CBT and anxiety management were found to reduce BDD symptoms, but CBT was found to be more effective. The proportion of responders (defined as a decrease of 30 % or

more on the Yale-Brown Obsessive Compulsive Scale for BDD) was 52 % after 16 sessions of CBT, which was similar to that in a randomized controlled trial of fluoxetine versus placebo in BDD [22].

Beyond CBT, a newer form of cognitive treatment has been proposed, aimed at targeting maladaptive thoughts, called acceptance and commitment therapy (ACT) [23]. ACT is organized around the concept of psychological flexibility. Psychological flexibility is characterized by six behavioral components, which include present-moment focus, cognitive diffusion, experiential avoidance, transcendent self-awareness, valued living, and committed action. In particular, cognitive diffusion (i.e. techniques to distance oneself between thoughts and reality as well as the realization that thoughts are only thoughts), acceptance (i.e. learning to avoid experiential avoidance), and mindfulness (i.e. learning to be in the present moment) have been proposed to be processes that may be particularly helpful in dealing with intrusive appearance-related thoughts [23].

A study compared the short-term effectiveness of an acceptance/mindfulness (AC) and a cognitive restructuring (CR) strategy for targeting negative appearance-related thoughts among individuals with BDD and AN [23]. This was further compared to a distraction strategy. It was found that all strategies led to decreased frequency of negative thoughts, as well as a reduction in the associated discomfort and distress related to the disorders. Further, the AC strategy seemed to provide an additional benefit in those with BDD by augmenting positive affect, as measured by a 20-item scale in which patients were asked to rate their feelings at the present moment.

Conclusion

In sum, there is undeniably a strong association between BDD and impaired psychosocial functioning, greater perceived stress, and reduced quality of life. While it can be interpreted that the BDD symptoms themselves are causing great distress in these individuals, many of these patients also report early life memories that are stress and anxiety provoking, such as experiences of abuse and neglect. It is plausible that these early experiences further contribute to the development of BDD. Therapies that are targeted at managing the negative thoughts and distress that accompany this disorder have been proposed, including methods to reduce anxiety, cognitively restructure, and promote mindfulness. These strategies have all proven to be somewhat effective in alleviating symptoms, although BDD continues to be a therapeutically challenging disorder.

References

1. Phillips KA, Diaz SF. Gender differences in body dysmorphic disorder. J Nerv Ment Dis. 1997;185:570–7.
2. Phillips KA, Menard W, Fay C, Weisberg R. Demographic characteristics, phenomenology, comorbidity, and family history in 200 individuals with body dysmorphic disorder. Psychosomatics. 2005;46:317–25.

3. Phillips KA. Quality of life for patients with body dysmorphic disorder. J Nerv Ment Dis. 2000;188:170–5.
4. Phillips KA, Menard W, Fay C, Pagano ME. Psychosocial functioning and quality of life in body dysmorphic disorder. Compr Psychiatry. 2005;46:254–60.
5. Buhlmann U, Glaesmer H, Mewes R, Fama JM, Wilhelm S, Brähler E, Rief W. Updates on the prevalence of body dysmorphic disorder: a population-based survey. Psychiatry Res. 2010;178:171–5.
6. IsHak WW, Bolton MA, Bensoussan JC, Dous GV, Nguyen TT, Powell-Hicks AL, Gardner JE, Ponton KM. Quality of life in body dysmorphic disorder. CNS Spectr. 2012;17:167–75.
7. Hrabosky JI, Cash TF, Veale D, Neziroglu F, Soll EA, Garner DM, Strachan-Kinser M, Bakke B, Clauss LJ, Phillips KA. Multidimensional body image comparisons among patients with eating disorders, body dysmorphic disorder, and clinical controls: a multisite study. Body Image. 2009;6:155–63.
8. Dyl J, Kittler J, Phillips KA, Hunt JI. Body dysmorphic disorder and other clinically significant body image concerns in adolescent psychiatric inpatients: prevalence and clinical characteristics. Child Psychiatry Hum Dev. 2006;36:369–82.
9. DeMarco LM, Li LC, Phillips KA, et al. Perceived stress in body dysmorphic disorder. J Nerv Ment Dis. 1998;186:724–6.
10. Veale D, Boocock A, Gournay K, Dryden W, Shah F, Willson R, Walburn J. Body dysmorphic disorder: a survey of fifty cases. Br J Psychiatry. 1996;169:196–201.
11. Osman S, Cooper M, Hackmann A, Veale D. Spontaneously occurring images and early memories in people with body dysmorphic disorder. Memory. 2004;12:428–36.
12. Didie ER, Tortolani CC, Pope CG, Menard W, Fay C, Phillips KA. Childhood abuse and neglect in body dysmorphic disorder. Child Abuse Negl. 2006;30:1105–15.
13. Buhlmann U, Marques LM, Wilhelm S. Traumatic experiences in individuals with body dysmorphic disorder. J Nerv Ment Dis. 2012;200:95–8.
14. Kremer I, Orbach I, Rosenbloom T. Body image among victims of sexual and physical abuse. Violence Vict. 2013;28:259–73.
15. Kearney-Cooke A, Ackard DM. The effects of sexual abuse on body image, self-image, and sexual activity of women. J Gend Specif Med. 2000;3:54–60.
16. Murphy YE, Flessner CA. Family functioning in paediatric obsessive compulsive and related disorders. Br J Clin Psychol. 2015;54:414–34.
17. Neziroglu F, Khemlani-Patel S, Veale D. Social learning theory and cognitive behavioral models of body dysmorphic disorder. Body Image. 2008;5:28–38.
18. Fang A, Sawyer AT, Aderka IM, Hofmann SG. Psychological treatment of social anxiety disorder improves body dysmorphic concerns. J Anxiety Disord. 2013;27(7):684–91.
19. Fang A, Hofmann SG. Relationship between social anxiety disorder and body dysmorphic disorder. Clin Psychol Rev. 2010;30:1040–8.
20. Wilhelm S, Otto MW, Zucker BG, Pollack MH. Prevalence of body dysmorphic disorder in patients with anxiety disorders. J Anxiety Disord. 1997;11:499–502.
21. Veale D, Anson M, Miles S, Pieta M, Costa A, Ellison N. Efficacy of cognitive behaviour therapy versus anxiety management for body dysmorphic disorder: a randomised controlled trial. Psychother Psychosom. 2014;83:341–53.
22. Phillips KA, Albertini RS, Rasmussen SA. A randomized placebo-controlled trial of fluoxetine in body dysmorphic disorder. Arch Gen Psychiatry. 2002;59:381–8.
23. Hartmann AS, Thomas JJ, Greenberg JL, Rosenfield EH, Wilhelm S. Accept, distract, or reframe? an exploratory experimental comparison of strategies for coping with intrusive body image thoughts in anorexia nervosa and body dysmorphic disorder. Psychiatry Res. 2015;225(3):643–50.

Chapter 12
Stress and Atopic Dermatitis

Christopher Bridgett and Peter Norén

Introduction

Despite the established acceptance that stress and the common dermatoses have important reciprocal relationships (Fig. 12.1) [1], atopic dermatitis [AD] remains largely managed without significant reference to psychosocial factors. Although AD was seen as one of the main psychosomatic diseases in the mid-twentieth-century, the original accounts in the psychodermatological literature [2] were based on Freudian psychoanalytic theory, and seemed "uncritical and uncontrolled" to many contemporary dermatologists [3]. This early negative reaction to psychodermatology may partly explain why since then more scientific discoveries in the psychobiological [4] and behavioural aspects of AD [5] have yet to be routinely incorporated into mainstream AD treatment. Refractory AD in particular is now treated increasingly with systemic treatments that can lead to serious adverse events. This is regrettable, as there are now simple psychodermatological approaches to AD that are both cost-effective and do not require specialist expertise to understand and use [6]. This chapter gives an account of one such practical approach, with an emphasis on the role played by stress. It is important however to emphasise that the successful treatment programme for chronic eczema described here is not *primarily* aimed at being a stress-relieving programme, although nearly always relief from the stress of living with chronic eczema is one of its commonly important reported outcomes.

C. Bridgett, MD (✉)
Chelsea and Westminster Hospital, Imperial College London, London, UK
e-mail: ckbridgett@doctors.org.uk

P. Norén, MD
Department of Dermatology, Uppsala University, Uppsala, Sweden

K. França, M. Jafferany (eds.), *Stress and Skin Disorders*,
DOI 10.1007/978-3-319-46352-0_12

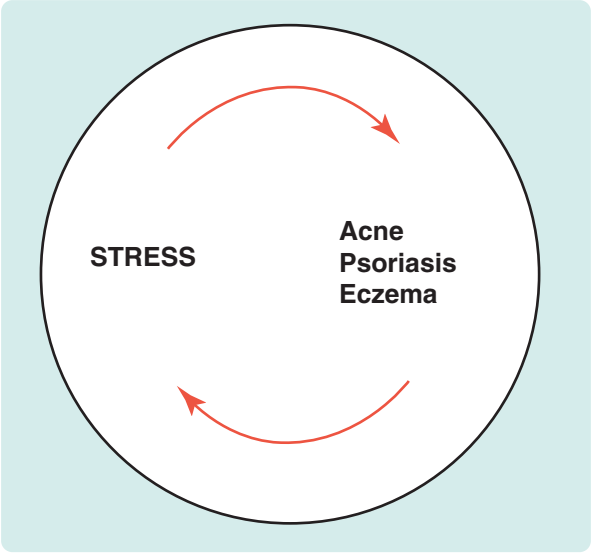


Fig. 12.1 The relationship between stress and three common skin conditions

The Combined Approach to Atopic Dermatitis [7, 8]

Background

The nervous origins of some aspects of AD were indicated by the French Dermatologists Brocq and Jacquet [9] when in 1891 they coined the term *neurodermite* for what would now be seen to be the lichenification of the skin characteristic of chronic AD. Such chronic eczema is found in areas that are easy to scratch and rub, for example the face, neck and hands. In the 1950s it was shown by using a scratching machine on normal skin that scratching alone can produce the histological findings seen in chronic AD [10]. In the 1980s a behaviour modification technique called *habit reversal* was combined with standard topical treatment for AD and a strong correlation found between reduction in scratching and improvement in skin status [11]. This research has led to the development of The Combined Approach, a treatment programme for routine clinical use. The management of stress is one of the important parts of this programme.

A Treatment Programme for Adults and Older Children[1]

The practitioner's manual [7] sets out protocols for several clinic visits over 5–7 weeks, with the initial visit devoted to assessment, and subsequent visits for the introduction of treatment, then troubleshooting and finally the planning of follow-up (Fig. 12.2). Keeping to this structure of a treatment programme is important. Each stage is supported by reference to a patient handbook and a website [8] devoted to the programme. As an exercise in behavioural dermatology The Combined Approach thus has a strong educational element, with an emphasis on the patient's perspective, and what takes place away from the clinic, between appointments. There is a recognition in the approach of an important need to empower the patient, and others too, with an active optimism. This new attitude should replace what is otherwise often seen: a somewhat passive pessimism associated with both having, and treating, chronic AD. With The Combined Approach patients can be shown how to control their dermatitis, rather than continuing to allow it to control them.

At the first visit assessment can usefully include a review of quality of life effects from chronic AD, and the role that stress is seen to play in causing eczema to flare up. High scores on quality of life effects can be an indication of the level of stress caused by AD [12], while reported association between acute flare-ups and stressful life factors indicate how stress is implicated as a causative influence. For many the treatment programme improves the skin status dramatically within 2 weeks of starting treatment. With this any reported stress associated with having AD is immediately relieved. One of the first knock-on effects is improved sleep, for the patient and for anyone who sleeps with them. Specific stress management techniques are not usually therefore considered until the third clinic visit – *see below*. Assessment

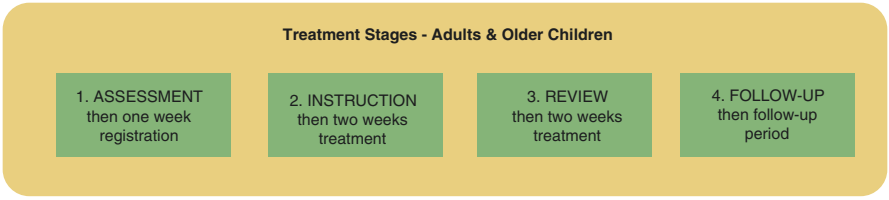


Fig. 12.2 The combined approach treatment stages

[1] The practitioner's manual [7] provides an adapted programme of younger children and their parents.

is completed by the patient being given a hand tally counter to be used over a week before the second appointment, to record the baseline frequency of scratching. This enables increased awareness of how the *normal* scratching response to an itch has become an *abnormal* automatic, unconscious and habitual self- damaging behaviour, linked not only to itch, but also triggered by a range of circumstances and emotional states, including stress. The tally counter remains involved throughout the programme to measure progress with habit reversal. Subsequently the counter is often identified as the most useful part of the programme. It represents the stress-relieving and welcome sense of relief that comes with learning how to achieve control over what has previously been counter-productive, habitual skin damaging behaviour.

The second visit completes assessment and introduces the treatment programme. The patient's record of scratching frequency and associated circumstances is reviewed and the discussion is usefully expanded to note *methods* of scratching employed. All methods of mechanically stimulating the skin are regarded as potentially damaging, including rubbing and massaging. Any use of implements or aids to scratching need to be identified and understood to be now undesirable.

The Combined Approach adds optimised conventional topical treatment to habit reversal training: there are therefore three levels of treatment, one for each of the three levels of the vicious circle that is operating with chronic AD (Fig. 12.3). It is relevant to note here that each level of this circle – dry skin [13], eczema and itch [4], and scratching [14] – may be exacerbated by psychological stress. Often it emerges at this stage that the principles of conventional treatment are poorly understood and the use of recommended topical treatment has been haphazard and inefficient [15]. With The Combined Approach, maximising the effectiveness of emollients and topical steroids is important, and this is both discussed in detail, and supported by the content of the patient handbook and by reference to the programme

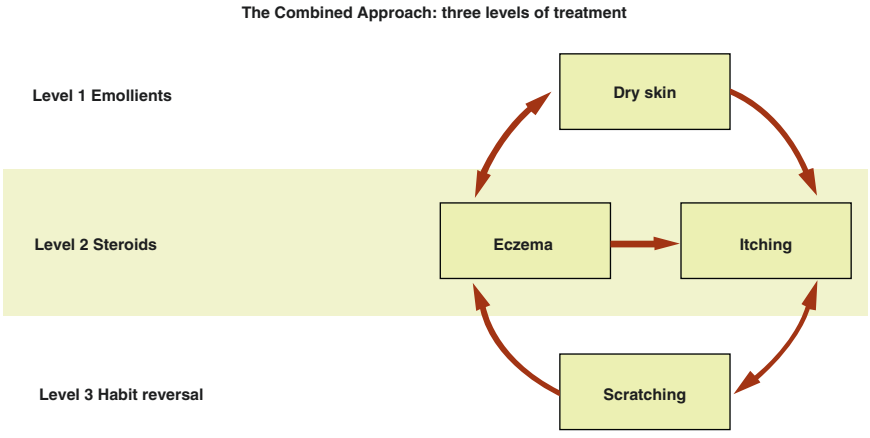


Fig. 12.3 The combined approach: three levels of treatment

website (www.atopicskindisease.com). Instruction in habit reversal follows review of the experience of recording scratching and rubbing behaviour over the first week of the programme. The frequency is often more than initially expected by the patient, and the link not only to itch but also to circumstances, activities and stress, is confirmed by the use of the hand tally counter.

The behaviour modification tactics involved in habit reversal for habitual scratching are easy to understand and explain, with an emphasis on what needs to be done, rather than what should be avoided. The specific instruction is to replace all scratching with fist clenching for 30 seconds, followed by light pinching or finger pressure on any itchy skin until itch has gone (Fig. 12.4). In our experience it is very important to suggest that this specific tactic is practised a few times each day for the first few days, whether or not there is any stimulus to scratch. This "dress rehearsal", together with taking any opportunity to explain the habit reversal to others, serves to firmly establish the response as an important new behaviour. In addition, more general instructions for coping from now on with identified difficult circumstances are then added, with an emphasis on planning ahead, doing things quickly and keeping hands safely occupied. It is important to emphasise that habit reversal is only required for a short period – 4–6 weeks, with most effort concentrated on the first 2 weeks – to allow chronic AD to heal. Habit reversal is then no longer part of the treatment programme.

At the third visit two or 3 weeks have passed using the full treatment programme, and review usually reveals that scratching frequency is reduced to as much as 10 % of the baseline frequency, with already a marked improvement in the skin condition, and an associated improvement in quality of life. It is useful now to review each level of treatment to ensure all is fully understood and being followed, especially the need to continue applying topical steroid beyond the time that healing seems complete if early relapse is to be avoided. Topical steroid treatment of chronic eczema seems often under-treated [15]: with The Combined Approach, several weeks of topical steroid treatment are often required for optimal results. From now

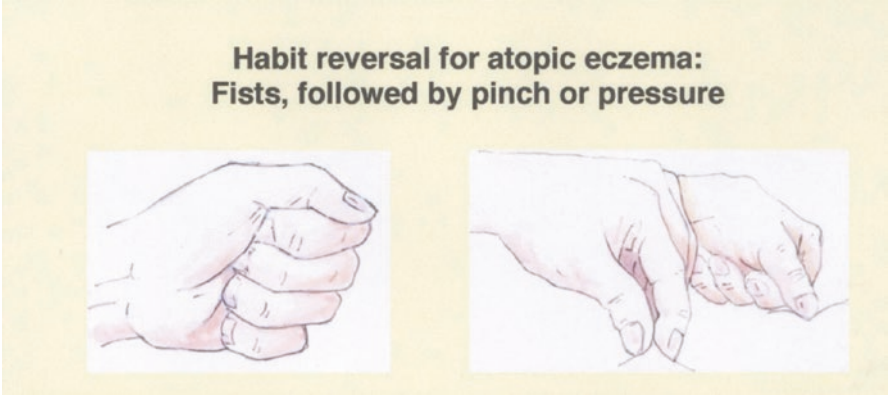


Fig. 12.4 Habit reversal for atopic eczema

on the use of habit reversal can focus especially on those times when scratching is especially likely – often this includes first thing in the morning, and last thing at night – with an emphasis on the patient anticipating when habit reversal tactics are especially needed. Hence, a personal plan or *behavioural prescription* is established for the next 2 weeks. If at the third visit things have not gone according to plan, the influence of stress may sometimes require specific attention. Introducing an additional stress management technique (see Chap. 22) may be warranted, if stress due to factors other than related to having AD is evidently significant. The sources of stress for an individual may be temporary, and timing the treatment programme to avoid such stress, thus allowing concentration on the treatment programme, is a simple effective strategy to consider. Otherwise now, the programme continues for another 2–3 weeks.

The fourth visit is timed to coincide with the clearing of chronic eczema through the influence of all three levels of treatment over 4–6 weeks of the programme. From now on treatment continues with the correct use of emollients and topical steroids alone: habit reversal is no longer required. Instruction is given to improve understanding, recognition and treatment of acute flare-ups, with an emphasis on managing triggers such as stress, using emollients to prevent skin drying and using topical steroids at the correct strength now intermittently for a few days at a time as needed. With this regime follow-up over 12 months usually shows subsequent successive flare-ups become increasingly less troublesome (Fig. 12.5). The improvement in morale associated with success using The Combined Approach evidently enables patient resilience and ability to cope generally with other sources of stress: being prone to having only acute episodes of AD is now seen to be very manageable indeed.

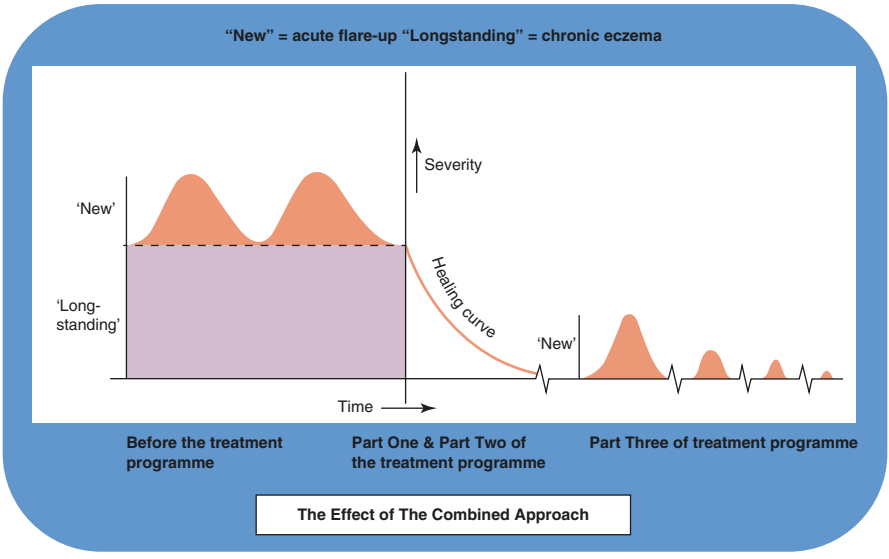


Fig. 12.5 The effect of the combined approach

Conclusion

Clinical experience of using The Combined Approach in the treatment of AD amply confirms that not only is stress an important causative factor in atopic eczema, it is also a very significant consequence of inadequately treated AD. Living with chronic atopic eczema is demoralising, dispiriting, and costly [16]. There is now a simple and cost-effective possibility of successfully managing chronic AD – without resorting to the use of systemic therapy – that is associated with marked improvement in the quality of life of both patients and their families.

References

1. Panconesi E. Stress and skin diseases: psychosomatic. Clin Dermatol. 1984;2(4):89–179.
2. Obermeyer M. Psychocutaneous medicine. Springfield: Thomas; 1955.
3. Rook A. Foreword pp v–vi. In: Whitlock FA, editor. Psychophysiological aspects of skin disease. London: Saunders; 1976.
4. Suarez AL, et al. Psychoneuroimmunology of psychological stress and atopic dermatitis: pathophysiologic and therapeutic updates. Acta Derm Venereol. 2012;92:7–15.
5. Norén P. Habit reversal; a turning point in the treatment of atopic dermatitis. Clin Exper Derm. 1995;20(1):2–5.
6. Daunton A, et al. Habit reversal for refractory atopic dermatitis; a review. Br J Dermatol. 2016;174:657–9. doi:10.1111/bjd.141762015.
7. Bridgett C, et al. Atopic skin disease: a manual for practitioners. Petersfield: Wrightson; 1996.
8. http://www.atopicskindisease.com.
9. Brocq L, Jacquet L. Note pour servir à l'histoire des neurodermites. Ann Dermatol Syphiligr. 1891;2:634.
10. Goldblum RW, Piper WN. Artificial lichenification produced by scratching machine. J Invest Dermatol. 1954;22:405–15.
11. Norén P, Melin L. The effect of combined topical steroids and habit reversal in patients with atopic dermatitis. Br J Dermatol. 1989;115:359–66.
12. Wittkowski A, et al. The impact of psychological and clinical factors on quality of life in individuals with atopic dermatitis. J Psychosom Res. 2004;57(2):195–200.
13. Orion E, Wolf R. Psychological stress and epidermal barrier function. Clinics in Dermatol. 2011;30(3):280–5.
14. Musaph H. Psychodermatology Psychother Psychosom. 1974;24:79–85.
15. Williams H. Perspective: acting on the evidence. Nature. 2011;479:S16. doi:10.1038/479S16a.
16. Carroll CL, et al. The burden of atopic dermatitis: impact on the patient, family and society. Pediatr Dermatol. 2005;22(3):192–9.

Chapter 13
Vitiligo

Ladan Mostaghimi

Introduction

Vitiligo is an acquired loss of pigmentation of skin. It affects 0.5–1 % of population [1, 2]. It causes white depigmented macules and patches on the skin due to loss of melanin and melanocytes in the epidermis.

Even though Vitiligo does not cause any physical symptoms such as pain or itching, it is a highly stigmatizing disease. A quick review of most medical literature and online sources describe Vitiligo as a disfiguring disease. The term disfiguring is a negative term that affects the psyche of people suffering from diseases known as disfiguring. Vitiligo could cause major psychological problems especially in individuals with darker skin where the contrast between diseased and normal skin is more visible.

Age of onset varies and peaks in second and third decades of life; there is no age, sex, or racial preference [3, 4].

Pathogenesis

Vitiligo is a multifactorial disease. The genetic predisposition as well as environmental triggers, altered immune response and metabolic abnormalities have all been implicated. About 20–30 % of patients have a family history of the disease.

There is an autoimmune process derived against melanocytes. Some authors postulate that in addition to autoimmune processes, intrinsic melanocytes abnormalities

L. Mostaghimi, MD
University of Wisconsin, Department of Dermatology, Madison, USA
e-mail: lmostaghimi@dermatology.wisc.edu

K. França, M. Jafferany (eds.), *Stress and Skin Disorders*,
DOI 10.1007/978-3-319-46352-0_13

causes them to send distress signals to the immune system and recruit cytotoxic reaction towards them [2].

Cellular and humoral immunity as well as different cytokines play a role in pathogenesis. The latest in pathogenesis is nicely described in Up to Date article in Ref. [1]. A brief summary includes:

Abnormalities in interleukin (IL)-6, interferon (IFN)-gamma, and tumor necrosis factor (TNF)-alpha levels as well as expression of granulocyte-monocyte colony stimulating factor (GM-CSF), stem cell factor (SCF), and basic fibroblastic growth factor (bFGF) in Vitiligo skin, and decreased serum level of transforming growth factor (TGF)-beta have all been reported in Vitiligo. All these play a role in function of pigmented cells and regulation of autoimmune response [1].

IL-6 is an inhibitor of melanocytic proliferation, IFN-gamma initiates apoptosis, TNF-alpha both inhibits melanocytes proliferation and initiates apoptosis [1].

GM-CSF, SCF, and bFGF stimulate melanocytes and their expression is decreased in skin with Vitiligo [1].

There is an increased risk of other autoimmune diseases (thyroid disease, pernicious anemia, Addison disease, and systemic lupus erythematosus) in patients with Vitiligo. Vitiligo is also a part of the polyglandular autoimmune syndrome type II that includes Graves' disease, Diabetes Mellitus type I, primary adrenal insufficiency, hypopituitarism, and other problems [1].

Other possible factors implicated in pathogenesis of Vitiligo include: intrinsic abnormality of melanocytes, local catecholamine release increase, problems with defense against toxic free radicals and cytomegalovirus [1].

Stress precipitates Vitiligo in some patients [5, 6]. Environmental factors and certain industrial chemicals exposure could also cause Vitiligo [7].

Stress System

Stress modulates immune system through following systems:

Acute stress increases IFN-gamma and enhances immune system,
Chronic stress causes immune suppression through glucocorticoids and HPA (Hypothalamic-Pituitary-Adrenal) axis.
Blunted response and altered HPA axis function in some people causes autoimmune susceptibility.

Physical or psychological stresses affect the brain and cause secretion of corticotropin-releasing hormone (CRH) by Hypothalamus paraventricular nucleus (PVN). CRH signals anterior lobe of the pituitary gland and stimulates secretion of Proopiomelanocortin (POMC)-derived peptides that include: adrenocorticotropic hormone (ACTH), melanocyte-stimulating hormone (MSH), and beta-endorphin. ACTH stimulates secretion of cortisol and Epinephrine from adrenal glands and they affect macrophages causing them to release interleukin (IL)-1, IL-6, and TNF-alpha. These cytokines signal the brain and cause sick behavior and somnolence.

There is a negative feedback loop with increased blood cortisol causing suppression of HPA axis activity.

Stress also activates Locus Ceruleus (LC), a nucleus in the Pons (part of the brainstem), which increases synthesis of norepinephrine and causes sympathetic nervous system activity.

At the level of dermal nerve endings stress causes release of neuropeptides and neurotrophins such as substance P, Vasoactive Intestinal Peptide (VIP), etc. These affect different functions of skin such as activating immune response and mast cell degranulation.

Human skin has its own local stress response system as well. CRH and POMC peptides are produced by skin and regulated by inflammatory and autocrine mechanisms (Fig. 13.1).

Stress response coupled with genetic susceptibility and environmental factors cause different diseases in susceptible individuals, hence reported association of stress with some skin disorders such as Vitiligo, Psoriasis, Atopic Dermatitis, etc.

Psychological stress could be a potential trigger in Vitiligo patients, so patients should be screened for stressors [8].

Trapp et al. study showed a higher vegetative arousal in Vitiligo patients comparing to age and gender matched healthy control group [9].

Clinical Features

Age of onset varies and peaks in second and third decades, there is no age, sex, or racial preference in Vitiligo [3, 4].

Vitiligo has different clinical subtypes including:

Generalized Vitiligo (*Vitiligo vulgaris*) is the most common form. It has widespread depigmented macules and patches usually symmetrically placed in acral areas/extensor surfaces and around body orifices.

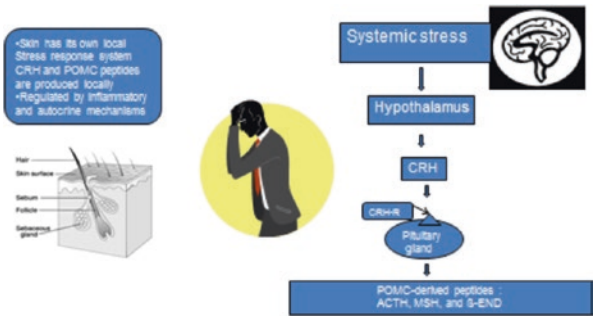


Fig. 13.1 Central nervous system and local skin stress response

Acrofacial Vitiligo is when the lesions are limited to acral and periorificial areas of the body.
The *Koebner phenomenon* is the occurrence of lesions on areas of injury. This happens in Vitiligo as well as some other skin diseases such as psoriasis.
Segmental Vitiligo is usually unilateral patches occurring on dermatomal distribution. This subtype has an earlier age of onset and is usually rapidly progressive.
Mixed Vitiligo is the coexistence of segmental and generalized Vitiligo. It usually starts as segmental form and spreads later. Halo nevi and Leukotrichia could be predictors of mixed forms [10].
Focal Vitiligo is when macules are present only in an isolated area.
Mucosal Vitiligo causes lesions on mucosal membranes only.
Universal Vitiligo causes complete or almost complete loss of pigment.

Clinical presentations within the subtypes include: Vitiligo punctué with confetti-like depigmented macules, inflammatory Vitiligo with erythematous rim around lesions. In trichrome and quadrichrome Vitiligo different hues from depigmented to pigmented skin are seen.

Figures 13.2 and 13.3 present the difference in contrast with normal skin comparing to diseased skin in darker and lighter skinned individuals.

Differential Diagnosis

Hypopigmented and depigmented skin lesions could be seen in:

- Nevus depigmentosus (achromic nevus); usually solitary, appears at birth or shortly after and is stable.
- Idiopathic guttate hypomelanosis; multiple small depigmented macules on extremities.

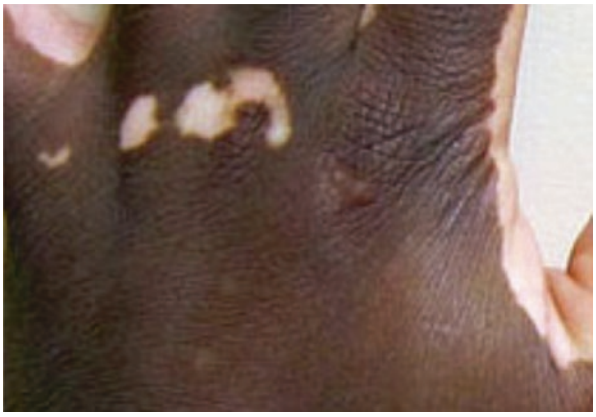


Fig. 13.2 Vitiligo on Fitzpatrick skin type VI

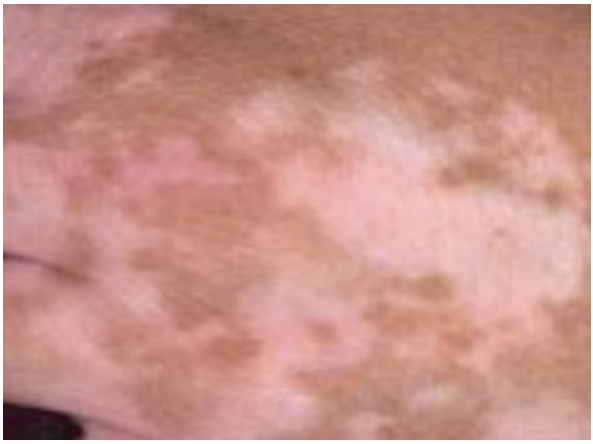


Fig. 13.3 Vitiligo on Fitzpatrick skin type II

- Postinflammatory hypopigmentation; after injuries and inflammation of skin.
- Chemical depigmentation with phenol or other depigmenting chemicals in hair dyes. Imiquimod could induce Vitiligo as well.
- Tinea versicolor in darkly pigmented individuals could cause hypopigmented macules with fine superficial scaling.
- Pityriasis alba; small patches of hypopigmentation usually on face but sometimes on extremities of children due to mild eczematous dermatitis. There is usually history of atopic dermatitis.
- Piebaldism; an inherited disorder of pigmentation characterized by depigmented patches with hyperpigmented borders on midline body and forehead.
- Hypomelanosis of ito (incontinential pigmenti achromians); typically appears at birth or shortly after with hypopigmented patches following lines of Blaschko. It is associated with other neurologic, ocular, and skeletal abnormalities.
- Morphea; skin texture on hypopigmented areas is sclerotic and firm.
- Lichen sclerosus; skin texture on lesions is atrophic and thinned or inflamed.
- Leprosy; hypopigmented anesthetic patches on skin. In the past, patients with Vitiligo would be chased out of town for fear of leprosy.
- Vogt-Koyanagi-Harada syndrome; associated with neurologic, ophthalmologic and skin manifestations including Meningismus, Uveitis, as well as Polisosis, Vitiligo, and Alopecia.
- Sometimes Vitiligo-like patches may precede melanoma and it is important to have a full skin check in patients to rule out melanoma.

Diagnosis

Diagnosis is usually clinical. Wood's lamp examination helps to distinguish hypopigmented from depigmented macules. Biopsy is usually not necessary unless other differentials such as morphea or lichen sclerosus are suspected.

Work up includes screening for other autoimmune diseases:

Recommendation includes evaluating thyroid function (TSH, anti-thyroid antibodies), fasting blood glucose, complete blood count with differential, B12 level (R/O pernicious anemia) and other autoantibodies based on clinical suspicious and family history.

Ophthalmology exam due to occasional association with ocular abnormalities in case of symptoms is important.

Treatment

Vitiligo could be very distressing. It is one of the highest stigmatizing skin disorders. It can affect patients' social functioning as well as intimate relationships.

Support groups play an important role in helping patients cope with the disease. Some examples include:

Vitiligo support international:
https://www.Vitiligosupport.org/

The American Vitiligo research foundation:

http://www.avrf.org/

There has been some research breakthrough in the discovery of Vitiligo susceptibility genes that may play an important role in future treatment.

In regards to treatment strategies, protection of Vitiligo affected skin is important to avoid sunburn and increased risk of skin cancer.

Cosmetic treatments to help camouflage the lesions and self-tanning lotions may improve appearance and help coping with the disease [11].

Vitiligo is a very challenging disease to treat, as there is no cure. Many times more than one treatment should be used for many months before considering patient resistant to treatment.

Treatment methods include topical and systemic treatments [4].

Topical steroids are usually the first line of treatment. In areas susceptible to steroid atrophy such as the face, topical Calcineurin inhibitors are another option.

Topical Calcipotriene has been used in combination with topical steroids and UV treatment.

If topical treatments are not enough, topical and systemic photochemotherapy (PUVA), narrowband UVB (NB-UVB), narrowband UVB and oral antioxidants, Excimer laser (308 nm), topical treatments plus phototherapy, and monochromatic excimer light are other options.

Other treatments include complete depigmentation in patients with severe and extended disease achieved via Monobenzyl ether of hydroquinone applications twice a day for up to 1 year.

Trials of dermabrasion combined with 5-fluorouracil cream have given good results in small groups of patients [12].

Surgical treatments include autologous melanocyte transfer via epidermal grafts and transplantation of cultured pure melanocyte suspension; both have moderate results. Thin split-thickness, punch and suction blister epidermal grafting have been the most effective surgical methods in patients with stable disease [4].

Combination of punch grafting and narrow band UV-B had good results in 66 patients with 86.36 % re-pigmentation [13].

Other types of lasers such as Ruby laser have been used in treatment.

Cosmetic tattooing could be another option in stable Vitiligo patches [14].

Psychological Interventions

Vitiligo causes deviance from normal appearing skin. Depending on age of onset, site of the disease, type of complexion and visibility of the lesions it could cause severe emotional distress for patients. Lesions located on visible areas of the body and lesions on genital areas are particularly problematic. In individuals with darker skin color the disease is more visible. In these cases, it is also more difficult and time consuming to use camouflage.

Since the treatments are not curative and the course of disease is chronic, attending to patients' psychological needs is of prime importance.

Vitiligo causes fear and embarrassments in many patients. Patients perceive discrimination from others and many feel that they do not receive adequate support from their doctors [15].

Some studies show that camouflage in patients with Vitiligo improves their quality of life [11, 16]. This, however, is time consuming and requires training to be done properly.

As stated previously, blunted stress response has been associated with autoimmune problems and may play a role in pathogenesis of Vitiligo.

Also, insecure attachment, poor social support and Alexithymia (a personality trait of inability to identify and describe self- emotions) increase susceptibility to Vitiligo [17].

Starting early in life, helping children with coping styles and increasing their resiliency, may have a protective rule in individuals with family history of autoimmune problems and genetic predisposition to Vitiligo. This needs to be investigated in prospective public health studies. Identifying children at risk and using methods such as early childhood mindfulness training will help problem solving and emotional self-regulation skills.

In patients affected by Vitiligo, stress could play an aggravating role for the disease [6].

Age of onset is important and some reports show that children in their preadolescent years may cope better with Vitiligo [18].

Support groups, such as Vitiligo Support International and The American Vitiligo Research Foundation, play an important role in helping patients and their families.

Their websites provide information about Vitiligo. This is helpful to educate schools, teachers, and peers about the disease, and to prevent discrimination and bullying.

Most reports reveal middle school and high school to be the times when bullying is most prevalent. These are also formative years in a child's life.

Helping children improve self-esteem (using other talents not related to physical appearance) and problem-solving skills, dealing with bullies and improving interpersonal relationships needs to be an integral part of the treatment plan.

Different psychotherapeutic techniques may be helpful for patients with Vitiligo including CBT (Cognitive Behavioral Therapy), relaxation techniques (to improve participating in social activities and decrease social anxiety), supportive therapy, interpersonal therapy, family therapy, and group therapy. The type of intervention needs to be tailored to each patient's need.

There are also some reports of hypnosis improving Vitiligo [19].

Success stories, such as top model with Vitiligo Chantelle Brown-Young (AKA; Chantelle Winnie or Winnie Harlow), could help children understand and invest in their uniqueness [20].

Vitiligo also affects parents' quality of life and mental health [21]. Support groups and psychoeducation for parents will help them to be more emotionally available for their children and cope better with having a child with a chronic skin condition.

Finally, if clinicians identify patients with depression or anxiety, appropriate referral for mental health treatment will help compliance with dermatological treatments and quality of life. Having self-screening questionnaires to identify depression and anxiety in dermatology clinics could help with proper identification of patients and appropriate intervention.

Psychocutaneous clinics provide the bridge for a holistic approach, treatment consistency and attending both body and mind needs of our patients.

References

1. Goldstein BG, Goldstein AD, Dellavalle RP, Levy ML, Vitiligo, UpToDate, www.uptodate.com@2015 up to Date, updated Jan 19, 2015. Accessed 5 Dec 2015.
2. Boniface K, Taïb A, Seneschal J, New insights into immune mechanisms of Vitiligo, G Ital Dermatol Venereol. 2015. (Epub ahead of print).
3. Honda S, Kaur I. Vitiligo: clinical findings in 1436 patients. J Dermatol. 1999;26:653.
4. Lebwohl MG, Heymann WR, Berth-Jones J, Coulson I. Chapter 245. Vitiligo. In: Hadi SM, Spencer JM, editors. Treatment of skin diseases. 4th ed. 2014, p. 794–8.
5. Papandopoulos L, Bor R, Legg C, Hawk JL. Impact of life events on the onset of Vitiligo in adults: preliminary evidence for a psychological dimension in aetiology. Clin Exp Dermatol. 1998;23:243.
6. Manolache L, Benea V. Stress in patients with alopecia areata and Vitiligo. J Eur Acad Dermatol Venereol. 2007;21(7):921–8.
7. O'Sullivan JJ, Stevenson CJ. Screening for occupational Vitiligo in workers exposed to hydroquinone monomethyl ether and to paratertiary-amyl-phenol. Br J Ind Med. 1981;38:381.

8. Silverberg JI, Silverberg NB. Vitiligo disease triggers: psychological stressors preceding the onset of the disease.
9. Trapp EM, Trapp M, Sampogna F, Rohrer PM, Egger JW, Wolf P, Kapfhammer HP, Linder MD, Richtig E, Baulmann J, Hofer A. Autonomic nervous tone in Vitiligo patients-a case control study. Acta Derm Venereol. 2015;95(2):169–72.
10. Ezzedine K, Lim HW, Suzuki T, et al. Revised classification/nomenclature of Vitiligo and related issues: the Vitiligo global issues consensus conference. Pigment Cell Melanoma Res. 2012;25:E1.
11. Tanioka M, Yamamoto Y, Kato M, Miyachi Y. Camouflage for patients with Vitiligo vulgaris improved their quality of life. J Cosmet Dermatol. 2010;9(1):72–5.
12. Sethi S, Mahajan BB, Gupta RR, Ohri A. Comparative evaluation of the therapeutic efficacy of dermabrasion, dermabrasion combined with topical 5 % 5-fluorouracil cream and dermabrasion combined with topical placentrex gel in localized stable Vitiligo. Int J Dermatol. 2007;46:875–9.
13. Lahiri K, Malakar S, Sarma N, Banerjee U. Repigmentation of Vitiligo with punch grafting and narrow-band UV-B. Int J Dermatol. 2006;45:649–55.
14. Mahajan BB, Garg G, Gupta RR. Evaluation of cosmetic tattoing in localized stable Vitiligo. J Dermatol. 2002;29:726–30.
15. Porter J, Beuf AH, Lerner A, Nordlund J. Response to cosmetic disfigurement: patients with Vitiligo. Cutis. 1987;39(6):493–4.
16. Ongenae K, Dierckxsens L, Brochez L, Van Geel N, Naeyaert JM. Quality of life and stigmatization profile in cohort of Vitiligo patients and effect of the use of camouflage. Dermatology. 2005;210(4):279–85.
17. Picardi A, Pasquini P, Cattaruzza MS, Gaetano P, Melchi CF, Baliva G, Camaioni D, Tiago A, Abeni D, Biondi M. Stressful life events, social support, attachement security and alexithymia in Vitiligo. A case–control study. Psychother Psychosom. 2003;72(3):150–8.
18. Prćić S, Durović D, Duran V, Vuković D, Gajinov Z. Some psychological characteristics of children and adolescnets with Vitiligo—our results. Med Pregl. 2006;59(5–6):265–9.
19. Shenefelt PD. Hypnosis in dermatology. Arch Dermatol. 2000;136(3):393–9.
20. Erin Clements. The clothing has dots and I have dots! ANTM contestant suffering from Michael Jackson's skin disorder scores her first fashion campaign as the face of Desigual; Daily mail.com UK 16 September 2014.
21. Amer AA, Mchepange UO, Gao XH, Hong Y, Qi R, Wu Y, Cai Y, Zhai J, Chen HD. Hidden victims of childhood Vitiligo: impact on parents' mental health and quality of life. Acta Derm Venereol. 2015;95:322–5.

Chapter 14
Hyperhidrosis and Stress

Vincent M. Hsu, Vidhi V. Shah, Adam S. Aldahan, Stephanie Mlacker, Sahal Samarkandy, and Keyvan Nouri

Abbreviations

ACTH	Adrenocorticotropic hormone
BTXA	Botulinum toxin type A
CRH	Corticotrophin-releasing hormone
DLQI	Dermatology Life Quality Index
HADS	Hospital Anxiety and Depression Scale
HDSS	Hyperhidrosis Disease Severity Scale
HPA	Hypothalamic-pituitary-adrenal
MMPI-2	Minnesota Multiphasic Personality Inventory-2
OCD	Obsessive-compulsive disorder
ORS	Olfactory reference syndrome
PAH	Primary axillary hyperhidrosis
SES	Subjective evaluation scale
VAS	Visual Analogue Scale

V.M. Hsu, BS • V.V. Shah, BA • A.S. Aldahan, BS • S. Mlacker, BS • K. Nouri, MD (✉)
University of Miami Miller School of Medicine, Department of Dermatology and Cutaneous Surgery, 1475 NW 12th Ave., Suite 2175, Miami, FL 33136, USA
e-mail: v.hsu@umiami.edu; shahvidhiv@gmail.com; aaldahan@med.miami.edu; mlackerstephanie@gmail.com; knouri@med.miami.edu

S. Samarkandy, MD
University of Miami Miller School of Medicine, Department of Dermatology and Cutaneous Surgery, 1475 NW 12th Ave., Suite 2175, Miami, FL 33136, USA

Department of Dermatology, King Abdulaziz Medical City, Jeddah, Saudi Arabia
e-mail: sahaljs@yahoo.com

K. França, M. Jafferany (eds.), *Stress and Skin Disorders*,
DOI 10.1007/978-3-319-46352-0_14

Introduction

Hyperhidrosis is a distressing skin condition characterized by excessive, uncontrollable amounts of sweat in specific body locations. Although not a physically debilitating condition, individuals affected with this condition commonly experience psychosocial stress during regular social encounters and experience low self-confidence, thus drastically affecting the quality of life of these individuals [1–3]. In severe cases, hyperhidrosis can dictate a person's career choices, hobbies, and sexual encounters [8]. This disorder affects both genders equally, typically beginning in adolescence and persists for life. There have been no documented cases of spontaneous remission [9]. In the United States, it is estimated that 2.8 % of the population is diagnosed with hyperhidrosis; similarly, up to 3 % of the population in the United Kingdom has hyperhidrosis [3, 8, 10].

Classification

There are two major types of hyperhidrosis, primary and secondary. Primary hyperhidrosis has a genetic basis and is inherited in an autosomal dominant pattern. Some criteria must be met for diagnoses of primary hyperhidrosis such as at least 6 months of focal, visible, excessive sweating without cause with at least two of the following conditions: bilateral and relatively symmetric sweating patterns, impairs daily activities, frequency of at least one episode per week, onset before 25 years, positive family history, and cessation of focal sweating during sleep [11]. A genetic basis for primary hyperhidrosis has been implicated. In 48–65 % of those affected individuals, there is a positive family history. Fifty-eight percent of patients with a positive family history were parent–child cases, lending some support to the claim that the disease is spread via an autosomal dominant inheritance pattern [3]. Furthermore, hyperhidrosis can be characterized according to anatomic location. Axillary hyperhidrosis is diagnosed when excess sweat is localized to the axilla regions of the patient [5]. These patients commonly change clothes several times a day in an effort to mask their condition from the general public. In volar hyperhidrosis, patients have excessive sweat in the volar regions, the palms and soles, and may experience shame and embarrassment while performing everyday daily activities such as writing or shaking hands [10]. Current research also suggests that the disorder results from a significant dysfunction of the sympathetic nervous system due to an imbalance in the hypothalamus [9].

Secondary hyperhidrosis is usually the result of another underlying health condition such as obesity, gout, menopause, tumors, diabetes mellitus, or hyperthyroidism, or a complication from medicines such as antidepressants [8, 12].

Pathophysiology of Hyperhidrosis

Sweat

Understanding the biology of hyperhidrosis requires an appreciation for sweat, the basic component of the sudoriferous gland system. Sweat, a liquid mixture of minerals, lactate, and urea, is secreted from sweat glands distributed all over the body and maintains homeostasis as it evaporates from the surface of the skin and lowers the internal body temperature by transferring heat via direct conduction from the vascular supply to the skin [2]. Though elevated internal body temperature due to exercise or external heat sources are normally the causes of perspiration, sweat may also be due to elevated anxiety and stress, hormonal imbalances, gustatory stimuli, and other psychological conditions [13].

Eccrine Sweat Glands

Approximately, 2–4 million eccrine sweat glands are distributed in various proportions of the body's surface. These glands primarily function to maintain homeostatic body temperatures and compensate for instances of increased internal (i.e., sweating during physical activity) or external heat (i.e., sweating in warm weather). Eccrine glands are composed of dark and clear cell types, which are organized into a secretory coil arrangement [2]. The secretory layer are encapsulated by myoepithelial cells that contract when stimulated by acetylcholine discharged by the sympathetic nervous system.

Apocrine Sweat Glands

Apocrine glands are limited to the axilla and perianal areas and are connected to hair follicles. These glands share the coil-like structure of eccrine glands and produce a thick, milky fluid into the hair follicle when triggered by androgen and possibly emotional stress [2]. This form of fatty sweat is naturally odorless, but is degraded into odorous fatty acids by local bacteria when expelled [14, 15]. Table 14.1 summarizes the differences between the apocrine and eccrine sweat glands.

Psychological Influence on Hyperhidrosis

The exact mechanism behind hyperhidrosis remains unknown, but an underlying neurological disorder may be involved. The disorder is likely secondary to a disordered, response to the sympathetic nervous system. Emotional stimuli from the

Table 14.1 Differences between apocrine and eccrine sweat glands [14, 15].

	Apocrine sweat gland	Eccrine sweat gland
Structure	Coiled tubular	Coiled tubular
Location	Axilla and perianal areas	All over the body
Odorous	Yes	No
Method of secretion	Secreted from canals of hair follicles	Directly onto surface of the skin
Timing of secretion	Emotional stress	Elevated body temperature
Function	Thermoregulation, hormonal balance	Thermoregulation, protection, secretion

limbic system and cortex trigger a hormonal imbalance in the hypothalamic sweat center [9, 13]. Thus, psychological triggers can contribute or exacerbate the signs and symptoms of hyperhidrosis. Several theories exist regarding the pathophysiology of hyperhidrosis with relation to stress and are explained below [16].

One theory is the increased sympathetic activity of the autonomic nervous system when over-stimulated by the hypothalamic-pituitary-adrenal (HPA) axis during times of psychosocial stress [17]. The hypothalamus's corticotrophin-releasing hormone (CRH) and arginine-vasopressin stimulates the anterior pituitary's production of adrenocorticotropic hormone (ACTH), which stimulates the adrenal gland secretion of cortisol, a stress hormone [17]. Cortisol levels can be quantified and used to help determine a correlation between stress and hyperhidrosis [17]. Furthermore, everyday activities may worsen and add psychological stress [17, 18].

Other studies suggest that hyperhidrosis is triggered by different psychological disorders including social anxiety disorder (SAD), olfactory reference syndrome (ORS), and obsessive-compulsive disorder (OCD). SAD is a social phobia characterized by persistent fear of regular social interactions that affects up to 13 % of the population [19]. Patients with this disorder have increased daily stress and anxiety levels [18]. There is controversy over whether SAD and hyperhidrosis are co-existent disorders. While some propose that patients with hyperhidrosis are no more at risk for anxiety and psychopathological disorders than the general population, Weber et al. discovered that symptoms of SAD was particularly common amongst patients who had been diagnosed with treatment-resistant hyperhidrosis. They also noted the potential correlation between OCD and hyperhidrosis. The excess sweat produced by hyperhidrosis patients may increase their paranoia about repulsive body odor and hygiene thereby increasing the likelihood that they develop ORS or OCD [20, 21].

Studies have also investigated the affects of depression and anxiety in the etiology of hyperhidrosis. Braganca et al. sought to determine the levels of anxiety, depression, and irritability in hyperhidrosis patients. All patients in the study were assessed by the same doctor and were asked to answer the questionnaire, "Hospital Anxiety and Depression Scale" (HADS) in an air-conditioned, private clinic. The results showed that prevalence of anxiety among hyperhidrosis patients was 49.2 %, approximately four times that for depression symptoms at just 11.2 %. They also discovered that age, gender, and skin tone were not significant variables related to hyperhidrosis [22]. In a study by Ruchinskas et al., hyperhidrosis patients were

administered the Minnesota Multiphasic Personality Inventory-2 (MMPI-2) and State-Trait Anxiety Inventory. The objective was to determine the degree of psychopathology in those patients by comparing their test results with established norms. The results were within the range of established norms, indicating that anxiety and depression were not significant and was likely not the primary cause of hyperhidrosis. Eighty-eight percent of the patients in this study demonstrated regular psychological profiles; the 12 % of the sample that scored above the average range of MMPI-2 results on the anxiety scale may be unique to hyperhidrosis patients, or may simply reflect the upper limits of anxiety in the general population, not exclusive to those with hyperhidrosis.

Krogstad et al. compared the variation of sweating between twenty patients with primary palmar hyperhidrosis and twenty healthy controls. Both groups self-reported their sweat patterns 24 h a day for 1 week. They were instructed to rate their perspiration with a subjective evaluation scale (SES) ranging from 0 (no sweat) to 10 (sweaty). A significant difference in the rate of sweating was found between the two groups. Although both groups demonstrated increases by scores of 2–5 with daily stress and exercise, there was a greater increase in patients with hyperhidrosis than controls. The time of day the self-assessment was conducted also fluctuated the SES scores; in hyperhidrosis patients, scores varied from 0 to 2 in the mornings and evenings, and rose to 5–6 around mid-day. During the same time period, control subjects reported SES scores close to 0. Krogstad et al. successfully demonstrated that sweating patterns of hyperhidrosis patients are not consistent; yet fluctuate throughout the day, especially during physical and emotional stimuli [23].

Treatment

Various treatment options exist to help alleviate the symptoms of hyperhidrosis. The clinical effectiveness, quantified by a variety of standardized scales including the Hyperhidrosis Disease Severity Scale (HDSS) and the Dermatology Life Quality Index (DLQI), are used to evaluate patients' quality of life. Invasive surgery is currently one of the only permanent solutions for primary axillary hyperhidrosis (PAH) patients, however other treatment options offer temporary relief and a brief period of decreased symptoms for 4–18 months, often requiring multiple treatments to yield optimal results [2, 7]. A few of the available treatment options include aluminum chloride antiperspirants, oral administration of anticholinergic drugs such as glycopyrronium bromide (glycopyrrolate), iontophoresis, botulinum toxin type A (BTXA) injections, and endoscopic thoracic sympathectomy [2–7].

Topical Therapy

Treatment with over-the-counter antiperspirants containing topical aluminum chloride or zirconium salt, is an easy option for patients with mild-to-moderate hyperhidrosis. Aluminum, or zirconium in some antiperspirants, precipitates with

mucopolysaccharides in the eccrine duct, thus obstructing the secretory coils of the lower dermis and preventing secretion of any fluids, providing temporary relief [10]. Patients with mild-to-moderate hyperhidrosis can purchase these antiperspirants with 10 % aluminum chloride concentration without a prescription, but those with more severe hyperhidrosis require concentrations of 20 % aluminum chloride in ethyl alcohol [24, 25]. Initial application should be during the night as sweat glands are less active during sleep. A stable sweat gland allows the metal salts in the antiperspirant to be absorbed easily. Haider et al. conducted a study with application of 20 % aluminum chloride in ethyl alcohol on the palms and axillae regions. Within 48 h there was substantial improvement, but the effect lasted only for another 48 h. These investigators study noted efficacy of topical treatment in 98 % of cases [26]. Topical application may result in adverse side effects like skin irritation, dry skin, and itchiness. Persistent treatment may reduce the skin irritation and pruritus [12]. Applying aluminum chloride in combination with 2–4 % salicyclic acid gel also may help reduce skin irritation and promotes penetration of the treatment [27]. Hydrocortisone cream is another method that has been reported to alleviate irritation [24, 28].

Oral Medication

Administration of oral anticholinergics such as glycopyrrolate is another available treatment. Bajaj et al. performed a retrospective analysis on 9 patients with generalized hyperhidrosis and 15 patients with localized hyperhidrosis and reported the efficacy of oral glycopyrrolate 2 mg twice daily, with dosages adjusted according to patients' ability to control sweating. Of the original 24 patients enrolled in the study, only 19 committed to follow up. 79 % (15/19) of hyperhidrosis patients responded well to oral glycopyrrolate. Adverse effects of glycopyrrolate included dry mouth, headaches, and urinary retention. There was no correlation between increasing dosages and adverse side effects [10, 12, 29].

Iontophoresis

Iontophoresis uses a direct electrical current to pass an ionized substance through the skin [30]. The mechanism of action of this treatment is poorly understood, though several theories have been proposed. Iontophoresis is indicated in patients with palmar and plantar hyperhidrosis whose symptoms persist despite treatment with topical therapy [10]. Physicians initially administer treatment, but eventually patients can self-administer iontophoresis once properly trained for appropriate home-use. In addition to the convenience of home application, patients prefer iontophoresis because of a financial incentive. Many insurance companies view treatment for hyperhidrosis medically necessary when topical therapies have failed and will pay for iontophoresis therapy. An observational study of 113 patients with

palmoplantar reported a 91 % response rate [30]. The side effects of iontophoresis are mild and include redness of skin, vesiculation in the affected area, burning sensations, and dryness. Many of the side effects can be prevented with proper knowledge of the procedures and precautionary measures are taken. In general, patients should refrain from touching the electrodes to prevent electrical shock [10, 12, 30].

Botox

Botulinum toxin type A (BTXA), Botox, is popularized for its beneficial, cosmetic effects on unwanted wrinkles and creases, however it can also be used to treat both axillary and palmar hyperhidrosis. In many studies, intradermal injections of BTXA demonstrates efficacy of 80–90 % [3, 31]. This toxin directly stimulates the eccrine glands, irreversibly obstructing acetylcholine release from presynaptic bulbs at postgangiolinc nerve endings, leading to anhidrosis for up to 6 months [12]. In each palm, 100 U are injected intradermally; 50–100 U are injected per axilla [31]. Although not a cure-all treatment for hyperhidrosis, many patients seek out this modality because it is less invasive with minimal side effects, which include slight discomfort during the procedure. and slight bruising immediately post-injection. Some patients have noted that application of ice and topical anesthesia alleviated their discomfort during injection [32, 33]. A significant downside of this option is the frequency of treatments the patient must endure to maintain efficacy; botox treatment of PAH calls for at least 15 injections per axilla, every few months [12, 31, 34].

Surgery

Surgical treatment is reserved for treatment of severe, recalcitrant hyperhidrosis. Several surgical methods such as the complete excision of sweat glands, subcutaneous curettage, and endoscopic thoracic sympathectomy can be employed. Complete excision of the sweat glands significantly reduces sweat production, but routinely results in unpleasant scars, the risk of infection, and restricted arm movement [12]. The risks and benefits of surgical removal of sweat glands should be thoroughly discussed with the patient.

Another surgical alternative for patients, one of few that renders a permanent solution is subcutaneous curettage. This option is simpler than complete excision of sweat glands, as it requires fewer preoperative preparative measures. First, the target axillary region is washed with antibacterial soap to ensure the axillary regions are free of dirt and other bacteria. Shaving is recommended prior to surgery, as the surgeon will have better visualization of the area, but this is not necessary. To prevent infection stemming from contamination of the incision, a precautionary dose of intravenous antibiotics should be administered. It is imperative that the patient's system be clear of any anticoagulant medications as these may induce excessive

bleeding and lead to additional complications in an otherwise simple procedure [35]. Before incision, the region of the patient's maximal sweating is marked with the starch and iodine method followed by marking the patient's skin to clearly outline the sweating area. An elliptical excision is made and subcutaneous fat and lower dermis in the targeted region is removed. Scarring is reduced if the coils of sweat glands at the lower dermis are removed. Ten of the 13 patients treated in this manner in a test conducted by Munro et al. experienced significant benefit [13]. Other side effects include bleeding, pain, hematoma, infection, seroma, and brachial plexus damage [12].

Tumescent superficial suction with curettage is another surgical alternative. First a tumescent solution is injected for local anesthesia. Then, a subcutaneous tunnel for curettage and suction is created with a modified vacuum curette and ophthalmic scissors. Vacuum aspiration curette is performed to remove the stringent substance [36]. Tronstad et al. conducted a study to compare the effectiveness of two surgical techniques: superficial tumescent suction curettage and curettage only. The investigators treated 22 patients each received one type of treatment at each side. Efficacy was determined from skin conductance, gravimetry, and visual analogue scale (VAS) scoring (Fig. 14.1) [9]. Comparing results post treatment indicated significantly better results with tumescent suction curettage than curettage only.

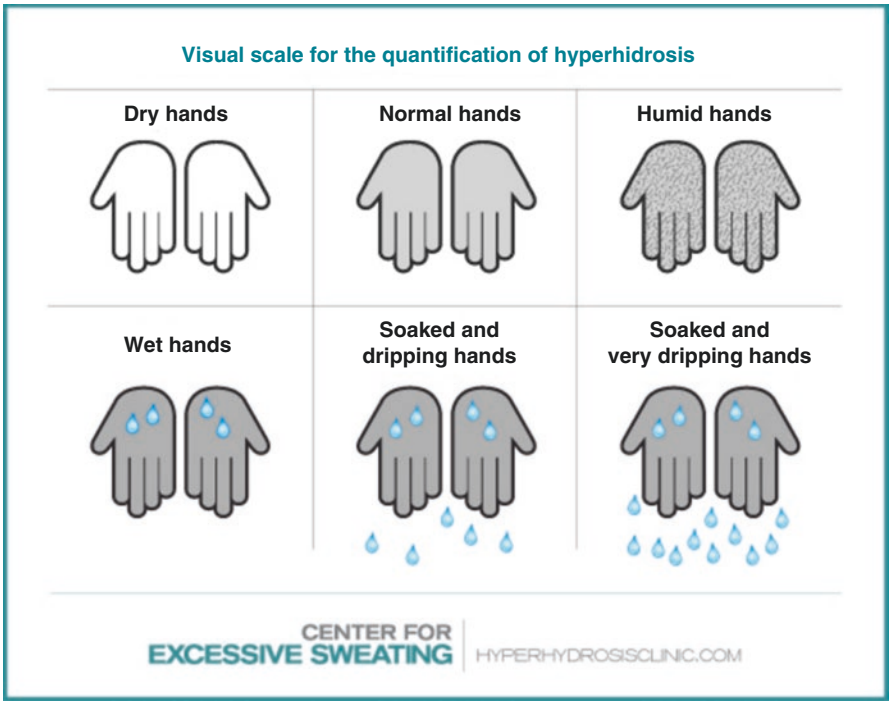


Fig. 14.1 A visual analogue scale used to visually quantify the severity of hyperhidrosis in patients (Image reproduced with permission from Dr. Hratch Karamanoukian MD, FACS)

Endoscopic thoracic sympathectomy is a surgical intervention endorsed by the National Institute for Health and Care Excellence (NIHCE) for upper-limb hyperhidrosis, including palmar and axillary. During this procedure, the T3 and T4 ganglia are de-nerved via clipping or cutting. Endoscopic symapathectomy is acclaimed for its 91 % success rate. However, one study demonstrated 88 % of patients complained of compensatory hyperhidrosis, a less-common form of localized hyperhidrosis in other locations whose onset is initiated by neurological damage, following the procedure. Many palmar hyperhidrosis patient's who opt for surgical sympathectomy report development of compensatory hyperhidrosis in areas innervated below C3–5 [10, 12].

Fractionated Microneedle Radiofrequency (FMR)

Fractionated microneedle radiofrequency (FMR) treatment is a method with minimal disruption of skin allowing the delivery of 1 MHz of radiofrequency current to the underlying layers of the dermis [12]. Fatemi et al. studied the efficacy of FMR as a noninvasive treatment option for PAH. Patients received three sessions of FMR therapy at 3-week intervals and efficacy was evaluated per results from the hyperhidrosis disease severity scale (HDSS), and VAS. The patients improved significantly following treatment, as the majority of patients showed a 1–2 score decrease in HDSS. Table 14.2. The survey administered to patients post-treatment revealed that 80 % of patients reported satisfaction with the results of the study [5].

Potential Future Treatment Therapies

Laser Treatment

As the field of cosmetics continues to expand into medical boundaries, the role of lasers in clinical medicine continues to expand. To determine the efficacy of lasers in treating hyperhidrosis, a 1300 nm Nd:YAG laser was tested on a patient who's hyperhidrosis persisted after surgery failed to alleviate his symptoms. The laser was directly applied to the underside of the dermis after first mechanically separating the

Table 14.2 The HDSS is a standardized survey given to hyperhidrosis patients and allows them to self-assess the severity of their condition [37]

Hyperhidrosis Disease Severity Scale (HDSS)	
My sweating is never **noticeable and** never **interferes with my daily activities**.	Score 1
My sweating is tolerable **but** sometimes **interferes with my daily activities**	Score 2
My sweating is barely **noticeable and** frequently **interferes with my daily activities**.	Score 3
My sweating is intolerable **and** always **interferes with my daily activities**.	Score 4

dermis from subcutaneous fat. The patient's symptoms appeared to be completely resolved and this was maintained at the 18-month follow up [12]. Laser treatment of hyperhidrosis appears to be a viable option for patients to consider in the future.

Microwave Thermolysis

Microwave thermolysis using a MiraDry is a relatively new, minimally invasive treatment therapy for axillary hyperhidrosis that promotes chemical decomposition of sweat glands induced by microwaves of frequency between 300 and 300 GHz [38, 39]. Microwave energy is preferentially absorbed sweat glands due to it's higher water content. The energy innervates rapid rotation of water molecules, which leads to frictional heat and cellular thermolysis [39]. Johnson et al. first proposed the use of microwaves in treating hyperhidrosis. The team tested a novel device they had created and evaluated results on porcine models with analytical programs on the computer. Few adverse side effects were reported, no skin blistering occurred, and although further studies are needed to further understand this treatment and determine its efficacy as a permanent solution to hyperhidrosis [12, 38].

Conclusion

Hyperhidrosis is an emotionally taxing condition that renders patients feeling socially vulnerable. Onset of the disorder is regularly seen in adolescents and although the exact mechanism of hyperhidrosis is still not completely understood, investigators continue to explore the psychological basis of hyperhidrosis in an effort to determine the role of stress in this condition. Endoscopic thoracic sympathectomy is the only current, permanent treatment option; however new therapeutic options on the horizon such as lasers and microwave thermolysis demonstrate promising results. Less invasive treatment options that range from over-the-counter options to botox injections administered by a medical professional are commonly available and provide temporary comfort. Patients living with hyperhidrosis must cope with additional stress and anxiety unparalleled to those around them. Physicians treating patients with hyperhidrosis should be aware of the available treatment options to help reduce the affects of this emotionally taxing disorder.

Citations

1. Coutinho dos Santos LH, Gomes AM, Giraldi S, Abagge KT, Marinoni LP. Palmar hyperhidrosis: long-term follow-up of nine children and adolescents treated with botulinum toxin type A. Pediatr Dermatol. 2009;26(4):439–44.
2. Glogau RG. Botulinum A neurotoxin for axillary hyperhidrosis. Dermatol Surg. 1998;24(8):817–9.

3. Kouris A, Armyra K, Stefanaki C, Christodoulou C, Karimali P, Kontochristopoulos G. Quality of life and social isolation in Greek adolescents with primary focal hyperhidrosis treated with botulinum toxin type A: a case series. Pediatr Dermatol. 2015;32(2):226–30.
4. Bajaj V, Langtry JA. Use of oral glycopyrronium bromide in hyperhidrosis. Br J Dermatol. 2007;157(1):118–21.
5. Fatemi Naeini F, Abtahi-Naeini B, Pourazizi M, Nilforoushzadeh MA, Mirmohammadkhani M. Fractionated microneedle radiofrequency for treatment of primary axillary hyperhidrosis: a sham control study. Australas J Dermatol. 2015;56(4):279–84.
6. Kobayashi K, Omote K, Homma E, Abe T, Iitoyo M. Sympathetic ganglion blockade for the management of hyperhidrosis. J Dermatol. 1994;21(8):575–81.
7. Rompel R, Scholz S. Subcutaneous curettage vs. injection of botulinum toxin A for treatment of axillary hyperhidrosis. J Eur Acad Dermatol Venereol. 2001;15(3):207–11.
8. Nordqvist C. What is hyperhidrosis? What caues hyperhidrosis? 2014. Available from: http://www.medicalnewstoday.com/articles/182130.php.
9. Tronstad C, Helsing P, Tonseth KA, Grimnes S, Krogstad AL. Tumescent suction curettage vs. curettage only for treatment of axillary hyperhidrosis evaluated by subjective and new objective methods. Acta Derm Venereol. 2014;94(2):215–20.
10. Vary Jr JC. Selected disorders of skin appendages--acne, alopecia, hyperhidrosis. Med Clin North Am. 2015;99(6):1195–211.
11. Hornberger J, Grimes K, Naumann M, Glaser DA, Lowe NJ, Naver H, et al. Recognition, diagnosis, and treatment of primary focal hyperhidrosis. J Am Acad Dermatol. 2004;51(2):274–86.
12. Singh S, Davis H, Wilson P. Axillary hyperhidrosis: a review of the extent of the problem and treatment modalities. Surgeon. 2015;13(5):279–85.
13. Munro DD, Verbov JL, O'Gorman DJ, du Vivier A. Axillary hyperhidrosis. Its quantification and surgical treatment. Br J Dermatol. 1974;90(3):325–9.
14. Britannica E. Sweat gland Britannica.com: Encyclopaedia Britannica; [Updated 8/19/2014; cited 2016 1/26/16]. Available from: http://www.britannica.com/science/sweat-gland.
15. Staff MC. Sweating and body odor Mayoclinic.org2014 [Cited 2016 1/26/16]. Available from: http://www.mayoclinic.org/diseases-conditions/sweating-and-body-odor/basics/causes/con-20014438.
16. Ruchinskas RA, Narayan RK, Meagher RJ, Furukawa S. The relationship of psychopathology and hyperhidrosis. Br J Dermatol. 2002;147(4):733–5.
17. Gross KM, Schote AB, Schneider KK, Schulz A, Meyer J. Elevated social stress levels and depressive symptoms in primary hyperhidrosis. PLoS One. 2014;9(3):e92412.
18. Bohaty BR, Hebert AA. Special considerations for children with hyperhidrosis. Dermatol Clin. 2014;32(4):477–84.
19. Lessa Lda R, Luz FB, De Rezende RM, Duraes SM, Harrison BJ, De Menezes GB, et al. The psychiatric facet of hyperhidrosis: demographics, disability, quality of life, and associated psychopathology. J Psychiatr Pract. 2014;20(4):316–23.
20. Weber A, Heger S, Sinkgraven R, Heckmann M, Elsner P, Rzany B. Psychosocial aspects of patients with focal hyperhidrosis. Marked reduction of social phobia, anxiety and depression and increased quality of life after treatment with botulinum toxin A. Br J Dermatol. 2005;152(2):342–5.
21. Ferrao YA, Shavitt RG, Prado H, Fontenelle LF, Malavazzi DM, de Mathis MA, et al. Sensory phenomena associated with repetitive behaviors in obsessive-compulsive disorder: an exploratory study of 1001 patients. Psychiatry Res. 2012;197(3):253–8.
22. Braganca GM, Lima SO, Pinto Neto AF, Marques LM, Melo EV, Reis FP. Evaluation of anxiety and depression prevalence in patients with primary severe hyperhidrosis. An Bras Dermatol. 2014;89(2):230–5.
23. Krogstad AL, Mork C, Piechnik SK. Daily pattern of sweating and response to stress and exercise in patients with palmar hyperhidrosis. Br J Dermatol. 2006;154(6):1118–22.
24. Reisfeld R, Berliner KI. Evidence-based review of the nonsurgical management of hyperhidrosis. Thorac Surg Clin. 2008;18(2):157–66.
25. Pariser DM, Ballard A. Topical therapies in hyperhidrosis care. Dermatol Clin. 2014;32(4):485–90.

26. Haider A, Solish N. Focal hyperhidrosis: diagnosis and management. CMAJ. 2005;172(1):69–75.
27. Hoorens I, Ongenae K. Primary focal hyperhidrosis: current treatment options and a step-by-step approach. J Eur Acad Dermatol Venereol. 2012;26(1):1–8.
28. Brown AL, Gordon J, Hill S. Hyperhidrosis: review of recent advances and new therapeutic options for primary hyperhidrosis. Curr Opin Pediatr. 2014;26(4):460–5.
29. Scuderi S, Manoharan P, Lim D, Manoharan S. A survey of patient satisfaction with use of microwave device for axillary hyperhidrosis. Australas J Dermatol. 2016.
30. Pariser DM, Ballard A. Iontophoresis for palmar and plantar hyperhidrosis. Dermatol Clin. 2014;32(4):491–4.
31. Weinberg T, Solish N, Murray C. Botulinum neurotoxin treatment of palmar and plantar hyperhidrosis. Dermatol Clin. 2014;32(4):505–15.
32. Benohanian A. Needle-free anaesthesia prior to botulinum toxin type A injection treatment of palmar and plantar hyperhidrosis. Br J Dermatol. 2007;156(3):593–6.
33. Smith KC, Comite SL, Storwick GS. Ice minimizes discomfort associated with injection of botulinum toxin type A for the treatment of palmar and plantar hyperhidrosis. Dermatol Surg. 2007;33(1 Spec No.):S88–91.
34. de Almeida AR, Montagner S. Botulinum toxin for axillary hyperhidrosis. Dermatol Clin. 2014;32(4):495–504.
35. Karpinski RHS. Surgical treatment of axillary hyperhidrosis treatment & management Medscape2014 [Cited 2016 1/23/16]. Available from: http://emedicine.medscape.com/article/1296530-treatment – d13.
36. Shi Z, Yan X, Ye X. Modified tumescent superficial suction with curettage treatment for axillary bromidrosis: clinical experience of 280 cases. Aesthetic Plast Surg. 2014;38(1):151–5.
37. Solish N, Bertucci V, Dansereau A, Hong HC, Lynde C, Lupin M, et al. A comprehensive approach to the recognition, diagnosis, and severity-based treatment of focal hyperhidrosis: recommendations of the Canadian Hyperhidrosis Advisory Committee. Dermatol Surg. 2007;33(8):908–23.
38. Johnson JE, O'Shaughnessy KF, Kim S. Microwave thermolysis of sweat glands. Lasers Surg Med. 2012;44(1):20–5.
39. Glaser DA, Galperin TA. Local procedural approaches for axillary hyperhidrosis. Dermatol Clin. 2014;32(4):533–40.

Chapter 15
Acne and Rosacea

Tulsie Patel, Shailee Patel, Katlein França, and Jonette Keri

Introduction

Acne vulgaris is a very common skin condition that affects individuals throughout their life, especially in their adolescent years [1]. It has been found that it affects over 80 % of adolescents and affects individuals of every race, ethnicity, and gender [2, 3]. Acne often persists throughout a patient's life and has therefore recently been considered a chronic disease [4, 5]. Because of the chronicity of this disorder, it can have lasting impact on the patient not only through the development of permanent physical scarring but also because of the psychosocial impact of this disorder [4, 6]. Numerous studies have shown the relationship between acne with social anxiety and depression [4–7]. This relationship has been illustrated further through a patient's marked psychological improvement following acne treatment and improvement [4–7].

There are four processes that are known to play a role in the formation of acne [2, 4, 8]. These processes include a change in keratinization that leads to comedo formation, increased sebum production, inflammation, and colonization by *Propionibacterium acnes* [2, 4]. Numerous treatment options are available in order to target the varied etiologies [5, 6]. For example, most treatments initially involve the combination of antibiotics with topical retinoids [5, 6]. Other therapies may also involve the use of lasers and light [5].

T. Patel, MD • S. Patel, MD • J. Keri, MD, PhD
Department of Dermatology and Cutaneous Surgery, University of Miami Miller School of Medicine, Miami, FL, USA

K. França, MD, PhD (✉)
Centro Studi per la Ricerca Multidisciplinare e Rigenerativa, Università Degli Studi "G. Marconi", Rome, Italy

Department of Dermatology and Cutaneous Surgery, Department of Psychiatry and Behavioral Sciences, Institute for Bioethics and Health Policy, University of Miami Miller School of Medicine, Miami, FL, USA
e-mail: k.franca@med.miami.edu

K. França, M. Jafferany (eds.), *Stress and Skin Disorders*,
DOI 10.1007/978-3-319-46352-0_15

The relationship between acne and stress is most clearly appreciated when speaking with patients who notably report this association [1, 5, 9]. As mentioned before, stress has often been associated as a result of the physical changes experienced by a patient who suffers from acne [4]. However, the reverse is also true as the body's stress response has also been related to an increase in the severity of acne [9]. This chapter, therefore, aims to investigate the unique relationship between acne and stress.

Acne and Stress

Psychological Stress

An association has been found in which reports show that acne lesions actually incite psychological stress [9]. This phenomenon is known as a psychophysiologic condition [10]. These conditions have been studied for many years by mental health professionals and include various other conditions including migraines and peptic ulcer disease [10]. The stress caused by acne affects various arenas in a patient's life including dressing, social interactions, and even schoolwork [1].

It has also been found that acne lesions are actually exacerbated by an underlying stressor [9]. Biofeedback relaxation and cognitive imagery techniques have been used to treat acne, thus illustrating that there is a relationship between acne and mental health and wellness [10–12]. These treatments specifically were found to significantly help treat acne in numerous patients [10]. This was confirmed further as termination of these therapies caused worsening of the patients' acne severity [10].

Research has been focused on determining the molecular mechanism that explains the relationship between acne and stress [8, 9, 11–13]. Stress has been known to activate cells that partake in acne pathogenesis [13]. This involvement is complex [11–13]. The hypothalamus and pituitary gland are involved in the stress response by ultimately causing the release of catecholamines and cortisol [13]. The skin, on the other hand, produces various neuropeptides [13]. These include factors such as corticotropin-releasing hormone (CRH) and substance P [11–13]. Studies have shown the role of CRH in the development of increased sebaceous lipids, which are present in acne [9]. Neuropeptide, substance P, also stimulates lipid synthesis in sebaceous cells upon release due to stress [11, 12]. Sebocytes have also been found to respond to other factors associated with a normal stress response including neuropeptide Y, melanocortins, and many others [9]. All of these factors work by causing an increase in the formation of inflammatory cytokines [9]. This eventually leads to proliferation, lipogenesis, and androgen metabolism in the sebocyte [9, 11, 12].

The relationship between stress and acne is complex [13]. Easily apparent is the effect that acne has on a patient's quality of life [13]. As stated previously, those affected by acne often experience psychological suffering as a consequence of their acne through depression and anxiety [13]. Studies have shown that patients with

acne are more likely to present with suicidal ideation [13]. Another significant finding in that study was that the mental health status of these patients often did not change in correlation with the disorder, thus indicating the importance of follow-up care [13]. Other studies, however, have found an improvement in stress and quality of life following improvement in acne severity [1]. On the same note, because of proven causal relationship between stress and acne, it is important for physicians to understand the etiology of stress for their patients as that may play a factor in the successful treatment of their acne [1]. Further, stress in general has been found to have a negative effect on wound healing, thus also propagating the effects it has on acne [11, 12].

Oxidative Stress

The role of oxidative stress has also been studied recently with regards to acne in the hopes of creating new therapies to treat a variety of skin conditions [2, 14, 15]. Oxidative stress is important because it is the result of the reaction of the body, more specifically neutrophils, in areas colonized by Propionibacterium acnes [15, 16]. The neutrophils lead to phagocytosis and development of inflammatory factors that eventually lead to the formation of reactive oxygen species which lead to tissue damage [15]. The body normally balances antioxidant defenses with reactive oxygen species with the help of superoxide dismutase and catalase [15, 17]. Disruptions in this balance such as when antioxidant levels are low or when there is an elevation in reactive oxygen species leads to oxidative stress [14, 15]. This stress is significant and may lead to DNA and membrane lipid damage at the site of inflammation and in surrounding healthy tissue [16]. Thus these new findings indicate that this process may be another cause of acne and another pathway that may be targeted by therapies moving forward [14].

Adult Female Acne

Although acne is often considered a disease of adolescence, studies have shown, however, that many adults also suffer from acne, especially adult females [9, 13, 18, 19]. About 14–54 % of adult females have reported suffering from acne [18]. Often, the patient's first experience with acne is in adulthood [18]. This is known as late-onset acne [18, 19]. Acne that continues from adolescence is known as persistent-acne [18, 19]. Adult acne is associated with specific hormonal and genetic factors that differ from acne of adolescence [7, 18]. Thus, the pathogenesis and treatment of adult versus adolescent acne may differ [18].

Adults, specifically, have been found to suffer from acne when faced with increased stress and anxiety in their lives [9, 18, 19]. These studies have been important because they have also illustrated a causal relationship with regards to stress

and acne exacerbation [9]. Adult females have also illustrated a greater psychological and emotional distress associated with their acne compared to adolescent patients [18]. It has been found that age, chronicity, and female gender are all characteristics that indicate a greater negative impact on the patient's quality of life when the individual is suffering from acne [19]. Although adult females tend to suffer from more moderate acne, negative self-perception of their disease increases with age [19]. This is also noted in a greater reporting of adult acne in self-surveys versus clinical assessments [7, 19]. It has even been found that adult acne is associated with increased unemployment rates [19]. Therefore, adult acne treatment may be quite complex, as it must address physical, psychological, emotional, and social challenges faced by the patient [19].

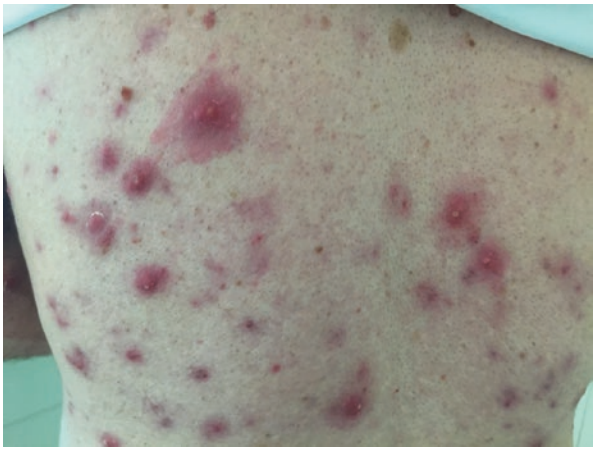
Rosacea and Stress

Rosacea is a skin condition most often found in fair, middle-aged, women that involves central facial flushing and erythema, rhinophyma, and telangiectasiae and papulopustular eruptions [9, 20]. This condition is also associated with stress and it has been found that certain emotions can exacerbate the disorder and even cause flushing [9, 20]. As in the pathogenesis of acne, the causal relationship between rosacea and stress is not well understood but it has been correlated to the formation of reactive oxygen species and inflammatory cytokines [9]. Flushing, specifically, is caused by central and autonomic responses to stress [20, 21]. This can have severe consequences on the patient's social interactions as it leads to anxiety and embarrassment [20, 21]. A study comparing the effects of stressful events in healthy patients and those with rosacea found that not only do patients with rosacea have a heightened response to stressors but also that stress also negatively affects their disease [9].

Rosacea is associated with increased psychiatric morbidity in patients in a disease severity-dependent manner [22]. It has been found that rosacea is often linked to depression, social anxiety, embarrassment, and overall mental distress [23, 24]. This lower quality of life is especially true in men [23, 24]. Thus, studies recommend applying psychological therapies along with dermatologic treatments when addressing the concerns of patients suffering from rosacea [23].

Conclusion

Thus, there is still a great deal of work that needs to be done in order to completely understand the full relationship between acne and other dermatologic conditions and stress. Studies completed thus far have been instrumental in providing insight into this phenomenon but the focus moving forward will undoubtedly aim to address the therapeutic interventions that should arise in order to successfully treat acne



Picture 15.1 A 18 year-old male patient with acne vulgaris on the back

with an ideal combination of both current pharmacologic therapies and behavioral interventions as well. Stress is a variable factor in one's life so these interventions will undoubtedly need to be adjusted as needed for the patient at specific moments in the course of his/her disease (Picture 15.1).

References

1. Tasoula E, Gregoriou S, Chalikias J, et al. The impact of acne vulgaris on quality of life and psychic health in young adolescents in Greece. Results of a population survey. An Bras Dermatol. 2012;87(6):862–9.
2. Suh DH, Kwon HH. What's new in the physiopathology of acne? Br J Dermatol. 2015;172 Suppl 1:13–9.
3. Kircik LH. Advances in the understanding of the pathogenesis of inflammatory acne. J Drugs Dermatol. 2016;15(1):s7–10.
4. Dawson AL, Dellavalle RP. Acne vulgaris. BMJ. 2013;346:f2634.
5. Thiboutot D, Gollnick H, Bettoli V, et al. New insights into the management of acne: an update from the Global Alliance to Improve Outcomes in Acne group. J Am Acad Dermatol. 2009;60(5 Suppl):S1–50.
6. Hahm BJ, Min SU, Yoon MY, et al. Changes of psychiatric parameters and their relationships by oral isotretinoin in acne patients. J Dermatol. 2009;36(5):255–61.
7. Lasek RJ, Chren MM. Acne vulgaris and the quality of life of adult dermatology patients. Arch Dermatol. 1998;134(4):454–8.
8. Eichenfield LF, Del rosso JQ, Mancini AJ, et al. Evolving perspectives on the etiology and pathogenesis of acne vulgaris. J Drugs Dermatol. 2015;14(3):263–72.
9. Orion E, Wolf R. Psychologic factors in the development of facial dermatoses. Clin Dermatol. 2014;32(6):763–6.
10. Koo JY, Smith LL. Psychologic aspects of acne. Pediatr Dermatol. 1991;8(3):185–8.
11. Lee WJ, Jung HD, Lee HJ, Kim BS, Lee SJ, Kim do W. Influence of substance-P on cultured sebocytes. Arch Dermatol Res. 2008;300(6):311–6.
12. Chiu A, Chon SY, Kimball AB. The response of skin disease to stress: changes in the severity of acne vulgaris as affected by examination stress. Arch Dermatol. 2003;139(7):897–900.

13. Misery L, Wolkenstein P, Amici JM, et al. Consequences of acne on stress, fatigue, sleep disorders and sexual activity: a population-based study. Acta Derm Venereol. 2015;95(4):485–8.
14. Sarici G, Cinar S, Armutcu F, Altinyazar C, Koca R, Tekin NS. Oxidative stress in acne vulgaris. J Eur Acad Dermatol Venereol. 2010;24(7):763–7.
15. Al-shobaili HA. Oxidants and anti-oxidants status in acne vulgaris patients with varying severity. Ann Clin Lab Sci. 2014;44(2):202–7.
16. Akamatsu H, Horio T, Hattori K. Increased hydrogen peroxide generation by neutrophils from patients with acne inflammation. Int J Dermatol. 2003;42(5):366–9.
17. Basak PY, Gultekin F, Kilinc I. The role of the antioxidative defense system in papulopustular acne. J Dermatol. 2001;28(3):123–7.
18. Dréno B. Treatment of adult female acne: a new challenge. J Eur Acad Dermatol Venereol. 2015;29 Suppl 5:14–9.
19. Holzmann R, Shakery K. Postadolescent acne in females. Skin Pharmacol Physiol. 2014;27 Suppl 1:3–8.
20. Patel S, Keri J. Rosacea and rhinophyma. In: Jafferany M, Franca K, editors. Geriatric psychodermatology: psychocutaneous disorders in the elderly. Saginaw: Nova Science Publishers, Inc; 2015.
21. Băr LH, Kuypers BR. Behaviour therapy in dermatological practice. Br J Dermatol. 1973;88(6):591–8.
22. Egeberg A, Hansen PR, Gislason GH, Thyssen JP. Patients with rosacea have increased risk of depression and anxiety disorders: a Danish nationwide cohort study. Dermatology (Basel). 2016;232(2):208–13.
23. Böhm D, Schwanitz P, Stock Gissendanner S, Schmid-Ott G, Schulz W. Symptom severity and psychological sequelae in rosacea: results of a survey. Psychol Health Med. 2014;19(5):586–91.
24. Moustafa F, Lewallen RS, Feldman SR. The psychological impact of rosacea and the influence of current management options. J Am Acad Dermatol. 2014;71(5):973–80.

Chapter 16
Stress Related Hair Disorders

Anna Skrok and Lidia Rudnicka

Introduction

Stress is an established and proven trigger of mental illness' development and stress-related disorders. It also provokes various skin and hair changes. The mechanisms are still not entirely discovered. Stress is a common possible cause of hair loss and other hair disorders. There have been published studies proving that stress alters hair growth and cycling in vivo in a murine model [1] confirmed by clinical observations of those disruptions in people.

Historically, samples of serum, saliva, and urine were used to measure cortisol levels [2]. Hair cortisol analysis is a new, non-invasive method providing an information about a previous cortisol secretion in response to stress [3, 4]. This innovative method could be useful primarily in the field of psychiatry, however it reflects a chronic stress, that commonly results in hair disorders, like alopecia, greying, trichotillomania or alopecia areata.

The existence of a 'brain-hair follicle axis' (BHA) has been postulated in recent years as the patomechanism of various skin changes triggered by a stress stimulus. It consists of a chain of stimulatory hormones and feedback loops under the control of higher cerebral centres determining its overall activity [5]. Cortisol is at the centre of a pathophysiological stress response. The brain-follicle axis explains the patomechanism of hair changes in case of stress-triggered hormonal changes, like hypercortisolism and up-regulation of CRH. Widely used topically active hair growth stimulator- minoxidil prevents a stress-triggered hair growth by down-regulation of the BHA [1]. As a result, it has been proven that minoxidil is not only effective in female androgenetic alopecia but, what is clinically often observed it helps numbers of patients with stress-induced hair loss.

A. Skrok, MD • L. Rudnicka, MD, Phd (✉)
Department of Dermatology, Medical University of Warsaw, Warszawa, Poland
e-mail: lidiarudnicka@gmail.com

K. França, M. Jafferany (eds.), *Stress and Skin Disorders*,
DOI 10.1007/978-3-319-46352-0_16

Patophysiology

For years stress has been suspected as a possible cause of hair loss [6], especially through an impact on hair follicle cycle.

The hair growth cycle consists of three main phases: anagen (growth phase), catagen (regression phase) and telogen (resting phase). Catagen is related to cessation of protein and pigment production, involution of the hair follicle and restructuring of the extracellular matrix. It precedes a telogen resting phase, when the hair follicle regresses. Increased telogen hairs ratio clinally cause hair loss [7, 8].

There is a great number of factors which have an impact on hair follicle cycle. A fascinating and composed pilo–neural–immune interactions and immune cells cross-react during the hair cycle. Numerous growth factors, cytokines, hormones and neuropeptides involved in a systemic stress response also act directly on hair cycle [9–11]. Stress causes a cascade of hormonal changes in the organism. Hormones affect follicular mesenchymal-epithelial interactions altering growing time, dermal papilla size and dermal papilla cell, keratinocyte and melanocyte activity [12]. Highly stress-vulnerable areas of the hair follicle are stem cells in the bulge region. Stress -changes could have wide-ranging consequences. This direct impact of stress and hormonally driven changes in hair cycle are explained by novel data indicating the existence of a 'brain-hair follicle axis' (BHA) [1]. It has been proven that there are hormones produced locally in the skin, where adequate receptors are also located. Cortisol and corticotropin-releasing hormone (CRH), the main hormones of the stress, are upregulated by stress, being released directly in the skin as a part of the BHA [13]. This causes a direct proinflammatory effect or activates mast cells. Among the neuromediators neuropeptide substance P (SP) is proposed to be a potential mediator by which stress exerts its inhibitory influence on hair growth [14, 15]. Stress-induced hair follicle apoptosis could also be driven by activated perifollicular macrophages and through a degranulation of mast cells which leads to an intense local inflammation. That results in destruction of the hair root as a consequence of stress-mediated mast cells degranulation [16]. Recently, it has been proven that exposure to an experimental psychoemotional stressor provokes a premature catagen and results in excessive telogen hairs ratio [13]. Changes of the hair growth cycle therefore result in alopecia. Telogen effluvium and alopecia areata are the most tightly associated with stress due to pathogenesis. However every type of hair loss results in a psychological impact that lowers quality of life and aggravates the stress.

Telogen Effluvium

Telogen effluvium (TE) was first described by Kligman in 1961. It is a most common cause of diffuse hair loss. There is a wide variety of potential triggers evoking telogen effluvium hair loss. Stress is one of them. Diffuse shedding of telogen hair takes place 3–4 months after a triggering, stressful event. It is diagnosed when the hair

loss refers to changes in trichogram with anagen to telogen ratio less than 70:30 % of hairs [17]. Telogen effluvium could occur as an acute (ATE) and chronic telogen effluvium (CTE). When acute telogen effluvium is related do stressful events, chronic TE is rather accompanying chronic illnesses. A sudden onset and great amounts of shedding hairs could bring some fear and upregulate existing psychological problems. The triggering factors are numerous. It could be a stress, an illness, metabolic changes, hormonal fluctuations, diet and malnutrition, vitamins and minerals deficiencies [18]. However, the severity of the hair loss here depends on the intensity and duration of exposure, rather than on the type of a trigger [19]. It also should be noticed that psychological stressful event and chronic imflammatory illnesses which cause a medical stress to organism result in the same hormonal and BHA changes in hair follicle cycling.

Despite the diagnostic process, the trigger in telogen effluvium (especially in its chronic type) often cannot be clearly defined. Also the real frequency of TE in the population seems to be underestimated as some part of the cases, especially those of chronic telogen effluvium are subclinical [20]. The most typical target group of acute TE are women after the childbirth (30–50 % of women have postpartum TE). However, in repeated studies women, especially older in age, seem to be more susceptible to acute form of telogen effluvium [21]. According to Whiting chronic telogen effluvium probably affects only women [22]. The most frequently it affects women aged 30–60 years and starts abruptly with or without a recognizable initiating factor. CTE is in fact considered as an age-related problem in women [23]. In TE a normal thickness of hairs and characteristic shorter regrowing hairs especially in the frontal and bitemporal areas could be observed in trichoscopy. Few patients may have a marked bitemporal recession. Hair pull test is commonly positive. However, a diagnosis of TE is always out of the exclusion of other causes of chronic diffuse hair loss [20].

Alopecia Areata

Alopecia areata (AA) is a nonscarring loss of hair on the skin of the head with possible affecting the entire skin of the head (alopecia totalis) or the entire body (alopecia universalis). The frequency in general population is estimated to be 0.2 and 2.1 % amongst dermatological ambulatory patients (Rochester Epidemiology Project, 1990–2009) [24]. Alopecia areata frequently starts in childhood, and, 60 % of patients with AA are younger than 20 [25]. The occurrence of the disease depends on the interaction between genetic factors, autoimmune and hormonal changes, psychological factors and disorders of the nervous system. The role of psychological factors, like acute or chronic stress in the course of AA is especially important [26, 27]. An emotional trauma associated with actual or symbolic loss, like death of a close individual, divorce, loss of job etc., commonly occurred prior to the first episode of the disease in 66 % of patients [24]. Other disorders that can also be triggered by a stress and/or commonly coexist with AA are: diabetes, Hashimoto disease, psoriasis, atopic dermatitis, urticaria, angioedema. As it has been proven

exposure to chronic stress induce a chronic course of alopecia areata. It is at least partly explained by a correlation of stress and changes in brain-hypothalamic-pituitaryadrenal axis (BHA), or immune and endocrine systems. However the exact patomechanism is still under investigation [28].

Trichotillomania

Trichotillomania is a form of traction alopecia resulting from habitual, repetitive removal of one's own hair [29–31]. From a psychiatric point of view, this term encompasses an entire syndrome of pathologic hair pulling. According to the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV), the diagnostic criteria for trichotillomania are (a) the recurrent pulling out of one's own hair, resulting in noticeable hair loss; (b) an increasing sense of tension immediately before pulling out the hair or when attempting to resist the behavior; (c) pleasure, gratification, or relief when pulling out the hair; (d) hair pulling that cannot be better accounted for by another mental disorder; and (e) significant distress or impairment in social, occupational, or other important areas of functioning [32]. This definition describes a mental disorder that perhaps should be called trichotillomania syndrome. Accordingly, the validity of the DSM-IV criteria recently was questioned by several authors [32, 33]. From a dermatologist's point of view, trichotillomania is self-induced hair loss due to the repetitive pulling of one's own hair [34, 35].

The condition is most frequently among children between the ages of 9 and 13 years and with a female predominance of 70–93 % [34]. Adult-onset trichotillomania possibly reveal an underlying psychiatric disorder [34]. Clinically, patients present patches of irregular-length hair or hairless areas. Commonly, the vertex is affected, what is characteristically named "tonsure trichotillomania," or the "Friar Tuck sign". Pull test is negative. Patients may pull hair at multiple sites, including the eyebrows, eyelashes, face, arms, legs, and pubic area [34, 35].

Trichotillomania is currently easily diagnosed by trichoscopy. The flame hairs, coiled hairs and presence of multiple broken hairs in a field of view are now considered the most typical trichoscopy signs of trichotillomania.

Stress and Chemotherapy Induced Alopecia

Chemotherapy-induced alopecia (CIA) is almost a constant side effect of chemotherapy [36]. The incidence and severity of CIA could by various and dependent on the chemotherapy protocol, but general prevalence of CIA is estimated to range from 65 to 85 % of chemotherapy patients [37]. Hair loss in this condition is associated with impaired regrowth of hair that are shorter, thinner and more fragile. Mechanisms connected to this process are multiple and depending on the type of chemotherapeutic agent. CIA is usually linked to apoptosis-related damage to the hair follicle [38].

It affects mainly scalp hair causing widespread alopecia especially in women and affecting the most intensely frontal and occipital hairlines [37, 39, 40]. It starts as anagen effluvium or rarely as telogen effluvium [41] in the first weeks after the initiation of the therapy [42]. The severity and the exact mechanism depends on the agent. Reversibility of alopecia is typical. Coping with cancer and with chemotherapy is a highly stressful situation. Associated telogen effluvium starting with a delay after anagen hair loss commonly takes part in a burden of alopecia.

The psychosocial impact of CIA is problematic, especially in women. Chemotherapy-induced alopecia stigmatizes patients and isolates them from the society. For women it is even more traumatic than losing breast [43, 44]). In a study with 638 cancer patients receiving chemotherapy, 86.6 % of women were worried about changes in their appearance and hair loss [26]. Although chemotherapy-induced hair loss is a stressor for both women and men, existing studies confirm that female patients concern hair loss as a more severe stressor than it is concerned among male cancer patients [24]. Among 47 % of female cancer patients who considered hair loss to be the most traumatic aspect of chemotherapy, 8 % consider a decision about a withdrawal of the chemotherapy because of the expected hair loss [45]. A treatment of chemotherapy induced alopecia is highly needed, but still there are no recommended models of prevention and therapy. As there is still no approved treatment for patients with CIA, the research seeking for the drug, especially topical is highly needed. There are numbers of ongoing studies, however more studies must be performed to find the way out of this problem.

Cicatricial Alopecia

Cicatricial alopecia (CA) term refers to scarring hair loss. The prevalence according to different studies ranges from 2 to 7 % of he hair loss causes [46]. The causes of CA could be classified as primary (PCA, primary cicatricial alopecias), secondary to various factors or hereditary/developmental defects [47, 48]. Cicatricial alopecia may occur secondary to trauma (burns, radiation, traction), extensive infiltrative processes (morphea, scleroderma, sarcoidosis, carcinomas) or infections [49]. In contrast, primary cicatricial alopecias (PCA) are a group of disorders, in which the hair follicle is the main target of destructive inflammation resulting in irreversible hair loss [48]. Primary cicatricial alopecias (PCA) represent uncommon inflammatory disorders that result in permanent loss of scalp hair. According to hormonal and neurophysiological changes during stressfull events, stress could be placed among factors which trigger or aggravate primary cicatricial alopecias.

Greying as a Result of Oxidative Stress

The perception of the grey hair is derived from the mixture of white non-pigmented and pigmented scalp hairs and it is called canities/or greying.

A relatively small number of melanocytes is capable to produce long pigmented hair shaft [50] however this enourmous capacity of melanocytes activity is greatest in the first few hair cycles and decreases with time as the cessation of melanogenesis seems to be genetically programmed. In certain situations triggered by a psychological stressor or resulting in a metabolic stress a premature or increased greying process could be observed [51]. The underlying causes of this phenomenon are genetic and hormonal changes that come along with age and other possible coexisting factors. The cessation of melanogenesis resulting in a clinically grey hair shaft correlates with a reduction in tyrosinase activity of hair bulbar melanocytes [52]. It is also thought that canities could be correlated with changes in innervation and neuropeptide stimulation, what could possibly refer to premature greying in some metabolic disturbances [53, 54]. Grey hair include only few melanocytes, highly vacuolated, defective as a result of oxidative stress [50, 55]. Metabolic and nutritional status, racial and gender differences, hormones, genes and age-related changes all impact on the regulation of hair pigmentation.

Coping with Stress Induced Hair Loss

Stress and hair loss are tightly associated. However, up to date, no specific medical intervention is available to manage stress-induced hair loss. On the other hand, stress-induced hair loss reduces the quality of life of affected patients and so, effective treatment of alopecia is more and more needed among patients who seek for help.

Minoxidil (MXL) was developed to treat hypertension. This ATP-sensitive potassium channel opener, has next been discovered as a topically applied stimulator of hair regrowth in androgenetic alopecia (AGA) [56–58] prolonging the anagen [59]. In that mechanism stress-induced hair follicle changes can be prevented by MXL. Application of 5 % MXL results in a significant increase of Ki67p, marker of proliferating intrafollicular cells in the bulb, bulge and infundibulum. In addition MXL treatment had been demonstrated to cause an early initiation of anagen, decreasing period of kenogen with lack of hair [60].

Minoxidil then reverts stress-driven changes in hair follicle cycle and stress-induced hair loss (e.g. in patients with alopecia areata (AA) or telogen effluvium) [1, 6]. Its mechanism of action with respect to the stimulation of hair growth is unknown, but it appears to be independent of vasodilatation [61].

Psychological Dimension of Stress Correlating with Hair Loss

Hair loss seems to be a medically benign condition, however it is a significant psychosocial burden for majority of affected patients.

It has been noted that psychiatric disorders are significantly more common among patients with alopecia. Resulting in a decreased quality of life, alopecia

causes additional stress, or mood disorders. A higher level of anxiety and depression, lower self esteem, poorer quality of life, and poorer body image almost constantly characterize patients with alopecia [45, 62]. This phenomenon seems not to be dependent on the age or a severity of the baldness. It seriously alters the satisfaction of life and patients themselves especially among women [63]. Women who experienced hair loss after chemotherapy experience constantly four reactions to CIA: they were not prepared or shocked or embarrassed [45, 64]. In fact hair loss for some women has been psychologically more difficult than the loss of a breast through breast cancer [64].

Recently, to assess the impact of diseases on patients' life QoL scales have been established. To date we know few dermatology-specific questionnaires, like: the Skindex [65], the Dermatology Life Quality Index (DLQI) [66], the Dermatology Quality of Life Scales (DQOLS) [67], the Dermatology Specific Quality of Life (DSQL) [68] the Qualità di Vita Italiana in Dermatologia (QUAVIDERM), HADS or UCLA-LS. However, the real psychosocial impact of hair loss is not adequate when using those scales, so there have been some specific-for hair loss questionnaires proposed (ex. PALSOS-PM) [69].

It should be remembered that dermatological treatment of alopecia is very frequently not sufficient in the case of the problem which aggravates psychosocial problems and therefore patients with hair disorders are a potential group of people needing additional psychological support [70]. It is worth to highlight that patients with scarring alopecia have poorer quality of life than patients with non-scarring alopecia [71], probably due to worse prognosis. A recent study of patients with lichen planopilaris and frontal fibrosing alopecia confirm that women are more affected by hair loss than men, like among cancer patients.

References

1. Arck PC, Handjiski B, Peters EM, Hagen E, Klapp BF, Paus R. Topical minoxidil counteracts stress-induced hair growth inhibition in mice. Exp Dermatol. 2003;12(5):580–90.
2. Pruessner JC, Kirschbaum C, Meinlschmid G, Hellhammer DH. Two formulas for computation of the area under the curve represent measures of total hormone concentration versus time-dependent change. Psychoneuroendocrinology. 2003;28(7):916–31.
3. Gow R, Thomson S, Rieder M, Van Uum S, Koren G. An assessment of cortisol analysis in hair and its clinical applications. Forensic Sci Int. 2010;196(1–3):32–7.
4. Karlen J, Ludvigsson J, Frostell A, Theodorsson E, Faresjo T. Cortisol in hair measured in young adults – a biomarker of major life stressors? BMC Clin Pathol. 2011;11:12.
5. Papadopoulos AS, Cleare AJ. Hypothalamic-pituitary-adrenal axis dysfunction in chronic fatigue syndrome. Nat Rev Endocrinol. 2012;8(1):22–32.
6. Paus R. Stress and the skin. Exp Dermatol. 2001;10(5):367.
7. Sehgal VN, Srivastava G, Aggarwal AK, Midha R. Hair biology and its comprehensive sequence in female pattern baldness: treatment modalities – part III. Skinmed. 2013;11(5):287–90.
8. Sehgal VN, Srivastava G, Aggarwal AK, Midha R. Hair biology and its comprehensive sequence in female pattern baldness: diagnosis and treatment modalities – Part I. Skinmed. 2013;11(1):39–45; quiz 45.

9. Ito T. Hair follicle is a target of stress hormone and autoimmune reactions. J Dermatol Sci. 2010;60(2):67–73.
10. Ito N, Sugawara K, Bodo E, Takigawa M, van Beek N, Ito T, Paus R. Corticotropin-releasing hormone stimulates the in situ generation of mast cells from precursors in the human hair follicle mesenchyme. J Invest Dermatol. 2010;130(4):995–1004.
11. Maurer M, Fischer E, Handjiski B, von Stebut E, Algermissen B, Bavandi A, Paus R. Activated skin mast cells are involved in murine hair follicle regression (catagen). Lab Invest. 1997;77(4):319–32.
12. Goryachkina VL, Ivanova MY, Tsomartova DA, Kartashkina NL, Kuznetsov SL. Regulation of hair follicle cycle. Morfologiia. 2014;146(5):83–7.
13. Arck PC, Handjiski B, Hagen E, Joachim R, Klapp BF, Paus R. Indications for a 'brain-hair follicle axis (BHA)': inhibition of keratinocyte proliferation and up-regulation of keratinocyte apoptosis in telogen hair follicles by stress and substance P. FASEB J. 2001;15(13):2536–8.
14. Liu N, Wang LH, Guo LL, Wang GQ, Zhou XP, Jiang Y, Shang J, Murao K, Chen JW, Fu WQ, Zhang GX. Chronic restraint stress inhibits hair growth via substance P mediated by reactive oxygen species in mice. PLoS One. 2013;8(4):e61574.
15. Wang L, Guo LL, Wang LH, Zhang GX, Shang J, Murao K, Chen DF, Fan XH, Fu WQ. Oxidative stress and substance P mediate psychological stress-induced autophagy and delay of hair growth in mice. Arch Dermatol Res. 2015;307(2):171–81.
16. Kawana S, Liang Z, Nagano M, Suzuki H. Role of substance P in stress-derived degranulation of dermal mast cells in mice. J Dermatol Sci. 2006;42(1):47–54.
17. McElwee KJ, Sinclair R. Hair physiology and its disorders. Drug Discovery Today: Disease Mechanisms. 2008;5(2):e163–71.
18. Whiting DA. Chronic telogen effluvium. Dermatol Clin. 1996;14(4):723–31.
19. Piraccini BM, Iorizzo M, Rech G, Tosti A. Drug-induced hair disorders. Curr Drug Saf. 2006;1(3):301–5.
20. Harrison S, Sinclair R. Telogen effluvium. Clin Exp Dermatol. 2002;27(5):389–5.
21. Nnoruka EN, Obiagboso I, Maduechesi C. Hair loss in children in South-East Nigeria: common and uncommon cases. Int J Dermatol. 2007;46 Suppl 1:18–22.
22. Whiting DA. Chronic telogen effluvium: increased scalp hair shedding in middle-aged women. J Am Acad Dermatol. 1996;35(6):899–906.
23. Horenstein VD, Williams LE, Brady AR, Abee CR, Horenstein MG. Age-related diffuse chronic telogen effluvium- type alopecia in female squirrel monkeys (Saimiri boliviensis boliviensis). Comp Med. 2005;55(2):169–74.
24. Mirzoyev SA, Schrum AG, Davis MD, Torgerson RR. Lifetime incidence risk of alopecia areata estimated at 2.1 % by Rochester Epidemiology Project, 1990–2009. J Invest Dermatol. 2014;134(4):1141–2.
25. Gulec AT, Tanriverdi N, Duru C, Saray Y, Akcali C. The role of psychological factors in alopecia areata and the impact of the disease on the quality of life. Int J Dermatol. 2004;43(5):352–6.
26. McDonagh AJ, Messenger AG. The aetiology and pathogenesis of alopecia areata. J Dermatol Sci. 1994;7(Suppl):S125–35.
27. McDonagh AJ, Messenger AG. The pathogenesis of alopecia areata. Dermatol Clin. 1996;14(4):661–70.
28. de Hollanda TR, Sodre CT, Brasil MA, Ramos ESM. Quality of life in alopecia areata: a case–control study. Int J Trichol. 2014;6(1):8–12.
29. Witkowski AM, Schwartz RA, Janniger CK. Trichotillomania: an important psychocutaneous disorder. Cutis. 2010;86(1):12–6.
30. Franklin ME, Zagrabbe K, Benavides KL. Trichotillomania and its treatment: a review and recommendations. Expert Rev Neurother. 2011;11(8):1165–74.
31. Walther MR, Snorrason I, Flessner CA, Franklin ME, Burkel R, Woods DW. The trichotillomania impact project in young children (TIP-YC): clinical characteristics, comorbidity, functional impairment and treatment utilization. Child Psychiatry Hum Dev. 2014;45(1):24–31.
32. Lochner C, Stein DJ, Woods D, Pauls DL, Franklin ME, Loerke EH, Keuthen NJ. The validity of DSM-IV-TR criteria B and C of hair-pulling disorder (trichotillomania): evidence from a clinical study. Psychiatry Res. 2011;189(2):276–80.

33. Stein DJ, Grant JE, Franklin ME, Keuthen N, Lochner C, Singer HS, Woods DW. Trichotillomania (hair pulling disorder), skin picking disorder, and stereotypic movement disorder: toward DSM-V. Depress Anxiety. 2010;27(6):611–26.
34. Sah DE, Koo J, Price VH. Trichotillomania. Dermatol Ther. 2008;21(1):13–21.
35. Hautmann G, Hercogova J, Lotti T. Trichotillomania. J Am Acad Dermatol. 2002;46(6):807–21; quiz 22–6.
36. Cline BW. Prevention of chemotherapy-induced alopecia: a review of the literature. Cancer Nurs. 1984;7(3):221–8.
37. Trueb RM. Chemotherapy-induced hair loss. Skin Therapy Lett. 2010;15(7):5–7.
38. Schilli MB, Paus R, Menrad A. Reduction of intrafollicular apoptosis in chemotherapy-induced alopecia by topical calcitriol-analogs. J Invest Dermatol. 1998;111(4):598–604.
39. Chon SY, Champion RW, Geddes ER, Rashid RM. Chemotherapy-induced alopecia. J Am Acad Dermatol. 2012;67(1):e37–47.
40. Yeager CE, Olsen EA. Treatment of chemotherapy-induced alopecia. Dermatol Ther. 2011;24(4):432–42.
41. Yun SJ, Kim SJ. Hair loss pattern due to chemotherapy-induced anagen effluvium: a cross-sectional observation. Dermatology. 2007;215(1):36–40.
42. Wang J, Lu Z, Au JL. Protection against chemotherapy-induced alopecia. Pharm Res. 2006;23(11):2505–14.
43. Benjamin B, Ziginskas D, Harman J, Meakin T. Pulsed electrostatic fields (ETG) to reduce hair loss in women undergoing chemotherapy for breast carcinoma: a pilot study. Psychooncology. 2002;11(3):244–8.
44. Pozo-Kaderman C, Kaderman RA, Toonkel R. The psychosocial aspects of breast cancer. Nurse Pract Forum. 1999;10(3):165–74.
45. McGarvey EL, Baum LD, Pinkerton RC, Rogers LM. Psychological sequelae and alopecia among women with cancer. Cancer Pract. 2001;9(6):283–9.
46. Whiting DA. Cicatricial alopecia: clinico-pathological findings and treatment. Clin Dermatol. 2001;19(2):211–25.
47. Ohyama M. Primary cicatricial alopecia: recent advances in understanding and management. J Dermatol. 2012;39(1):18–26.
48. Dogra S, Sarangal R. What's new in cicatricial alopecia? Indian J Dermatol Venereol Leprol. 2013;79(5):576–90.
49. Olsen E, Stenn K, Bergfeld W, Cotsarelis G, Price V, Shapiro J, Sinclair R, Solomon A, Sperling L, Whiting D. Update on cicatricial alopecia. J Invest Dermatol Symp Proc/Soc Invest Dermatol, Inc [and] Eur Soc Dermatol Res. 2003;8(1):18–9.
50. Van Neste D, Tobin DJ. Hair cycle and hair pigmentation: dynamic interactions and changes associated with aging. Micron. 2004;35(3):193–200.
51. Keogh EV, Walsh RJ. Rate of greying of human hair. Nature. 1965;207(999):877–8.
52. Tobin DJ, Paus R. Graying: gerontobiology of the hair follicle pigmentary unit. Exp Gerontol. 2001;36(1):29–54.
53. Lerner AB. Gray hair and sympathectomy. Report of a case. Arch Dermatol. 1966;93(2):235–6.
54. Levine N, Sheftel SN, Eytan T, Dorr RT, Hadley ME, Weinrach JC, Ertl GA, Toth K, McGee DL, Hruby VJ. Induction of skin tanning by subcutaneous administration of a potent synthetic melanotropin. JAMA. 1991;266(19):2730–6.
55. Nordlund JJ. The pigmentary system and inflammation. Pigment Cell Res/sponsored by the Eur Soc Pigment Cell Res Int Pigment Cell Soc. 1992;5(5 Pt 2):362–5.
56. Meidan VM, Touitou E. Treatments for androgenetic alopecia and alopecia areata: current options and future prospects. Drugs. 2001;61(1):53–69.
57. Zappacosta AR. Reversal of baldness in patient receiving minoxidil for hypertension. N Engl J Med. 1980;303(25):1480–1.
58. Sinclair RD. Management of male pattern hair loss. Cutis. 2001;68(1):35–40.
59. Buhl AE, Waldon DJ, Baker CA, Johnson GA. Minoxidil sulfate is the active metabolite that stimulates hair follicles. J Invest Dermatol. 1990;95(5):553–7.
60. Kamiya T, Shirai A, Kawashima S, Sato S, Tamaoki T. Hair follicle elongation in organ culture of skin from newborn and adult mice. J Dermatol Sci. 1998;17(1):54–60.

61. Kubilus J, Kvedar JC, Baden HP. Effect of minoxidil on pre- and postconfluent keratinocytes. J Am Acad Dermatol. 1987;16(3 Pt 2):648–52.
62. Carpenter JS, Brockopp DY. Evaluation of self-esteem of women with cancer receiving chemotherapy. Oncol Nurs Forum. 1994;21(4):751–7.
63. Girman CJ, Hartmaier S, Roberts J, Bergfeld W, Waldstreicher J. Patient-perceived importance of negative effects of androgenetic alopecia in women. J Womens Health Gend Based Med. 1999;8(8):1091–5.
64. Freedman TG. Social and cultural dimensions of hair loss in women treated for breast cancer. Cancer Nurs. 1994;17(4):334–41.
65. Dubois M, Baumstarck-Barrau K, Gaudy-Marqueste C, Richard MA, Loundou A, Auquier P, Grob JJ. Quality of life in alopecia areata: a study of 60 cases. J Invest Dermatol. 2010;130(12):2830–3. Epub 2010/08/20. doi: 10.1038/jid.2010.232. PubMed PMID: 20720568.
66. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI) – a simple practical measure for routine clinical use. Clin Exp Dermatol. 1994;19(3):210–6.
67. Morgan M, McCreedy R, Simpson J, Hay RJ. Dermatology quality of life scales – a measure of the impact of skin diseases. Br J Dermatol. 1997;136(2):202–6.
68. Anderson RT, Rajagopalan R. Development and validation of a quality of life instrument for cutaneous diseases. J Am Acad Dermatol. 1997;37(1):41–50.
69. Fabbrocini G, Panariello L, De Vita V, Vincenzi C, Lauro C, Nappo D, Ayala F, Tosti A. Quality of life in alopecia areata: a disease-specific questionnaire. J Eur Acad Dermatol Venereol. 2013;27(3):e276–81.
70. Sehgal VN, Kak R, Aggarwal A, Srivastava G, Rajput P. Male pattern androgenetic alopecia in an Indian context: a perspective study. J Eur Acad Dermatol Venereol: JEADV. 2007;21(4):473–9.
71. Katoulis AC, Christodoulou C, Liakou AI, Kouris A, Korkoliakou P, Kaloudi E, Kanelleas A, Papageorgiou C, Rigopoulos D. Quality of life and psychosocial impact of scarring and non-scarring alopecia in women. J Dtsch Dermatol Ges. 2015;13(2):137–42.

Chapter 17
Seborrheic Dermatitis

Clinton Enos, Tulsie Patel, Shailee Patel, and Katlein França

Introduction

Seborrheic dermatitis (SD) is a chronic relapsing inflammatory process in the skin characterized generally by erythematous macules and patches with overlying, flaking white or yellow scale. The affected areas are commonly described as being greasy, which correlates with locals of greater sebaceous gland density (e.g. scalp, face, upper chest, and back) [1–5]. SD is one of the most common diseases of the skin with a prevalence of 11.6 % reported in the United States of America [6]. SD can occur at any age, however its occurrence is reported to peak in two age groups: infants (<3 months) and adults ages 30–60 years old [4, 5, 7]. SD has multiple clinical variations depending on the individual and the region of the skin involved. As such, SD has been identified as both a primary skin disease as well as a sign of underlying disease. The variants can be considered by the population they impact: pediatric, adults, special populations (immunocompromised, neurologic disorders), and iatrogenic.

In the pediatric population, an infantile variant affects upwards of 70 % of infants within the first three months of life [2, 4, 6]. When it affects the scalp, infantile SD has been commonly referred to as "cradle-cap" and consists of thick, greasy scale

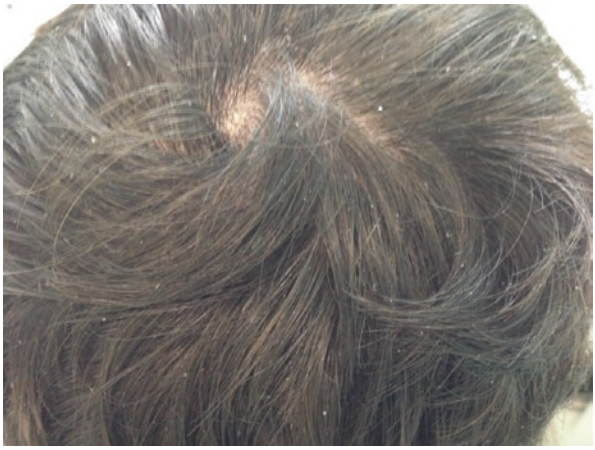
C. Enos, MD
Eastern Virginia Medical School, Norfolk, VA, USA

T. Patel, MD • S. Patel, MD
Department of Dermatology and Cutaneous Surgery, University of Miami Miller School of Medicine, Miami, FL, USA

K. França, MD, PhD (✉)
Centro Studi per la Ricerca Multidisciplinare e Rigenerativa, Università Degli Studi "G. Marconi", Rome, Italy

Department of Dermatology and Cutaneous Surgery, Department of Psychiatry and Behavioral Sciences, Institute for Bioethics and Health Policy, University of Miami Miller School of Medicine, Miami, FL, USA
e-mail: k.franca@med.miami.edu

K. França, M. Jafferany (eds.), *Stress and Skin Disorders*,
DOI 10.1007/978-3-319-46352-0_17



Picture 17.1 A 32-year old male patient with seborrheic dermatitis in the scalp

on the vertex [5, 8]. Infants may also be affected in flexural areas and present with an apparent diaper rash. Flaking on the central face, ears, and forehead may also occur in infants. SD in infants tends to have a good prognosis and self-resolves within a few-weeks of presentation [9]. If generalized SD occurs, a concern for an immunodeficiency may be warranted [5]. Leiner's disease has been reported in infants with generalized SD and concomitant diarrhea and failure to thrive [10]. In children, SD affecting the scalp may present as pityriasis amiantacea, which consists of thick scales encircling and matting down tufts of hair [2]. Temporary or permanent alopecia has the potential to result from these, which can significantly impact self-image and quality of life [11, 12]

In healthy adults, SD impacts 1–3 % of the population, with the face and scalp being the most frequently affected areas [7] (Picture 17.1). Pityriasis capitis, often referred to as dandruff, consists of mild SD of the scalp with scale. Scaling can also be seen around the ears, central face, nasolabial folds, and beard areas [2, 5]. SD can affect the margin of the eyelid (blepharitis), causing erythema and flaky debris that can fall into the eye leading to conjunctival irritation and red eye [2, 13]. Flexural regions are also commonly involved, especially retroauricular areas, the inner thighs, the genitalia, and the breast folds [2, 5]. The course of SD includes periods of remission and flares, with number of episodes ranging from 3 to 7.8 per year [7, 14].

The incidence of SD has been shown to be increased in special populations, specifically those who are immunocompromised (especially patients with HIV/AIDS) and those with Parkinsonism or other neurologic disease [4, 5]. In the HIV/AIDS population the incidence increases as high as 83 %, depending on the population studied [4, 15, 16]. The incidence is not only increased but also a more diffuse and inflammatory form of SD has been described in patients with HIV/AIDS [15, 17]. There is some debate as to whether the severity of SD correlates with severity of HIV-1 infection [18–20]. Still, the association of SD in HIV/AIDS is significant: of the HIV-patients studied in an infectious disease clinic in 2010, 98 % were impacted by some dermatologic finding, the second most common (31 %) being SD [21].

Associations between SD and Parkinson's disease have been linked to increased sebum excretion ratios, increased yeast density, as well as high phosphatase and lipase activity in a recent laboratory-based study [22]. Other reported factors include increased levels of circulating melanocytic stimulating hormone and decreased motility of the face [23, 24]. There is an interesting connection to neurologic stress and SD with reports describing unilateral SD following nerve lesions [25, 26]. SD has also been linked to familial amyloidotic polyneuropathy and Trisomy 21 [27, 28]. Few cases of SD as a paraneoplastic syndrome have also been described [29–32].

SD may be an undesired side-effect following treatment with psoralen and ultraviolet A light [33]. SD has also been associated with erlotinib and sorafenib use [2].

Seborrheic Dermatitis and Stress

The cause of SD is multifactorial but incompletely understood. Endogenous factors such as lipids, hormones, and the host immune system as well as exogenous factors including seasonality and the skin flora, in particular *Malassezia* species, have been discussed [4, 34]. A recurring factor in the appearance of SD episodes has been the psychological status of the patient: stress, anxiety, and emotion have been suggested and described as triggering flares [7, 14, 35–38]. Stress and psychological comorbidities have commonly been accepted to be linked with exacerbations of dermatologic disease, including SD [35, 38–40]. Likewise, dermatologic disease has been known to negatively impact quality of life [40, 41]. Formal studies of the link between SD and stress are few. A study of 2159 patients with SD found that the most common clinical profile included a history of stress, depression, or fatigue prior to the flare 76.4 % ($P < .0001$) [7]. In a study of 82 patients, Misery et al. found that stress was reported as the main triggering factor, whether it be the initial outbreak or a flare [37]. The stress associated with these flares was more associated with anxiety than depression; however, based on the Beck Depression Index Score, patients with facial involvement were more depressed [37]. Öztas et al. reported increased dermatology life quality index (DLQI) scores compared to healthy controls in patients with SD and suggested that SD may predispose patients to depression [36]. In a recent study by Araya et al., 28.3 % of participants identified emotional stress as a trigger for their SD outbreak [14]. Further, using the DLQI, Araya et al. report that SD has a moderate impact on patient quality of life, however, of note 3.6 % of patients reported an extreme affect; embarrassment was among the greatest complaints [14].

Conclusion

SD is a common dermatologic disease with a varying clinical course and degree of severity. The link between stress and SD, both as an exacerbating factor and as a consequence of the disease, should be carefully considered when caring for patients.

Management of both patients' psychological wellbeing and skin will have a potential synergistic effect on prognosis. Special attention should be given to patients with life-altering comorbidities in order to anticipate SD flares and to aid in the patients' ability to maintain a positive and realistic outlook. It is highly suggested to inform all patients that SD is likely to recur and that ongoing treatment may be necessary. Ultimately, more well designed, large studies are required to better understand the relationship between stress and SD, and how co-management of the mind and the skin can impact prognosis.

References

1. Gary G. Optimizing treatment approaches in seborrheic dermatitis. J Clin Aesthet Dermatol. 2013;6:44–9.
2. Naldi L, Rebora A. Clinical practice. Seborrheic dermatitis. N Engl J Med. 2009;360:387–96.
3. Berk T, Scheinfeld N. Seborrheic dermatitis. Pharm Ther. 2010;35:348–52.
4. Gupta AK, Bluhm R. Seborrheic dermatitis. J Eur Acad Dermatol Venereol JEADV. 2004;18:13–26; quiz 19–20.
5. Schwartz RA, Janusz CA, Janniger CK. Seborrheic dermatitis: an overview. Am Fam Physician. 2006;74:125–30.
6. Johnson MT, Roberts J. Skin conditions and related need for medical care among persons 1-74 years. United States, 1971–1974. Vital Health Stat 11. 1978:i–v, 1–72.
7. Peyrí J, Lleonart M, Grupo español del Estudio SEBDERM. Clinical and therapeutic profile and quality of life of patients with seborrheic dermatitis. Actas Dermosifiliogr. 2007;98:476–82.
8. Janniger CK. Infantile seborrheic dermatitis: an approach to cradle cap. Cutis. 1993;51:233–5.
9. Ooi ET, Tidman MJ. Improving the management of seborrhoeic dermatitis. Practitioner. 2014;258:23–6, 3.
10. Sonea MJ, Moroz BE, Reece ER. Leiner's disease associated with diminished third component of complement. Pediatr Dermatol. 1987;4:105–7.
11. Sarifakioglu E, Yilmaz AE, Gorpelioglu C, Orun E. Prevalence of scalp disorders and hair loss in children. Cutis. 2012;90:225–9.
12. Williamson D, Gonzalez M, Finlay AY. The effect of hair loss on quality of life. J Eur Acad Dermatol Venereol JEADV. 2001;15:137–9.
13. Wolf R, Orion E, Tüzün Y. Periorbital (eyelid) dermatides. Clin Dermatol. 2014;32:131–40.
14. Araya M, Kulthanan K, Jiamton S. Clinical characteristics and quality of life of seborrheic dermatitis patients in a tropical country. Indian J Dermatol. 2015;60:519.
15. Mathes BM, Douglass MC. Seborrheic dermatitis in patients with acquired immunodeficiency syndrome. J Am Acad Dermatol. 1985;13:947–51.
16. Motswaledi MH, Visser W. The spectrum of HIV-associated infective and inflammatory dermatoses in pigmented skin. Dermatol Clin. 2014;32:211–25.
17. Soeprono FF, Schinella RA, Cockerell CJ, Comite SL. Seborrheic-like dermatitis of acquired immunodeficiency syndrome. A clinicopathologic study. J Am Acad Dermatol. 1986;14:242–8.
18. Senaldi G, Di Perri G, Di Silverio A, Minoli L. Seborrhoeic dermatitis: an early manifestation in AIDS. Clin Exp Dermatol. 1987;12:72–3.
19. Vidal C et al. Seborrheic dermatitis and HIV infection. Qualitative analysis of skin surface lipids in men seropositive and seronegative for HIV. J Am Acad Dermatol. 1990;23:1106–10.

20. Alessi E, Cusini M, Zerboni R. Mucocutaneous manifestations in patients infected with human immunodeficiency virus. J Am Acad Dermatol. 1988;19:290–7.
21. Blanes M et al. Current prevalence and characteristics of dermatoses associated with human immunodeficiency virus infection. Actas Dermosifiliogr. 2010;101:702–9.
22. Arsic Arsenijevic VS et al. A laboratory-based study on patients with Parkinson's disease and seborrheic dermatitis: the presence and density of Malassezia yeasts, their different species and enzymes production. BMC Dermatol. 2014;14:5.
23. Shuster S et al. Melanocyte-stimulating hormone and parkinsonism. Lancet Lond Engl. 1973;1:463–4.
24. Cowley NC, Farr PM, Shuster S. The permissive effect of sebum in seborrhoeic dermatitis: an explanation of the rash in neurological disorders. Br J Dermatol. 1990;122:71–6.
25. Bettley FR, Marten RH. Unilateral seborrheic dermatitis following a nerve lesion. AMA Arch Dermatol. 1956;73:110–5.
26. Chen TM, Fitzpatrick JE. Unilateral seborrheic dermatitis after decompression of Chiari I malformation and syringomyelia. J Am Acad Dermatol. 2006;55:356–7.
27. Rocha N, Velho G, Horta M, Martins A, Massa A. Cutaneous manifestations of familial amyloidotic polyneuropathy. J Eur Acad Dermatol Venereol JEADV. 2005;19:605–7.
28. Ercis M, Balci S, Atakan N. Dermatological manifestations of 71 Down syndrome children admitted to a clinical genetics unit. Clin Genet. 1996;50:317–20.
29. Okada K et al. Refractory seborrheic dermatitis of the head in a patient with malignant lymphoma. Case Rep Dermatol. 2014;6:279–82.
30. Kokturk A et al. Seborrhoeic dermatitis-like manifestation of lung cancer evolving into erythrodermia. J Eur Acad Dermatol Venereol JEADV. 2004;18:381–2.
31. Venkateswaran S, Garg BR, Reddy BS, Narasimhan R. Cutaneous lymphoma mimicking seborrhoeic dermatitis. Indian J Dermatol Venereol Leprol. 1995;61:45–7.
32. Bittencourt AL, de Oliveira Mde FP. Cutaneous manifestations associated with HTLV-1 infection. Int J Dermatol. 2010;49:1099–110.
33. Tegner E. Seborrhoeic dermatitis of the face induced by PUVA treatment. Acta Derm Venereol. 1983;63:335–9.
34. Weiss SC, Rowell R, Krochmal L. Impact of seasonality on conducting clinical studies in dermatology. Clin Dermatol. 2008;26:565–9.
35. Picardi A, Abeni D. Stressful life events and skin diseases: disentangling evidence from myth. Psychother Psychosom. 2001;70:118–36.
36. Oztas P, Calikoglu E, Cetin I. Psychiatric tests in seborrhoeic dermatitis. Acta Derm Venereol. 2005;85:68–9.
37. Misery L et al. Stress and seborrheic dermatitis. Ann Dermatol Vénéréologie. 2007;134:833–7.
38. Maietta G, Fornaro P, Rongioletti F, Rebora A. Patients with mood depression have a high prevalence of seborrhoeic dermatitis. Acta Derm Venereol. 1990;70:432–4.
39. Orion E, Wolf R. Psychologic factors in the development of facial dermatoses. Clin Dermatol. 2014;32:763–6.
40. Humphreys F, Humphreys MS. Psychiatric morbidity and skin disease: what dermatologists think they see. Br J Dermatol. 1998;139:679–81.
41. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI) – a simple practical measure for routine clinical use. Clin Exp Dermatol. 1994;19:210–6.

Chapter 18
Role of Stress in Urticaria Syndrome

Kinza N. Tareen and Ruqiya Shama Tareen

Introduction

Stress is a very vague term open to interpretation, as it can be defined in different ways in different contexts. It is a subjective term just like pain and thus it is difficult to measure objectively. The term stress was first used by Hans Selye an Austrian-Canadian endocrinologist of Hungarian origin who proposed in 1936 that " stress is the non-specific response of body to any kind of demand for change." He noted that doesn't matter what was the disease a patient was suffering from they all shred some common constellation of symptoms [1].

Stress is generally described as a state of strain, pressure or tension experienced by an object due to adverse circumstances or challenges. The term stress is usually used very broadly and in various contexts. Stress can be good or bad, acute or chronic, and can be equally impactful weather it is physical, environmental or psychological in nature. Survival of an organism is dependent on the level of stress it encounters. While stress can bring on survival instincts and can be an impetus to develop or enhance adaptive changes that help us to cope with challenges it can also be damaging and debilitating when it is chronic and unrelenting (Fig. 18.1) [2].

K.N. Tareen, BS(✉)
Michigan State University, College of Human Medicne, Lansing, MI, USA
e-mail: tareenki@msu.edu

R.S. Tareen, MD
Western Michigan University Homer Stryker M.D. School of Medicine, Department of Psychiatry, Kalamazoo, MI, USA

K. França, M. Jafferany (eds.), *Stress and Skin Disorders*,
DOI 10.1007/978-3-319-46352-0_18

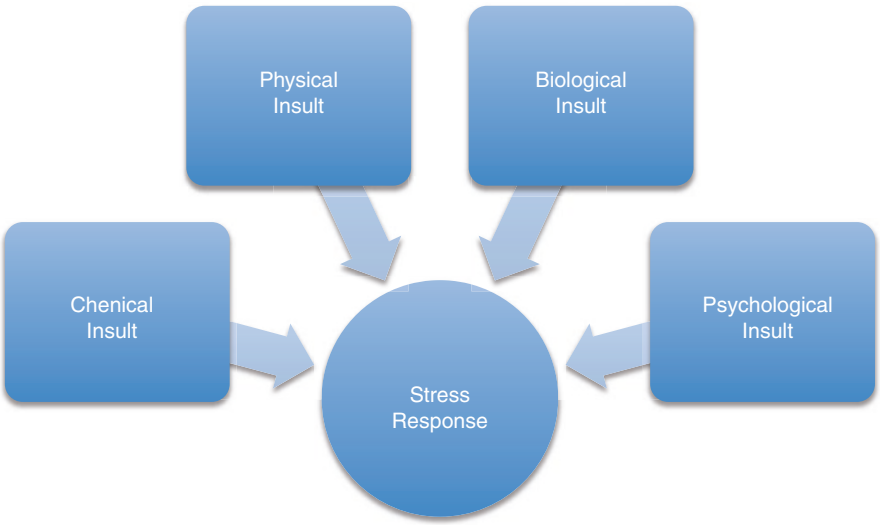


Fig. 18.1 Stress response

Urticaria-Nomenclature and Classification

Urticaria is derived from the two latin words "urtic" which means nettle and "uere" that means burn. The name suffices the stinging or burning itchy sensation produce by the urticarial rash. The incidence of urticaria ranges from 0.5 to 1.0 % of population and although can be seen in any age group although acute criteria is more common in children the chronic urticaria is most commonly seen in people in 20–40 years of range, and affect more females. The typical lesion is called wheal or hive which appears as smooth raised soft erythematous plaques caused by the swelling in superficial layers of skin resulting from mast cell degranulation. The urticarial lesions are highly pruritic and may last for several hours, they heal without any scarring [3].

Urticaria is mainly divided in two classes based on onset and recurrence, acute urticaria and chronic urticaria.

Acute Urticaria The urticaria when last less then 6 weeks is called acute urticaria. The acute urticaria is usually a reaction to an identifiable etiological agent and is further classified based on type of the etiology. Acute urticaria may occur in absence of any triggering agent and in that case is called acute spontaneous urticaria. The urticarial lesions can appears in close temporal relationship with the etiological agent sometimes within hours and getting a good history may help delineate the causative factors. Common causative agents are food, chemicals, medications and viral infections. Acute urticaria usually resolves in few days and if recurrent my resolve completely in less than 6 weeks with no further recurrence [3].

Chronic Urticaria The chronic urticaria is a relapsing and remitting condition lasting for 6 weeks or more. About 2–3 % of population suffers from chronic urticaria. The etiology of the chronic urticaria can be multifactorial but stress plays a

significant role. The relationship of stress with urticaria is bidirectional. Psychological stress is known to play a major etiological role in chronic urticaria and having chronic urticaria and it's symptoms like recurring wheals, pruritus and it's impact on quality of life can cause further create psychological stress [4].

Chronic urticaria is further classified in two main classes: chronic spontaneous and chronic inducible urticaria. The chronic spontaneous urticaria has no identifiable causative agent while chronic inducible urticaria occur in response to an identifiable causative agent. Common agents known to cause chronic inducible urticaria are more physical in nature like application of pressure, exercise, exposure to heat or cold, solar or water exposure. Although not classified separately psychological stress can be a major factor contributing to the onset of continuation of chronic urticaria (Fig. 18.2) [5].

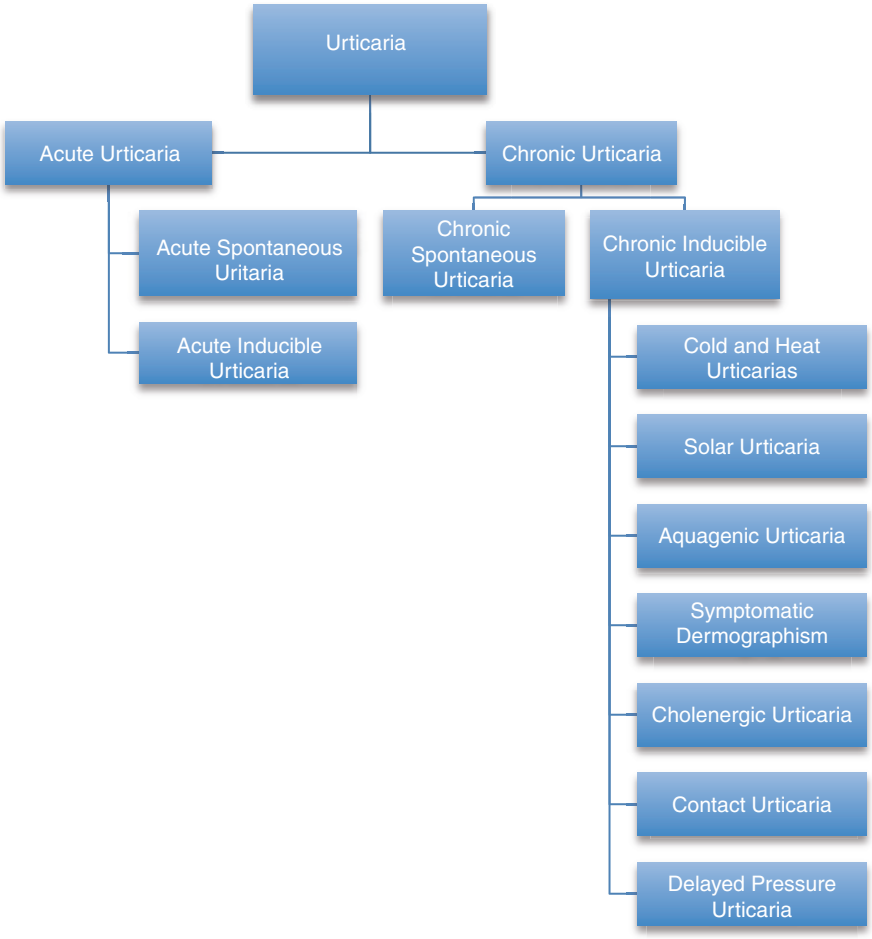


Fig. 18.2 Classification of urticarias

Stress, Skin and Neuroendocrine System

Stressful events activate the HPA axis, starting with the release of Corticotrophin-releasing hormone. CRH is the key component considered as the conductor of this orchestra of HPA-Axis hormonal symphony. CRH is produced in the paraventricular nuclei of the hypothalamus and in turns it controls the release of proopiomelanocortin (POMC) and different POMC-derived peptides including adrenocorticotrophin releasing hormone (ACTH), α-melanocyte-stimulating hormone (α-MSH) from the anterior pituitary gland [5, 6]. Activation of ACTH by CRH in turn leads to stimulation if adrenal cortex causing release of glucocorticoids, which returns to its base line when stressful event has passed and HPA axis activation subsides. The ACTH is released in a diurnal fashion with peak secretion in mornings and reaches a trough at midnight. This diurnal secretion gets disrupted when the CRH-ACTH system is under stress. ACTH exerts its action by binding with melanocortin receptors 2 (MC2) and stimulating adenyl cyclase, and generating cAMP that activates downstream enzyme pathways in steroidogenesis [5–7]. Glucocorticoid synthesis mainly takes place in the zona fasciculata of the adrenal cortex and is responsible for activating the negative feedback loop to terminate the stress response at suprahypothalamic centers, hypothalamus, and pituitary gland [5–7].

In cases when stress is chronic and gives rise to continual hypersecretion of CRH, perpetuating an unrelenting activation of the HPA axis a syndromal state characterized by physical changes leading to disease traits and states causing central obesity, diabetes mellitus, metabolic syndrome, hyperthyroidism, osteoporosis, atherosclerosis, chronic immunosuppression leading to increased susceptibility to infectious and even neoplastic diseases. This chronic stress induced altered homeostasis is also responsible for many neurovegetative symptoms like lack of appetite, insomnia, low energy, chronic fatigue and psychological difficulties like anxiety disorders, depression, anorexia nervosa [6, 7].

Persistent or frequent stimulation of HPA axis due to stress leads to elevation of glucocorticoids. It has been postulated that constant or more frequent elevation of glucocorticoids can be damaging to the cells leading to insulin resistance, release of proinflammatory cytokines release and increasing the organism susceptibility to disease [8, 9]. CRH is also mediating the stress response via another system by activating locus coeruleus in the brain stem releasing arginine vasopressin (AVP) and other nonapeptides [6, 7].

Pathophysiology of Urticaria: The Skin HPA-Axis

It has been postulated that skin has its own HPA-axis equivalent to the central HPA-Axis. Unlike most other body cell the skin cells especially keratinocyte, melanocyte, and mast cells can secrete CRH in response to a stress full situation. Skin cells also have abilities to induce expression of specific receptors on their surface to engage molecules of ACTH, CRH, urocortin, α-MSH and β-endorphin all of which are important players in the skin response to stress. CRH action is mediated through

two different types of receptors CRH-1 and CRH-2. CRH manage the different skin cells by inducing proliferation, and differentiation of cells while on the other hand it can also inhibit the proliferation and inducing apoptosis of different skin cell lines. It also induces proinflammatory changes by activating mast cells [10–13].

The mast cells plays such a critical role that they are called as "central switchboard" of skin-stress response [14]. Skin mast cells are regulated by various factors; they are activated and promoted by stress mediators such as CRH, ACTH, NGF (nerve growth factor), SP (substance P), and stem-cell factor; they are inhibited by glucocorticoids and catecholamines [13, 14].

The CRH-1 receptors located on mast cells when activated cause mast cells to degranulate and release histamine. CRH also induces the release of IL-4, IL-6, IL-10, and IL-13 from mast cells. CRH and mast cells plays a major role in delayed hypersensitivity reaction. The self-regulatory nature of the CRH-Glucocorticoid cycle prevents adverse consequences of prolonged adaptive changes like catabolism and immunosuppression that initially are a integral response to deal with stress can become harmful for the body [5–7].

Stress can cause the HPA-axis to become over burdened especially if stress is prolonged, this is called allostatic overload [14]. When compromised due to allostatic overload the HPA-axis is not able to respond to the new stressors resulting in various levels of dysregulation ranging from inflammation to immunosuppression [14]. Skin mast cells are crucial in maintaining an allostatic balance. Skin mast cells also express several neuropeptides receptors on their surface leading them to orchestrate the different aspects of this localized psycho-immuno-neuro-endocrine axis. Skin mast cells produce different pro-inflammatory and vasoactive peptides beside histamine. The release of histamine, bradykinin, leukotriene C4, prostaglandin D2, leads to extravasation of plasma producing the urticarial lesions [15]. Keratinocytes produces Interleukin -8 (IL-18) a proinflammatory cytokines that is known to play a role during state of stress [16]. Any stressful event leading to psychological stress can easily cause a fare up of urticaria perpetuating this chronic cycle of suffering [15, 16]. Unrelenting pruritus can cause significant anxiety and mood problems [17].

Mast cell degranulation is prominent in physical urticaria induced by temperature changes, sun or water exposure as well as cholinergic or dermatographic urticaria. In urticaria, histamine-releasing autoantibodies have shown to activate mast cells and basophils via activation of complement system and thus causing histamine release. Mast cells and basophils both play an important role in intensity and duration of urticarial episode [18]. Oxidative stress may play a role in chronic spontaneous urticaria [19].

Pathophysiology of Urticaria: The Psychological Stress

The relationship between stress and urticaria is well known but still vaguely understood when it comes to direct cause and effects. It has been postulated that certain early life events predispose people to develop particular personality traits in adult life making them at high risk of responding to psychological stress with conditions like

urticaria. Patient with urticaria are shown to have high likelihood of having a major psychological stressful event in preceding 6–12 months, with maximal events occurring in month preceding the onset or recurrence of urticaria [20]. Various studies have found different level of association of stressful events and urticaria ranging from 16 % to as high as 51 % in different samples [18–20]. The most likely stressor reported was death of a loved one followed by interpersonal conflict in family, financial stressors, illness is a family member, work related challenges, extramarital affairs, and sexual difficulties. Interestingly, presumably positive life events such as traveling for pleasure, or getting engaged or married, were equally likely to predispose people to develop uticaria within a year of the event. [20].

Chronic Urticaria and Psychiatric Comorbidity

Chronic urticaria is known to cause profound psychological impact on patients leading to significant negative impact on functional abilities and expression of different psychiatric illness. Shoemaker RJ et al. postulated a few decades ago that patients suffering from chronoic urticaria are replaying the dependency traits learned from adverse childhood events and in face of psychological stress they are unable to utilize mature ego defences and tend to have more emotional dependency needs which when unmet or are feared to not be met create a emotional climate for an episode of urticaria [21].

It has been reported that patients suffering from chronic urticaria for many years may develop psychological traits such as alexithymia and repression that can lead to development of long-term psychiatric difficulties. There is increased risk of developing comorbid anxiety disorders including posttraumatic stress disorder, somatoform disorders and depression in patients with chronic urticaria. Adolescents who suffered from non infective urticaria were found to have higher risks of developing major depressive disorder when compared to the age matched control who did not suffer from urticaria [22–26].

Stubach P et al. studied relationship of the psychiatric disorders and urticaria in 100 patients [27]. The patients were evaluated with validated scales to establish the diagnosis and severity of urticaria and using the The Mini-DIPS, a shortened German version of the common international diagnostic interview for mental disorders (DIPS) based on the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) along with well validated scales like Hospital Anxiety and Depression Scale (HADS) for anxiety and depression and the Symptom Check List (SCL-90R) for assessment of level of emotional distress and somatoform disorders [27]. Patients were also thoroughly evaluated to identify underlying causes of CSU to identify any triggering stimulus causing urticaria like food and other allergens, histamine intolerance and autoreactivity any underlying autoimmune diseases, chronic infection or any other medical condition that can including sensitize a person to type I allergens. Patients in whom no definitive causative stimulus was identified were classified as having chronic idiopathic urticaria (CIU). The study concluded

that the out of the 100 patients studied (69 females, mean age 43.8 years) 48 patients were found to be suffering from one or more psychiatric disorders [27]. Anxiety disorders were among the most common, comprising 30 % of the patients followed by depressive disorders 17 %, and somatoform disorders 17 % [27].The commonest anxiety disorder was agoraphobia followed by social and specific phobia and panic disorder. Major depressive disorder recurrent and dysthymic disorder were equally prevalent in the depressed patients followed by adjustment disorder. In the somatoform group, somatization disorder and somatoform autonomic function were followed by undifferentiated somatoform disorder [27]. Other disorders seen in this population were alcohol and other substance use or multiple substance dependence in about 1–3 %. The patient who were found to have psychiatric disorder and CSU were also likely to report higher level of emotional distress [27].

The prevalence of axis I and axis II psychiatric disorders was explored by another study in 89 patients of CIU and compared with a control group [28]. The study utilized the standardized an validated tools of Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV) (SCID-I) for axis I disorders and the Structured Clinical Interview for DSM, Revised Third Edition Personality Disorders for diagnosis of axis II disorders [28]. Overall study found the about half of the patients (49.4 %) with CIU had an axis I or axis II disorder compared to only 12.5 % of control group. The most prevalent disorder in this population was obsessive compulsive Disorder affecting a quarter (25.8 %) of patients [28]. The depressive disorder including major depression 13.5 % and dysthymic disorder at 9 % were the second commonest disorder along with social phobia at 9 % [28]. The personality disorders were also much commoner in the group with CIU at 44.9 % with commonest personality disorder being obsessive compulsive personality disorder at 30.3 % followed by avoidant personality disorder at 18 % [28]. The patients with CIU and axis I psychiatric disorders were also more likely to have a personality disorder (Ungz 2008). The authors recommended routine screening for psychiatric disorder in CIU patients in out patient dermatological setting to optimize their treatment with psychiatric referrals when indicated [28].

Chronic Urticaria and Quality of Life

Many skin diseases can impact the quality of life significantly and chronic urticaria is no exception. Although a relapsing remitting condition chronic urticaria is shown to impact the quality of life (QoL) in similar way as most of other severe and chronic dermatological diseases like atopic dermatitis, psoriasis, acne, and even vitiligo. However, it is more surprising that chronic urticaria is considered to have as much burden on quality of life as much as caused by coronary artery disease [29].

A specific quality of life questionnaire called Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL) has been developed to evaluate different aspects on impact on patient suffering from chronic urticaria. This questionnaire examines the

physical, emotional and psychological impacts of chronic urticaria. This tool has been well validated and has been translated in many languages [30].

Ungz et al. used World Health Organization QoL Assessment-Brief (WHOWOL-BREF) to evaluate the quality of life in CIU patients with and without any comorbid psychiatric disorder including axis-I and axis-II disorders. The study found that patients with CIU who had any comorbid psychiatric conditions reported much lower quality of life especially in subscales of physical health, psychological well being and social relationships when compared to the CIU patients without any psychiatric condition [31].

Management of Urticaria

In the case of chronic inducible urticaria, identifying, avoidance, and eliminating the triggers of CIU is the key factor is managing the CIU. Common triggers include food allergy, medications, infection and inflammation, cold or heat, water and solar exposure. The difficulty in this approach is that the remission of CIU after elimination of a stimulus does not guarantee that CIU was definitively produced by that stimulus spontaneous remission of CIU is common. This can only be said with confidence if the subject is challenged with an already identified stimulus in a double blind provocation test [30].

For many decades the mainstay of the treatment of urticaria remained the older antihistamines however, in light of new evidence they are falling out of favor. There are concerns about their significant anticholinergic effects, which last much longer then the their short lasting antipruritic effects [30]. There is also concern about potential of drug-drug interactions with other commonly used medications resulting in excessive sedation, cognitive effects and anticholinergic delirium. The recent guideline recommends use of second-generation antihistamines. The advantage of newer antihistamines is in their ability to provide better antipruritic and ant allergic effects while avoiding the excessive sedation and other serious side effects [30].

Second generation antihistamines with less sedative and anticholinergic effects are effective but not all of them are studied specifically to treat urticaria [30]. Only few of second-generation antihistamines including cetirizine, loratadine, fexofenadine, desloratadine, bilastine, levocetirizine and rupatadine have been studied in urticaria management [30]. Some of the studies support that if initial treatment with conventional doses of second-generation antihistamines is not successful then higher doses of second-generation antihistamines up to four-folds of the usual recommended dose can be used safely and effectively. Patients who are refractory are refractory to antihistamines especially suffering from can benefit form anti IgE agent Omalizumab [30]. It is especially effective against Chronic spontaneous urticaria, but has also shown to be effective in treating symptomatic dermatographism, solar urticaria, delayed pressure urticaria, cold and heat urticaria. Cyclosporine by its inhibitory action on histamine release from basophils and mast cell mediators can be effective in treating severe disease refractory cases of urticaria [30].

Leukotriene receptor antagonists like montelukast has been used alone or in conjunctions of antihistamines but the evidence of efficacy is low [30]. Systemic corticosteroids can be used as a third line agent is severe cases of treatment refractory urticaria, however long term use of corticosteroids is not recommended due to the concerns about serious systemic side effects [30].

Psychotheraputic Management of Psychological Stress

Traditional medicine has been compartmentalized with doctors treating the condition, which is their specialty and not worrying about how that particular condition affects this patient as a person. Focusing on the dermatologic management alone may not be successful, as we will not be addressing the emotional burden and psychological well being of these patients who are struggling to maintain a homeostasis in their lives.

Evidence is emerging that we need to employ multidimensional treatment approach and to change our tendency to focus at just the presenting complaint and go beyond that to maximize our chances to treat the disease successfully and to improve our patient's quality of life over all. Utilizing a whole person' treatment approach is important in the patients suffering from chronic urticaria even in patients who do not have any underlying psychiatric comorbidity [32]. Patients with chronic urticaria are always faced with the uncertainty of having a relapse of condition [32]. Since psychological stress is known to have significant impact on disease activity and possibly response to dermatological treatment it is important for clinician to consider patients for referral to a psychotherapist if indicated. Psychoeducation and brief therapeutic approaches like mindfulness therapy, social rhythm therapy and psychoeducational groups or group therapy for patients suffering from chronic urticaria may be all that is needed for a person who is overwhelmed with the disease and need some skills to overcome the psychological challenges that can impact the quality of life and prognosis of their illness. Patient with chronic urticaria who also has comorbid anxiety, depressive or personality disorders may benefit from proper screening and referral to appropriate sources if needed.

Supportive Psychotherapy (ST)

Supportive psychotherapy (ST) is a something that can easily be provided in most out patient clinic by most clinicians even in a busy dermatological practice. ST can be as simple as letting your patient know that you are aware of the psychological stressors may be playing a perpetuating role and to be supportive to the patient about their emotional struggles and give them time to discuss it with you. ST can be provided by a trained clinician like a social worker or therapist within the clinic setting as an integral part of their visit to the dermatology clinic and in that instance it

can involve use of more explorative and interpretative techniques if needed [4]. ST can be helpful to patients dealing with acute changes in their life due to their dermatological condition which can affect their emotional wellbeing and their ability to function in life. ST aim to strengthen a patient's ego by supporting their existing ego strengths and to help them identify how they can better deal with current psychological stressors so that they can better deal with these challenges [33].

Interpersonal Therapy (IPT)

Interpersonal conflicts and relationship issues are considered some of the main psychological stressors preceding the onset or relapse of urticaria and may play a perpetuating factor in activity of disease IPT may be a good therapeutic approach for these patients. IPT is a derived from the psychodynamic insight oriented model but is unique in that it is time limited and structured therapy consisting of 16 weekly sessions focusing on four main areas where interpersonal relationship that can give rise to psychiatric disturbance especially depression. These four focus areas of focus in IPT are grief, interpersonal disputes (role disputes), role transitions and interpersonal sensitivity (Interpersonal deficits). Once it is identified that patient is dealing with difficulties in any one of these areas the therapist then the works to delineate the interpersonal factors contributing to the depression and anxiety. IPT has shown to be effective when the therapist is able to analyzes the pertinent interpersonal incidents and communication styles patient is employing and help patient develop an understanding that some of the psychological difficulties they are having in dealing with tasks at hand [34].

Cognitive Behavior Therapy (CBT)

Cognitive therapy (CT) is based on earlier information processing theory, which required a more active role from therapist as well as the patient, by utilizing a structured approach by recruiting patient to do more active self-reflection and to complete assignments to assess and monitor progress. CBT has shown to been effective in helping patients overcome the negative schema they may develop about themselves and their disease, the people around them and the world itself. The foundation of CBT is that the chronic stressors especially earlier in life predispose people to develop maladaptive coping mechanisms resulting in negative behavior that ultimately leads to decreased response and decreased positive reinforcement. The therapist task is to help patients identify the automatic negative thoughts and help them link that these negative thoughts are invoking negative feelings that ultimately results in them either acting out or retracting in a shell and leading to dysfunctional behaviors. In CBT patient is forced to play an active role in their own recovery and to master the task to make a conscious effort to identify and link the negative

thoughts to unpleasant feeling ensuing in maladaptive behaviors. Once mastery is achieved of connecting the thoughts to feeling to behavior and the patient has practiced how to recognize the automatic negative thoughts at its outset to early to replace it with a positive thoughts that will eventually leads to a positive behavior patient would achieve functional outcomes [35].

Pharmacological Management of Psychiatric Disorders

Antidepressants and anxiolytic medications may be needed to control the symptoms of depression and different anxiety spectrum disorders when psychotheraputic approaches alone are not beneficial. Most commonly used antidepressant medication which also has anxiolytic properties are tricyclic antidepressants, *Selective serotonin reuptake inhibitors* (SSRIs) and SSRIs with added properties like Selective serotonin and norephinepherine reuptake inhibitors (SSNRIs) and Selective serotonin norepinephine dopamine reuptake inhibitor (SSNDRI). Older antidepressant monoaminoxidase inhibitors (MAOI) although very effective are not commonly used due to strict dietary restriction one has to observe while taking these. SSRIs are considered the first line medications for the management of anxiety and depression in patients suffering from moderate to severe depressive and anxiety disorders including obsessive compulsive disorder, social phobias, posttraumatic stress disorder.

Tricyclic antidepressants (TCAs) are the older antidepressants that are less commonly used nowadays mostly because of their unfavorable side effects profile. In dermatological practices TCAs have been used both systemically and topically more frequently due to their effects on wide variety of neurotansmitters especially H1 and H2 antihistaminic and anticholinergic properties which enables TCAs to provide much needed relief of some of the associated dermatological symptoms like pain and itch. Some of the TCAs like doxepin, amitriptyline and trimipramine has more potent H1 receptors and H2 receptor antagonists then other TCAs. Amitriptyline and desipramine has significant analgesic effects beside their impact on depression and anxiety and can he more helpful in certain cases. Doxepin has shown effectiveness in chronic idiopathic urticaria, idiopathic cold urticaria and in other dermatological conditions with difficult to treat pruritus. Topical doxepin has been used in recalcitrant pruritic conditions [35].

How one decides to choose an SSRI depends on various factors such as: the specific side effect profile especially any dermatological side effects, whether this medication has been used with good results in this patient before or has shown a good response in a family member, any contraindications to that particular medications, possibilities of drug-drug interactions, and most importantly the cost of the medication. Akso to take in account is the formulation and the dosing, some patient may not be able to swallow capsules and would prefer tablets and their compliance will improve with right type of formulation and with once daily dosing as apposed to two or three times a day dosing [36]. Some SSRIs has shown effectiveness in

improving the frequency an intensity of neurotic excoriations and stress related urticaria [37]. Since many of the patients dealing with chronic urticaria will be using other medications it will be prudent to pay attention to the possibility of Drug–drug interactions involving the cytochrome P450 (CYP) isoenzyme. Fluoxetine, paroxetine and sertraline, are inhibitors of CYP 2D6 isoenzyme. Fluoxetine, fluvoxamine and sertraline are moderate inhibitors of cytochrome P450 (CYP) 3A3/4 isoenzyme and can impeded or inhibit the metabolisms of the medications that are substrate of this isoenzyme. Two such substrates pertinent to patients with chronic urticaria is antihistamines astemizole that is a CYP3A3/4 substrates that can result in potentially fatal QT prolongation and torsades des pointes [37].

Conclusion

Urticaria, especially in its chronic form, has been shown to have significant association with psychological stress and comorbidity with psychiatric illness affecting the course of urticaria and its prognosis. Assessment of psychological distress and proper treatment that can improve the psychological well being will also improve the quality of life of the patient and may improve the prognosis of chronic urticaria.

References

1. Szabo S, Tache Y, Somogyi A. The legacy of Hans Selye and the origins of stress research: a retrospective 75 years after his landmark brief “Letter” to the Editor of Nature. Stress. 2012;15(5):472–8.
2. Aschbacher K, O’Donovan A, Wolkowitz OM, Dhabhar FS, Su Y, Epel E. Good stress, bad stress and oxidative stress: insights from anticipatory cortisol reactivity. Psychoneuroendocraniology. 2013;38:1698–708.
3. Moolani Y, Lynde C, Sussman G. Advances in understanding and managing chronic urticaria. [Internet]. 2016;5(0):1–7. Available from: http://f1000research.com/articles/5-177/v1.
4. Dilek F, Ozceker D, Ozkaya E, Guler N, Tamay Z, Kesgin S, et al. Oxidative stress in children with chronic spontaneous urticaria. Oxid Med Cell Longev [Internet]. 2016;2016:1–8. Available from: http://www.hindawi.com/journals/omcl/2016/3831071/.
5. Kyrou I, Tsigos C. Hypothalamic-pituitary-adrenal axis. In: Linos D, Heerden J, editors. Adrenal glands. Berlin: Springer; 2005. p. 19–32.
6. Ader R, Cohen N, Felten D. Psychoneuroimmunology: interactions between the nervous system and the immune system. Lancet. 1995;345:99–103.
7. Tareen RS. Psychoneuroimmunology and other interactions between skin and psyche. In: Tareen RS, Greydanus DE, Jafferney M, Patel DR, De Gruyter MJ, editors. Pediatric psychodermatology: a clinical manual of child and adolescent psychocutaneous disorders. Berlin; 2012, p. 67–79.
8. Warne JP. Shaping the stress response: interplay of palatable food choices, glucocorticoids, insulin and abdominal obesity. Mol Cell Endocrinol. 2009;5:137–46.
9. Elenkov IJ, Chrousos GP. Stress hormones, Th1/Th2 patterns, pro/anti-inflammatory cytokines and susceptibility to disease. Trends Endocrinol Metab. 1999;10:359–68.

10. Slominski A, Wortsman J, Pisarchik A, Zbytek B, Linton EA, Mazurkiewicz JE, et al. Cutaneous expression of corticotropin-releasing hormone (CRH), urocortin, and CRH receptors. FASEB J. 2001;15:1678–93.
11. Pisarchik A, Slominski A. Molecular and functional characterization of novel CRFR1 isoforms from the skin. Eur J Biochem. 2004;271:2821–30.
12. Slominski A, Wortsman J, Luger T, Paus R, Solomon S. Corticotropin releasing hormone and proopiomelanocortin involvement in the cutaneous response to stress. Physiol Rev. 2000;80:979–1020.
13. Slominski A, Pisarchik A, Tobin DJ, Mazurkiewicz JE, Wortsman J. Differential expression of a cutaneous corticotropin-releasing hormone system. Endocrinology. 2004;145:941–50.
14. Paus R, Theoharides TC, Arck PC. Neuroimmunoendocrine circuitry of the "brain-skin connection.". Trends Immunol. 2008;27(1):32–9.
15. Hide M, Francis DM, Grattan CE, Hakimi J, Kochan JP, Greaves MW. Autoantibodies against the high-affinity IgE receptor as a cause of histamine release in chronic urticaria. N Engl J Med. 1993;328(22):1599–604.
16. Kim JE, Cho BK, Cho DH, Park HJ. Expression of hypothalamic-pituitary-adrenal axis in common skin diseases: evidence of its association with stress-related disease activity. Acta Derm Venereol. 2013;93(4):387–93.
17. Suárez AL, Feramisco JD, Koo J, Steinhoff M. Psychoneuroimmunology if psychological stress and atopic dermatitis: pathophysiologic and therapeutic updates. Acta Derm Venereol. 2012;92:7–15.
18. Gober LM, Saini SS. Allergic urticaria. Clin Basic Immunodermatol. 2008;2:459–77.
19. Sagdic A, Sener O, Bulucu F, Karadurmus N, Yamanel L, Tasci C, et al. Oxidative stress status in patients with chronic idiopathic urticaria. Allergol Immunopathol (Madr). 2011;39(3):150–3.
20. Malhotra SK, Mehta V. Role of stressful life events in induction or exacerbation of psoriasis and chronic urticaria. Indian J Dermatol Venereol Leprol. 2008;74(6):594–9.
21. Shoemaker RJ, Shipman WC, Mally MM. Search for the affective determinants of chronic urticaria. Psychosomatics. 1963;4:125–32.
22. Kuo C-L, Chen C-Y, Huang H-L, Chen W-L, Lee H-C, Chang C-Y, et al. Increased risk of major depression subsequent to a first-attack and non-infection caused urticaria in adolescence: a nationwide population-based study. BMC Pediatr [Internet]. 2014;14(1):181.
23. Hunkin V, Chung MC. Chronic idiopathic urticaria, psychological co-morbidity and posttraumatic stress: the impact of alexithymia and repression. Psychiatr Q. 2012;83(4):431–47.
24. Badoux A, Levy D. Psychologic symptoms in asthma and chronic urticaria. Ann Allergy. 1994;72:229–34.
25. Süheyla Ü, Oguz B, Gülay K, Erdal K. Psychological symptoms in patients with chronic urticaria and allergic rhinitis. Turk Psikiyatri Dergis. 1991;2:289–93.
26. Gupta MA, Gupta AK. Chronic idiopathic urticaria and post-traumatic stress disorder (PTSD): an under-recognized comorbidity. Clin Dermatol. 2012;30(3):351–4.
27. Staubach P, Dechene M, Metz M, Magerl M, Siebenhaar F, Weller K, et al. High prevalence of mental disorders and emotional distress in patients with chronic spontaneous urticaria. Acta Derm Venereol. 2011;91(5):557–61.
28. Uguz F, Engin B, Yilmaz E. Axis I and Axis II diagnoses in patients with chronic idiopathic urticaria. J Psychosom Res. 2008;64(2):225–9.
29. O'Donnell BF, Lawlor F, Simpson J, Morgan M, Greaves MW. The impact of chronic urticaria on the quality of life. Br J Dermatol. 1997;136:197–201.
30. Zuberbier T, Aberer W, Asero R, Bindslev-Jensen C, Brzoza Z, Canonica GW, et al. The EAACI/GA2LEN/EDF/WAO guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. Allergy Eur J Allergy Clin Immunol. 2014;69(7):868–87.
31. Uguz F, Engin B, Yilmaz E. Quality of life in patients with chronic idiopathic urticaria: the impact of Axis I and Axis II psychiatric disorders. Gen Hosp Psychiatry. 2008;30(5):453–7.

32. Lindsay K, Goulding J, Solomon M, Broom B. Treating chronic spontaneous urticaria using a brief “whole person” treatment approach: a proof-of-concept study. BioMed Central. 2015;5:40.
33. Karel MJ, Hinrichsen G. Treatment of depression in late life: psychotheraputic interventions. Clin Psychol Rev. 2000;20(6):707–29.
34. Robertson M, Rushton P, Wurm C. Interpersonal psychotherapy: an overview. Psychother Aust. 2008;14(3):46–55.
35. Dobson KS, editor. Problem- solving therapy. In: Handbook of cognitive-behavioral therapies. 3rd ed. New York: Guilford Press; 2010.
36. Kamboj MK, Tareen RS. Management of nonpsychiatric medical conditions presenting with psychiatric manifestations. Pediatr Clin North Am. 2011;58:219–41.
37. Gupta MA, Gupta AK. The use of antidepressant drugs in dermatology. J Eur Acad Dermatology Venereol. 2001;15(6):512–5.

Chapter 19
Stress and Wound Healing

Olivia Hughes, Flor MacQuhae, Adele Rakosi, Ingrid Herskovitz, and Robert S. Kirsner

Introduction

For the purpose of this chapter we define stress as a process in which environmental demands tax or exceed the adaptive capacity of an organism, resulting in psychological and biological changes that may place persons at risk for disease [1]. Stress can be classified as physical or psychological, and acute, episodic acute, or chronic [2, 3]. Acute stress is a short lived event (minutes to hours), whereas chronic stress usually lasts days to months. It is worth noting that stress can have negative or positive implications. Eustress is an example of stress that is beneficial [4, 5]. It is "positive stress" that motivates the individual to achieve and has been implicated in evolutionary survival. Eustress can be psychological, physical, or biochemical in nature, and can alter gene expression in a way that positively affects the health of the individual [6]. Distress is "negative stress" that has detrimental effects on health and survival. It can arise in patients with chronic diseases that are difficult to cope with and impair normal healing processes [7]. Other forms of stress to be considered are lifestyle practices such as smoking, drinking alcohol, lack of physical activity, and poor sleep. These habits may lead to nutritional deficiencies which are important for the wound healing process such as glucose; vitamins A, C, and E; polyunsaturated fatty acids; proteins; and zinc. Additionally, poor sleep hygiene can lead to a decrease in growth hormones which are key components of wound healing. Thus the relationship between distress and the impairment of wound healing has a behavioral origin that depresses the immune system and in turn impacts wound healing [8].

O. Hughes, BS • F. MacQuhae, MD • A. Rakosi, MD • I. Herskovitz, MD
R.S. Kirsner, MD, PhD (✉)
Department of Dermatology and Cutaneous Surgery, University of Miami Miller School of Medicine, Miami, FL, USA
e-mail: RKirsner@med.miami.edu

K. França, M. Jafferany (eds.), *Stress and Skin Disorders*,
DOI 10.1007/978-3-319-46352-0_19

Stress may be a challenge to measure. An external event or stressor can produce different effects depending on the affect, psychological resources, coping mechanisms and experiences of a person. A gold standard has not been established for measuring stress levels objectively. There has been debate as to whether a quality of life assessment questionnaire should be administered or biological markers (e.g. cortisol levels) should be used [1]. As a result, perceived stress might be the best variable to study [9]. The purpose of this chapter is to focus on stress and its impact on wound healing.

A wound can be defined as a disruption in the normal structure and function of the skin and soft tissues. Caused by a variety of different etiologies and mechanisms, wounds are further divided into acute or chronic wounds [10]. An acute wound is defined as wounds, such as burns or other traumatic injuries and surgically created wounds which heal in a timely fashion. Not only do they heal in a reasonable time frame, but do so by going through the normal, overlapping stages of wound healing, inflammation, proliferation, and maturation. Chronic wounds on the other hand do not go through those three stages in an orderly and timely manner. In chronic wounds, parts of the wound have lost synchronicity and thus are at different stages of the healing process which leads to delayed wound healing [11]. Chronic wounds can be further divided by their etiology, including neuropathic (most often from diabetes mellitus), venous, pressure-related, and ischemic ulcers. A loop may ensue as these wounds may also create stress. Their pathomechanisms and the type of stress they generate vary. For example, venous leg ulcers are commonly painful and thus patients can have stress induced by pain. For patients with diabetes mellitus, the fear of having a new ulcer generates anxiety and distress. Patients healing from burn wounds often suffer from post-traumatic stress disorder (7 % at discharge and 22 % at follow up) [12]. Moreover, stress and pain can result from wound care itself. Dressing changes are often painful for patients, doctor's appointments and wound care visits can be taxing financially and time consuming, thus inducing anxiety and stress [13].

Stages of Normal Wound Healing

Normal wound healing is a dynamic process that progresses through three overlapping phases in a predictable, timely manner. These three phases are the inflammatory, proliferative, and remodeling phases of wound healing [3, 14]. Cytokines, immune cells, growth factors, and the extracellular matrix (ECM) play a role in this coordinated effort. When dysregulation of the interactions between these cells and substances occurs, impaired wound healing results [15].

Inflammatory Phase

The inflammatory phase occurs within seconds of a wound developing and can last for 2–5 days, and even as long as 2 weeks [3, 11]. It begins with hemostasis (which some consider to be the first phase of healing, thus creating 4 phases of healing),

achieved through fibrin, platelets, endothelial cells and other mediators of the clotting cascade. These components not only function to achieve hemostasis but serve as a matrix for recruited inflammatory cells, fibroblasts, and growth factors. Activated platelets increase surface receptors, granule release, and aggregation important for clotting and wound healing. Platelet granules contain proteins that stimulate matrix production and growth factors such as platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF-beta), fibroblast growth factor-2 (FGF-2), vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), insulin-like growth factor-1 (IGF), and epidermal growth factor (EGF). These growth factors and cytokines such as IL-1alpha, IL-1beta, IL-6, and tumor necrosis factor-alpha (TNF-alpha), have downstream effects on fibroblasts, keratinocytes, and endothelial cells throughout the wound healing process and are essential for tissue repair [16–18].

Inflammation is characterized by erythema, swelling, pain, and heat as a result of capillary vasodilation and increased permeability allowing for extravasation of proteins and cells from the circulation to the site of injury. Vasodilation and capillary permeability is the result of a coordinated effort by sources including neural input, mast cell degranulation, histamine release, and kinin production [17, 19–23]. Within 24 h of injury, neutrophils and macrophages are recruited to the site of injury to remove debris, bacteria, and damaged tissue, and release proinflammatory cytokines that activate keratinocytes and promote wound healing [3]. Macrophages release chemotactic factors, angiogenic factors, and growth factors which recruit cells (e.g. fibroblasts), induce formation of new blood vessels, and stimulate cellular proliferation and extracellular matrix (ECM) production [11, 24].

Proliferative Phase

Over the course of a few days to 3 weeks, the inflammatory phase progresses to the proliferative phase, where the extracellular matrix laid down in the inflammatory phase is replaced by granulation tissue. Granulation tissue is characterized by capillary loops in a matrix of collagen and ground substance which will become the dermis. Capillary networks are actively laid down in response to PDGF and other growth factors. Fibroblasts migrate into the wound and produce collagen and other components of the ground substance. Collagen provides tensile strength and facilitates movement of cells that are important for wound healing [25]. In healthy, intact skin and mature scars, 80–90 % of dermal collagen is type I collagen and the remaining 10–20 % is type III collagen. In the early stages of wound healing, there is increased type III collagen production which peaks around days 5–7 post-injury, and makes up approximately 30 % of dermal collagen [11, 17, 26]. Fibroblasts release cytokines and growth factors such as IL-1 and TNF-alpha, and fibroblast growth factor-7 (FGF-7) which regulates keratinocyte activity. Migration of cells is a highly regulated process whereby cells move from the wound edges into the wound bed along the fibers of the extracellular matrix through interactions involving cell adhesion proteins (e.g. integrins) and matrix metalloproteinases (MMPs)

[17, 27]. Keratinocytes reestablish an epidermal covering, and myofibroblasts cause wound contraction [3, 17]. Proteoglycans and glycosaminoglycans (GAG) are important components of the extracellular matrix. They have increased expression in response to tissue injury and play a role in regulating cellular events, vascular endothelial cells, cytokines, enzymes, and growth factors in the ECM involved in immune function and cellular repair [28]. The primary GAGs found in the dermis are hyaluronic acid, dermatan sulfate, chondrointin sulfate, and heparin sulfate. Hyaluronic acid is the most prevalent GAG present in the ECM during the first 2 weeks of wound repair. Chondrointin and dermatan sulfate predominate later on in the healing process, until they are later replaced by hyaluronic acid as the most prevalent GAG. Interestingly, Gallo et al. demonstrated a link between antimicrobial peptides in the wound bed and increased expression of heparin sulfate proteoglycans, which are integral in promoting cellular proliferation and migration in wound healing. This demonstrates the interrelatedness of the immune system and tissue repair [17, 28, 29]. Additionally, FGF-2 is unable to stimulate keratinocytes and other cells in the absence of heparin sulfate, demonstrating the role GAGs play in regulating cellular activity in tissue repair [30, 31]. Reepithelialization is the process whereby intact epidermis is established over granulation tissue. This process can take anywhere from 24 to 48 h for superficial wounds, or as long as months to years for chronic wounds. Cells migrate in clusters from the wound edge through a process called contact guidance, where mechanical, chemical, and topographic cues play a role in coordinating cellular movement until the wound edges approximate [32]. There are two primary sources of keratinocytes that participate in reepithelialization–those cells near the wound margins, and keratinocyte stem cells derived from nearby follicular bulges, a rich source of stem cells [33]. Keratinocyte migration is stimulated by FGF-2, −7, −10, nerve growth factor (NGF), hepatocyte growth factor (HGF), fibrin, plasminogen, and matrix metalloproteinases (MMPs). Collagenase, also known as MMP-1, is particularly important for keratinocyte migration initiation in wound healing. In the presence of peptide hydroxymates, potent inhibitors of MMPs, keratinocyte migration was completely disrupted [34]. In addition to NGF and HGF, keratinocyte proliferation is stimulated by HB-EGF, growth-related oncogene (GRO)-alpha/CXCL-1 chemokine (C-X-C motif) ligand, IL-6, granulocyte-macrophage colony-stimulating factor (GM-CSF), and nitric oxide [17]. Reepithelialization is accomplished when there is an epidermal covering over the wound. It takes approximately 7–9 days after reepithelialization has occurred for the basement membrane zone between the epidermis and dermis to form [11].

Maturation

The maturation and remodeling phase is the final phase of normal wound healing that takes place over the course of 3 weeks to 2 years post-injury [11, 17]. Fibroblasts, collagen, MMPs, tissue inhibitors of MMPs, and blood vessels are the primary

contributors to wound maturation and remodeling. There is a delicate balance among collagen production, collagen breakdown, and collagen reorganization primarily mediated by MMPs. During this period, type III collagen is replaced by type I collagen. By 6 months, with reorganization of collagen fibrils, the healed tissue regains 70–80 % of its pre-injury tensile strength [3, 11, 17]. Fibroblasts undergo phenotype switching into myofibroblasts in response to PDGF, TGF-beta, and peroxisome proliferator-activated receptor (PPAR) [35]. Myofibroblasts are responsible for wound contraction due to increased levels of actin filaments that give them contractile properties. Elevated IL-8 has been found to inhibit wound contraction and decrease keratinocyte replication which may explain why wounds that have a prolonged inflammatory phase with prolonged exposure to IL-8 experience delayed wound healing and improper maturation [16, 36]. Remodeling is most active in the first 6 months after tissue injury, decreases over the next 6 months, and is minimal after that. Scar maturation is the result of decreased blood vessels and fibroblasts in the area [17].

Relationship Between Stress and Wound Healing

Now that the normal process of wound healing has been described, it is important to consider how stress affects tissue repair. Recall Cohen et al. define stress as a process in which environmental demands tax or exceed the adaptive capacity of an organism, resulting in psychological and biological changes that may place persons at risk for disease [1]. Another definition of stress is a physical, mental, or emotional factor, from external (environment, psychological, or social situations) or internal (illness, medical procedure) origin, that causes bodily or mental tension [37]. How the individual responds to stress depends on a variety of factors including age, health status, experiences, coping mechanisms, and host defenses. According to the American Psychological Association, there are 3 kinds of stress: acute, episodic acute, and chronic stress [2]. In general, stress activates the hypothalamic-pituitary-adrenal (HPA) axis, and chronic stress leads to impaired wound healing [38].

Psychoneuroimmunology is the study of the interactions between the nervous system and the immune system including behavioral and endocrine responses. Immune cells such as lymphocytes, macrophages, and granulocytes express receptors for various neurotransmitters allowing for the stress response to have modulatory effects on the immune system [39]. Kiecolt-Glaser et al. evaluated psychological stress on wound healing in humans. They found that psychological stress in the form of caring for a demented loved one caused significantly delayed wound healing of a 3.5 mm punch biopsy and decreased IL-1beta mRNA expression in peripheral leukocytes in response to lipopolysaccharide stimulation [40]. Additionally, Malarkey et al. evaluated caregiver stress on gene expression of growth hormones (GH) in human immune cells. Chronic stress in the form of being a caregiver for a sick loved one was associated with a significant decrease (50 %) in GH mRNA expression in peripheral blood mononuclear cells compared to the age- and weight-

matched control group. Decreased GH expression was correlated with elevated levels of adrenocorticotropic hormone (ACTH) and norepinephrine, important mediators of the stress response, reflecting the impact of stress on immune function and impaired wound healing [41]. Richards et al. demonstrated that neural innervation is important for wound healing to occur. Rate of wound healing in a denervated 1 cm wound flap was significantly decreased compared to a 1 cm control wound [42]. Studies evaluating thrombocytopenic rats and wound healing demonstrated an altered inflammatory response and immune function, measured by increased number of macrophages and T cells, in thrombocytopenic rats compared to control animals. However there was no difference in wound closure, angiogenesis, and collagen synthesis in this study [43]. Cell-mediated immunity can have both beneficial (bacterial, fungal, viral, and cancer immunity) and detrimental (autoimmunity, allergic dermatitis) modulatory effects on immune function. One study in rats demonstrated that acute and chronic stress have different effects on T-cell activity in delayed type hypersensitivity reactions. Acute stress caused T-cells to be redistributed into the skin, whereas chronic stress diverted the T-cells away from the skin. Based on these findings, they concluded that acute stress enhances the immune response, while chronic stress suppresses it [44]. This model was challenged by Sapolsky (1998) and Dopp et al. who endorsed the model where stress activates the innate immune response and suppresses the adaptive immune response. This is based on the assumption that the innate immune response is better suited to defend the body against life threatening events because the response is faster, subject to fewer inhibitions, and requires less energy [45].

Fontoura de Almeida et al. conducted a study that demonstrated the role of stress hormones in healing impairment. They found that treatment with a glucocorticoid receptor antagonist, RU486, in stressed mice improved full thickness wound healing, measured by earlier wound contraction and improved angiogenesis, compared to untreated stressed mice [38]. Elevations in blood glucose are associated with impaired immune function and delays in wound healing. HbA1c is a test that evaluates the average blood glucose level over a 3 month period through measurement of hemoglobin glycosylation in red blood cells. When the HbA1c is greater than 12, it is associated with decreased neutrophil chemotaxis and impaired leukocyte function, thereby impairing the healing process [46, 47]. A study by Graham et al., evaluated the relationship between pain level and time to recovery of barrier function after forearm skin injury. They found that higher levels of pain were correlated with faster recovery of skin barrier function. The implications of this study are that acute pain may alter immune function and improve healing after minor dermal abrasions [48]. McGuire et al. evaluated the relationship between post-surgical pain intensity and healing of a standard 2 mm punch biopsy wound in women. In this study, patients who reported higher levels of acute post-operative pain experienced slower wound healing. Those who experienced lower levels of persistent post-operative pain exhibited faster wound healing. In both instances, greater post-operative pain intensity was associated with significantly slower wound healing. Interestingly, depressive symptoms on the day of surgery and smoking status did not affect wound healing, however depressive symptoms directly correlated with presence of persistent pain [49].

Studies in animal models established that restraint stress is associated with higher circulating corticosteroid levels and with a 27 % reduction in wound healing [50]. Patients with diabetic foot ulcers (DFUs) often experience depression, anger about their condition, sadness, frustration, and fear of amputation [47]. The frustration and anger in patients with chronic ulcers can be related to the limitations in mobility and the subsequent impact on their work, lifestyle, and self-perception [51]. Biochemically, diabetes-associated depression can be linked to abnormal circulating cytokines. For this reason, stress and depression cannot be left untreated [52, 53]. Results from observational, experimental, and interventional studies provide strong evidence that psychological and physical stress can influence the wound healing process [54].

Management

As demonstrated above, psychological and behavioral factors can affect wound repair [55, 56]. Since the healing process can be disrupted by a variety of acute and chronic stressors, and psychological stress can influence the wound healing process, it is important to include psychologic and stress management in the wound treatment plan, addressing these psychological issues at each patient visit [54]. Chronic leg ulceration can have a profound impact on a patient's quality of life. One such method of determining quality of life in patients with chronic venous disease is the Chronic Venous Insufficiency Questionnaire (CVIQ) scale. In this questionnaire, the health care provider can assesses the psychological, physical, and social concerns that chronic venous disease has on a patient's life [57].

Intervention studies have demonstrated improvement in healing outcomes when psychological stress is reduced. Behavioral stress management interventions to reduce psychological stress prior to surgery include patient education on the surgical procedure and behavioral techniques. Meta-analyses of clinical studies evaluating the effect of behavioral stress management interventions on surgical outcomes found that these pre-operative interventions are associated with better post-operative outcomes, such as fewer medical complications, faster ambulation, reduced use of analgesia, and a decreased hospital length of stay [55, 56]. Chronic venous ulceration causes psychological and functional limitations. Jones et al. found that pain and odor were the two findings commonly associated with depression and anxiety in chronic venous ulcer patients [58]. Interestingly, they found no association between living alone, decreased mobility, or presence of exudate. There are multiple modalities for pain and odor management including debridement, pharmacological treatment, exercise, leg elevation, antibiotics in the presence of infection, and special wound dressings. Debridement, which is the standard of care in chronic wounds, consists of the removal of bacteria, necrotic tissue, senescent cells, and foreign debris [59]. It is associated with pain relief and odor minimization. Furthermore, Phillips et al. evaluated 73 patients with venous ulcers and found a correlation between the amount of time spent on wound care and the patient's feelings of anger and resentment [60]. 68 % of patients reported that the ulcer had a negative emotional

impact on their lives, including feelings of fear, social isolation, anger, depression, and negative self-image. Another study found a statistically significant relationship between psychological factors and wound healing. Depression and anxiety in the setting of an acute wound has been shown to contribute to slower wound healing [61]. This could be secondary to direct factors such as increased cortisol levels, which lead to impairment of both cellular and humoral immunity, or due to indirect factors more common in depressed patients such as self-neglect, disturbed sleep, and poor appetite [62]. Wilson found that although a number of studies have evaluated quality of life in patients with leg ulceration, there is little evidence to suggest that these issues are addressed as part of management [63]. For instance, compression therapy, the standard of care for venous leg ulceration, can cause discomfort and limitation in social activities and activities of daily living [62]. Franks et al. confirmed that patients experience improvements in quality of life during periods of active treatment. Patients whose ulcers were healing, experienced significant improvements in lower extremity pain, increased energy, decreased anxiety, and better sleep [64]. Stress management, though difficult, is an important component of wound care. Treatment options include, but are not limited to, written emotional disclosure interventions, physical exercise, social support, pharmacological agents, relaxation/mindfulness-based stress reduction meditation, hypnosis, and cognitive-behavioral stress management.

Written emotional disclosure is a technique designed to encourage the disclosure of negative and traumatic experiences. This enables emotional and cognitive processing in patients, allowing them to access, express and process inhibited emotions. It has been reported that written emotional disclosure has physical and mental health benefits, as evidenced by decreased psychological distress, improved self-reported health, decreased anxiety and depressive behaviors, enhanced aspects of cellular immunity, and decreased healthcare utilization [65]. In a study, men were randomized to a written emotional disclosure intervention or a non-intervention control group, and received a punch biopsy on the nondominant forearm. Healing was assessed using ultrasound biomicroscopy at 3 occasions during a 21-day period. Men who participated in the emotional disclosure intervention had smaller wounds at 14 and 21 days, compared to control participants [66].

Physical exercise is another stress management technique. In addition to improving cardiovascular function and decreasing the risk of heart disease, type 2 diabetes, and obesity, physical exercise can reduce psychological distress [67]. In a study evaluating the effect of exercise on wound healing in older adults, subjects were randomized to an exercise intervention 3 days per week or a non-intervention control group. Each exercise session consisted of 10 min of floor warm-up and stretching, 30 min of cycling while maintaining a heart rate within the assigned training range, 15 min of brisk walking and/or jogging, 15 min of arm-strengthening exercises, and 5 min of cool-down exercises. One month after initiating the intervention, participants had a 3.5 mm punch biopsy taken from the back of their nondominant arm. Out of 28 older adults undergoing dermal punch biopsy, those engaging in regular exercise experienced wound healing in a mean of 29 days, compared to 39 days for the inactive control group [68]. In animal studies, older mice

that were randomized to a 30-min daily exercise program for 8 days experienced faster wound healing of a punch biopsy than sedentary control mice [69].

Social support is another resource for stress management that is associated with improved health outcomes. It can be emotional, tangible or intangible, informational, or through companionship [70]. Social networking may improve mood, self-image, and feelings of physical limitations while decreasing emotional distress, pain, fatigue, anxiety and depression in patients with chronic wounds. In animal studies, monogamous rodents who were housed in pairs healed a standard punch biopsy wound faster than rodents housed alone [71]. Paired housing also reduced the impact of restraint stress on wound healing. When evaluating immobilization stress on cutaneous wound healing in Siberian hamsters, it was found that those who were housed alone experienced impaired wound healing while hamsters housed in pairs did not [72]. Married persons generally have lower morbidity and mortality rates, however marital stress is associated with reduction in blister wound healing. Reduced cytokine levels in the wound as well as increased circulating IL-6 and tumor necrosis factor (TNF)-α are found in unsympathetic or hostile couples [73].

Pharmacological stress reduction may improve wound healing. Fluoxetine, a selective serotonin reuptake inhibitor (SSRI) antidepressant, is commonly used in the treatment of mood and anxiety disorders [74]. In a study using alternating isolation and crowding stress, stressed Wistar rats who received fluoxetine healed at a similar rate as their non-stressed counterparts, and faster than stressed control animals [75]. Propranolol is a beta-adrenergic receptor antagonist used in the treatment of hypertension, arrhythmias, thyrotoxicosis, capillary hemangiomas, performance anxiety, and essential tremors. Beta-adrenergic receptor signaling, among many other factors, plays a regulatory role in keratinocyte migration which is a critical component of wound repair [76]. Denda et al. demonstrated that stimulation of the beta2-adrenergic receptor (B2AR) pathway delays wound repair, while blockade promotes the wound healing process through increasing migratory speed and accelerating wound re-epithelialization [77–80]. Pullar et al. further demonstrated this effect with isoproterenol, a synthetic beta2-adrenergic agonist which decreased keratinocyte migratory speed, reduced *in vitro* scratch-wound closure, and delayed *ex vivo* human wound re-epithelialization [81, 82]. A study measuring expression levels of the beta2-adrenergic receptor (B2AR), and the catecholamine synthetic enzymes tyrosine hydroxylase and phenylethanolamine-N-methyltransferase in cultured keratinocytes showed that wounding down-regulated B2AR, tyrosine hydroxylase, and phenylethanolamine-N-methyltransferase expression, but pre-exposure to timolol, a beta-adrenergic receptor antagonist, delayed this effect [76]. Norepinephrine presence in acute wounds impairs healing by local B2AR activation in keratinocytes at the wound margins. Keratinocytes modulate catecholamine synthesis and release norepinephrine in response to a wound. This seems to be a stress-related mediator that impairs keratinocyte migration through activation of the B2AR [76]. B-adrenergic receptor antagonists block catecholamine-induced effects on healing and improve wound healing in burns [79, 83]. In a study investigating the effects of propranolol, a non-selective beta-blocker, it was observed macroscopically and microscopically that b-adrenergic receptors participate in stress-induced impairment of cutaneous wound healing through b1- and b2-adrenergic receptor acti-

Table 19.1 Effects of acute and chronic stress on wound healing and immune function

Type of stress	Study design	Results	Reference
Acute	Evaluated relationship between acute post-operative pain intensity and time to healing of a standard 2 mm punch biopsy wound in women	Women who reported higher levels of acute post-operative pain experienced slower wound healing while those who reported lower levels of persistent post-operative pain experienced faster wound healing; depressive symptoms on day of surgery did not affect wound healing but directly correlated with presence of persistent pain	Mcguire et al. [49]
Acute	Evaluated effect of thrombocytopenia on immune function and dermal wound healing in thrombocytopenic rats versus control rats	Thrombocytopenia altered the inflammatory response and immune function measured by increased number of macrophages and T cells in thrombocytopenic rats compared to control rats; there was no difference in wound closure, angiogenesis, or collagen synthesis between groups	Szpaderska et al. [43]
Acute	Evaluated effect of acute pain on time to recovery of barrier function after forearm skin injury in healthy men and women	Greater acute pain was associated with faster recovery of barrier function in men and women with dermal abrasions compared to their own control abrasion and subjects who reported lower pain levels	Graham et al. [48]
Acute and Chronic	Evaluated effect of acute and chronic stress on cell-mediated immune response in rats	Acute stress enhanced cell-mediated immunity by causing T-cells to be redistributed to the skin whereas chronic stress suppressed cell-mediated immunity by causing T-cells to be diverted away from the skin in a delayed type hypersensitivity reaction	Dhabhar et al. [44]
Chronic	Evaluated effect of caregiver stress on sympathetic-adrenal-medullary and hypothalamic-pituitary-adrenal axes in 10 caregivers and 10 age- and weight-matched control subjects	Chronic caregiver stress was associated with a significant decrease (50 %) in GH mRNA expression in peripheral blood mononuclear cells compated to age- and weight-matched controls; GH mRNA levels were negatively correlated with plasma ACTH and norepinephrine levels	Malarkey et al. [41]

(continued)

Table 19.1 (continued)

Type of stress	Study design	Results	Reference
Chronic	Evaluated healing of a 3.5 mm punch biopsy wound in 13 women caring for a relative with Alzheimer's disease and 13 controls matched for age and family income	Chronic psychological stress caused significantly delayed wound healing of a 3.5 mm punch biopsy wound (48.7 vs 39.3 days) and decreased IL-1 mRNA expression in peripheral leukocytes in response to lipopolysaccharide stimulation compared to control subjects	Kiecolt-Glaser et al. [40]
Chronic	Evaluated effect of glucocorticoid receptor antagonist, RU486, on cutaneous wound healing in chronically stressed mice	Glucocorticoid receptor antagonist improved cutaneous wound healing as measured by earlier wound contraction and improved angiogenesis in treated stressed mice compared to untreated stressed mice	Almeida et al. [38]
Chronic	Evaluated effect of chronic restraint stress on cutaneous wound healing of a 3.5 mm punch biopsy in mice	Restraint stress was associated with higher circulating corticosteroid levels and with a 27 % reduction in cutaneous wound healing in stressed mice compared to control mice	Padgett et al. [50]

vation. Propranolol administration appears to counteract the stress-induced delay in wound contraction and re-epithelialization, reverse the reduction in epidermal proliferation, attenuate the delay in the inflammatory response and the impairment in granulation tissue formation, as well as reduce metalloproteinase activity [84].

Relaxation/mindfulness based stress reduction meditation can promote wound healing. A RCT conducted by Broadbent et al. demonstrated that a brief relaxation intervention can reduce stress and improve collagen deposition in surgical wounds [85]. Yoga has been attributed to shorter postoperative hospital stays, earlier drain removal, and decreased TNF-alpha levels for wound healing in early operable breast cancer patients undergoing surgery [86]. Patients receiving relaxation guided imagery exhibited reduced anxiety, erythema, and cortisol levels on post-operative day 1 [87].

Hypnosis has demonstrated benefits in stress reduction and wound healing. A RCT demonstrated faster wound healing rates in patients who underwent targeted hypnosis intervention [88]. A single blind study found that hypnosis induced vasodilation in the healing of burn wounds. Patients that had a bilateral symmetric burn wound were treated hypnotically on one side of their body. Both the hypnosis practitioner and the patient were aware of the side being treated, but the nurse and surgical team were not. Four out of five patients showed accelerated healing on the treated side. The 5th patient showed equal healing on both sides [89]. A RCT comparing the levels of $CD3^+$- and $CD4^+$ T-lymphocytes, and interleukin-1 production at two different stress states, with and without hypnosis intervention, showed an increase of $CD3^+$- and $CD4^+$ T-lymphocytes with the use of hypnosis. Hypnosis

Table 19.2 Impact of stress management on wound healing

Type of stress	Intervention	Study	Results	Reference
Acute	Patient education: Behavioral stress management interventions before surgical procedures	Meta-analyses of clinical studies providing patient information about the surgical procedure and behavioral instructions	Demonstrated better post-operative outcomes, such as fewer medical complications, faster ambulation, decreased hospital length of stay, and reduced use of analgesia	Johnston et al. [55]
Acute	Written emotional disclosure	Evaluated healing of a punch biopsy wound on the nondominant forearm in men randomized to a written emotional disclosure intervention or a non-intervention control group	Healing was assessed using ultrasound biomicroscopy at 3 occasions during a 21-day period. Those who participated in the emotional disclosure intervention had smaller wounds at 14 and 21 days compared to control participants	Weinman et al. [66]
Acute	Physical exercise	Evaluated healing of 3.5 mm punch biopsy wound in older adults randomized to an exercise intervention with aerobic workouts 3 days per week or a non-intervention control group. Evaluated healing of punch biopsy wound in older mice, randomized to a 30-min daily exercise program for 8 days, or a sedentary control group	Those engaging in regular exercise experienced wound healing in a mean of 29 days compared to 39 days for the inactive control group. Older mice that were randomized to a daily exercise program experienced faster wound healing of a punch biopsy than sedentary control mice	Emery et al. [67] Keylock et al. [69]

Type of stress	Intervention	Study	Results	Reference
Chronic	Determine quality of life using Chronic Venous Insufficiency Questionnaire (CVIQ) scale	Evaluated the relationship between the amount of time spent on wound care and the patient's feelings of anger and resentment in 73 patients with venous ulcers	Found that there is a strong correlation between the amount of time spent on ulcer care and feelings of anger and resentment. 68 % of patients reported that the ulcer had a negative emotional impact on their lives including feelings of fear, social isolation, anger, depression, and negative self-image	Wilson [63] Phillips et al. [60]
Chronic	Compression therapy	Examined the effects of standard wound care treatment on health-related quality of life in patients with leg ulcers.	Patients whose ulcers were healing experienced significant improvements in lower extremity pain, increased energy, decreased anxiety, and better sleep.	Franks et al. [64]
Chronic	Wound treatment: Debridement, local and systemic pharmacological treatment, exercise, leg elevation, antibiotics in the presence of infection, and special wound dressings	Evaluated the prevalence of anxiety and depression in 190 patients with chronic venous ulceration	Demonstrated that pain and odor were the two findings commonly associated with depression and anxiety in chronic venous ulcer patients. Living alone, decreased mobility, and presence of exudate was not associated with depression and anxiety. Local wound treatment is associated with pain relief and odor minimization	Jones et al. [58] Lebrun et al. [59]

(continued)

Table 19.2 (continued)

Type of stress	Intervention	Study	Results	Reference
Chronic	Social support or social networking	Evaluated healing of punch biopsy wound in monogamous rodents who were housed in pairs compared with rodents housed alone. Evaluated cytokine levels in the wounds and circulating proinflammatory cytokines IL-6 and TNF-α in hostile couples	Rodents in pairs healed a standard punch biopsy wound faster than rodents housed alone. Paired housing also reduced the impact of restraint stress on wound healing. Reduced cytokine levels in the wound as well as increased circulating IL-6 and tumor necrosis factor (TNF)-α are found in unsympathetic or hostile couples. This is associated with a reduction in wound healing	Glasper et al. [71] Detillion et al. [72] Kiecolt-Glaser et al. [40]

Type of stress	Intervention	Study	Results	Reference
Chronic	Pharmacological stress reduction	Evaluated the effect of fluoxetine in Wistar rats undergoing alternating isolation and crowding stress. Evaluated the effect of propranolol on the wound healing process in burns. Evaluated the effect of isoproterenol on the wound healing process. Evaluated the effect of timolol on expression levels of the beta2-adrenergic receptor (B2AR), and the catecholamine synthetic enzymes tyrosine hydroxylase and phenylethanolamine-N-methyltransferase.	Stressed Wistar rats who received fluoxetine healed at a similar rate as their non-stressed counterparts, and faster than stressed control animals. Propranolol administration appears to counteract the stress-induced delay in wound contraction and re-epithelialization, reverse the reduction in epidermal proliferation, attenuate the delay in the inflammatory response and the impairment in granulation tissue formation, as well as reduce metalloproteinase activity. Isoproterenol decreased keratinocyte migratory speed, reduced *in vitro* scratch-wound closure, and delayed *ex vivo* human wound re-epithelialization. Cultured keratinocytes showed that wounding downregulated B2AR, tyrosine hydroxylase, and phenylethanolamine-N-methyltransferase expression, but pre-exposure to timolol delayed this effect	Farahani et al. [75] Denda et al. [77] Pullar et al. [78] Sivamani et al. [79] Pullar et al. [80] Pullar et al. [81] Pullar et al. [78] Sivamani et al. [76] Romana-Souza et al. [83] Sivamani et al. [79]

(continued)

Table 19.2 (continued)

Type of stress	Intervention	Study	Results	Reference
Acute and chronic	Relaxation/mindfulness based stress reduction: Meditation, Yoga	Evaluated effect of relaxation and mindfulness based stress reduction on surgical wounds	A brief relaxation intervention can reduce stress and improve collagen deposition in surgical wounds. Yoga has been attributed to shorter postoperative hospital stays, earlier drain removal, and decreased TNF-alpha levels for wound healing in early operable breast cancer patients undergoing surgery. Patients receiving relaxation guided imagery exhibited reduced anxiety, erythema, and cortisol levels on post-operative day 1	Broadbent et al. [85] Raghuram et al. [86] Holden-lund et al. [87]

Type of stress	Intervention	Study	Results	Reference
Acute and chronic	Hypnosis	Evaluated the effect of hypnosis on wound healing. Evaluated the effect of hypnosis on wound healing in patients that had a bilateral symmetric burn wound where only one side was treated. Evaluated the levels of $CD3^+$- and $CD4^+$ T-lymphocytes, and interleukin-1 production at two different stress states, with and without hypnosis intervention. Evaluated hypnosis and pain	Found that wound healing occurred at a faster rate in patients who underwent targeted hypnosis intervention. Four out of five patients showed accelerated healing on the treated side. The 5th patient showed equal healing on both sides. Showed an increase of $CD3^+$- and $CD4^+$ T-lymphocytes with the use of hypnosis. Hypnosis could have a beneficial effect on the immunological dysregulation from acute stress. Hypnosis was shown to decrease pain during wound debridement and thus could be used to decrease patient distress	Ginandes et al. [88] Moore and Kaplan [89] Kiecolt-Glaser et al. [90] Patterson et al. [91]
Acute and chronic	Cognitive-behavioral stress management (CBSM)	Evaluated cognitive-behavioral stress management (CBSM) therapy in patients with stage I and II breast cancer. Evaluated CBSM therapy in patients with prostate cancer. Evaluated pro-inflammatory leukocyte gene expression in patients receiving 10 weeks of CBSM therapy	Patients receiving CBSM showed a decrease in cortisol levels in comparison to the control group. CBSM was shown to improve the quality of life in patients with prostate cancer. CBSM was shown to reverse upregulation of gene expression	Cruess et al. [93] Penedo et al. [94] Antoni et al. [95]

could have a beneficial effect on the immunological dysregulation from acute stress [90]. As already discussed pain is a major component of stress and can induce distress in patients. Hypnosis has been shown to decrease pain during wound debridement and thus could be used to decrease patient distress [91].

Cognitive-behavioral stress management (CBSM) is a short-term therapy that focuses on the interaction of thoughts, feelings and behaviors. The most common type of CBSM aims to alter irrational thoughts related to negative psychological states (depression, anger, anxiety), recognizing internal and external stressors, learning stress management skills, and developing adaptive behavioral coping strategies [92]. Patients with stage I and II breast cancer that received cognitive-behavioral stress management therapy showed a decrease in cortisol levels in comparison to the control group not receiving an intervention [93]. CBSM has been shown to improve the quality of life in patients with prostate cancer [94]. Chronic stress and anxiety have been shown to upregulate pro-inflammatory leukocyte gene expression via the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis. A 10 week cognitive-behavioral stress management intervention was shown to reverse this upregulation of gene expression [95]. Although, no studies have been pursued to attest the usefulness and effectiveness of CBSM interventions for wounds it can nevertheless be part of the management of patients with wounds given its proven benefits for stress inducing diseases (Tables 19.1 and 19.2).

Conclusion

Stress impacts the immune system, surgical outcomes, metabolism, as well as risks of various diseases including obesity and cardiovascular disease. The skin is the largest organ of the human body. It is vital for fluid balance, thermoregulation, Vitamin D production, as well as protection from pathogens and mechanical injury. Wounds occur when there is a disruption in the anatomic and physiologic continuity of the skin. As aforementioned, wounds can be classified as acute or chronic, depending on the time course of healing; according to etiology, including, but not limited to, venous insufficiency, arterial disease, autoimmune disorders, pressure, diabetes and neuropathy, trauma, surgery, and burns; or by location (lower extremity, foot, etc.). Maintenance of skin integrity and timely wound healing is critical. When this process is disrupted, chronic wounds result, bringing about a large physical, psychological, and economic burden to the patient. Chronic stress impairs proper wound healing, alters immune function, and is associated with worse surgical outcomes, therefore it is necessary to address stress reduction as part of the treatment plan for patients with wounds.

References

1. Cohen S., Kessler RC, Underwood LG. Measuring stress: a guide for health and social scientists. New York: Oxford University Press. 1995. Retrieved from: http://www.psy.cmu.edu/~scohen/Cohen,%20S%20et%20al%20(1995).pdf.
2. Miller LH, Smith AD (n.d.). Retrieved 1 Mar 2016, from http://www.apa.org/helpcenter/stress-kinds.aspx.

3. Lucas VS. Psychological stress and wound healing in humans: what we know. Wounds. 2011;23(4):76–83.
4. Dhabhar FS. Acute stress enhances while chronic stress suppresses skin immunity: the role of stress hormones and leukocyte trafficking. Ann N Y Acad Sci. 2000;917(1):876–93.
5. Korte SM, Koolhaas JM, Wingfield JC, McEwen BS. The Darwinian concept of stress: benefits of allostasis and costs of allostatic load and the trade-offs in health and disease. Neurosci Biobehav Rev. 2005;29(1):3–38.
6. Sanchis-Gomar F, Garcia-Gimenez JL, Perez-Quilis C, Gomez-Cabrera MC, Pallardo FV, Lippi G. Physical exercise as an epigenetic modulator. J Strength Cond Res. 2012;26(12):3469–72.
7. Zabora J, BrintzenhofeSzoc K, Curbow B, Hooker C, Piantadosi S. The prevalence of psychological distress by cancer site. Psycho Oncol. 2001;10(1):19–28.
8. Ebrecht M, Hextall J, Kirtley LG, Taylor A, Dyson M, Weinman J. Perceived stress and cortisol levels predict speed of wound healing in healthy male adults. Psychoneuroendocrinology. 2004;29(6):798–809.
9. Levenstein S, Prantera C, Varvo V, Scribano ML, Berto E, Luzi C, Andreoli A. Development of the perceived stress questionnaire: a new tool for psychosomatic research. J Psychosom Res. 1993;37(1):19–32.
10. Atiyeh BS, Ioannovich J, Al-Amm CA, El-Musa KA. Management of acute and chronic open wounds: the importance of moist environment in optimal wound healing. Curr Pharm Biotechnol. 2002;3(3):179–95.
11. Li J, Chen J, Kirsner R. Pathophysiology of acute wound healing. Clin Dermatol. 2007;25(1):9–18.
12. Roca RP, Spence RJ, Munster AM. Posttraumatic adaptation and distress among adult burn survivors. Am J Psychiatry. 1992;149(9):1234–8.
13. Upton D, Solowiej K, Hender C, Woo KY. Stress and pain associated with dressing change in patients with chronic wounds. J Wound Care. 2012;21(2):53–4.
14. Kirsner RS, Bohn G, Driver VR, Mills JL, Nanney LB, Williams ML, Wu SC. Human acellular dermal wound matrix: evidence and experience. Int Wound J. 2013;12(6):646–54.
15. Baltzis D, Eleftheriadou I, Veves A. Pathogenesis and treatment of impaired wound healing in diabetes mellitus: new insights. Adv Ther. 2014;31(8):817–36.
16. Werner S, Grose R. Regulation of wound healing by growth factors and cytokines. Physiol Rev. 2003;83(3):835–70.
17. Baum CL, Arpey CJ. Normal cutaneous wound healing: clinical correlation with cellular and molecular events. Dermatol Surg. 2006;31(6):674–86.
18. Shah M, Foreman DM, Ferguson MW. Neutralization of TGF-beta 1 and TGF-beta 2 or exogenous addition of TGF-beta 3 to cutaneous rat wounds reduces scarring. J Cell Sci. 1995;108(Pt 3):985–1002.
19. Kim LR, Whelpdale K, Zurowski M, Pomeranz B. Sympathetic denervation impairs epidermal healing in cutaneous wounds. Wound Repair Regen. 1998;6(3):194–201.
20. Cooper CL, Malik KU. Prostaglandin synthesis and renal vasoconstriction elicited by adrenergic stimuli are linked to activation of alpha-1 adrenergic receptors in the isolated rat kidney. J Pharmacol Exp Ther. 1985;233(1):24–31.
21. Gonzales R, Goldyne ME, Taiwo YO, Levine JD. Production of hyperalgesic prostaglandins by sympathetic postganglionic neurons. J Neurochem. 1989;53(5):1595–8.
22. Malik K. Interaction of arachidonic acid metabolites and adrenergic nervous system. Am J Med Sci. 1988;295(4):280–6.
23. Hebda PA, Collins MA, Tharp MD. Mast cell and myofibroblast in wound healing. Dermatol Clin. 1993;11(4):685–96.
24. Falanga V. Growth factors and wound healing. J Dermatol Surg Oncol. 1993;19(8):711–4.
25. Broder C, Arnold P, Goff SV, Konerding MA, Bahr K, Muller S, Overallf CM, Bondg JS, Koudelkah T, Tholeyh A, Hulmesc DJS, Moalic C, Becker-Pauly C. Metalloproteases meprin and meprin are C- and N-procollagen proteinases important for collagen assembly and tensile strength. Proc Natl Acad Sci. 2013;110(35):14219–24.
26. Merkel JR, Dipaolo BR, Hallock GG, Rice DC. Type I and type III collagen content of healing wounds in fetal and adult rats. Exp Biol Med. 1988;187(4):493–7.

27. Even-Ram S, Yamada KM. Cell migration in 3D matrix. Curr Opin Cell Biol. 2005;17(5):524–32.
28. Gallo RL. Proteoglycans and cutaneous vascular defense and repair. J Investig Dermatol Symp Proc. 2000;5(1):55–60.
29. Gallo RL, Ono M, Povsic T, Page C, Eriksson E, Klagsbrun M, Bernfield M. Syndecans, cell surface heparan sulfate proteoglycans, are induced by a proline-rich antimicrobial peptide from wounds. Proc Natl Acad Sci. 1994;91(23):11035–9.
30. Yayon A, Klagsbrun M, Esko JD, Leder P, Ornitz DM. Cell surface, heparin-like molecules are required for binding of basic fibroblast growth factor to its high affinity receptor. Cell. 1991;64(4):841–8.
31. Rapraeger A, Krufka A, Olwin B. Requirement of heparan sulfate for bFGF-mediated fibroblast growth and myoblast differentiation. Science. 1991;252(5013):1705–8.
32. Londono C, Loureiro MJ, Slater B, Lücker PB, Soleas J, Sathananthan S, Aitchison JS, Kabla A, Mcguigan AP. Nonautonomous contact guidance signaling during collective cell migration. Proc Natl Acad Sci U S A. 2014;111(5):1807–12.
33. Taylor G, Lehrer MS, Jensen PJ, Sun T, Lavker RM. Involvement of follicular stem cells in forming not only the follicle but also the epidermis. Cell. 2000;102(4):451–61.
34. Pilcher BK, Dumin JA, Sudbeck BD, Krane SM, Welgus HG, Parks WC. The activity of collagenase-1 is required for keratinocyte migration on a type I collagen matrix. J Cell Biol. 1997;137(6):1445–57.
35. Ham SA, Hwang JS, Yoo T, Lee WJ, Paek KS, Oh JW, Park CK, Kim JH, Do JT, Kim JH, Seo HG. Ligand-activated PPARδ upregulates α-smooth muscle actin expression in human dermal fibroblasts: a potential role for PPARδ in wound healing. J Dermatol Sci. 2015;80(3):186–95.
36. Iocono JA, Colleran KR, Remick DG, Gillespie BW, Ehrlich HP, Garner WL. Interleukin-8 levels and activity in delayed-healing human thermal wounds. Wound Repair Regen. 2000;8(3):216–25.
37. Stress (2012, September 20). Retrieved 27 Feb 2016, from http://www.medicinenet.com/script/main/art.asp?articlekey=20104.
38. Almeida TF, Pires TD, Monte-Alto-Costa A. Blockade of glucocorticoid receptors improves cutaneous wound healing in stressed mice. Exp Biol Med. 2015;241(4):353–8.
39. Ader R, Nicholas C, Felten D. Psychoneuroimmunology: interactions between the nervous system and the immune system. Lancet. 1995;345:99–103.
40. Kiecolt-Glaser J, Marucha P, Mercado A, Malarkey W, Glaser R. Slowing of wound healing by psychological stress. Lancet. 1995;346(8984):1194–6. doi:10.1016/s0140-6736(95)92899-5.
41. Malarkey WB, Wu H, Cacioppo JT, Malarkey KL, Poehlmann KM, Glaser R, Kiecolt-Glaser JK. Chronic stress down-regulates growth hormone gene expression in peripheral blood mononuclear cells of older adults. Endocrine. 1996;5(1):33–9. doi:10.1007/bf02738653.
42. Richards A, Mitsou J, Floyd D, Terenghi G, Mcgrouther D. Neural innervation and healing. Lancet. 1997;350(9074):339–40.
43. Szpaderska AM, Egozi EI, Gamelli RL, Dipietro LA. The effect of thrombocytopenia on dermal wound healing. J Invest Dermatol. 2003;120(6):1130–7.
44. Dhabhar FS, Mcewen BS. Acute stress enhances while chronic stress suppresses cell-mediated immunity in vivo: a potential role for leukocyte trafficking. Brain Behav Immun. 1997;11(4):286–306.
45. Segerstrom SC, Miller GE. Psychological stress and the human immune system: a meta-analytic study of 30 years of inquiry. Psychol Bull. 2004;130(4):601.
46. McMurray Jr JF. Wound healing with diabetes mellitus. Better glucose control for better wound healing in diabetes. Surg Clin North Am. 1984;64(4):769–78.
47. Alavi A, Sibbald RG, Mayer D, Goodman L, Botros M, Armstrong DG, Woo K, Boeni T, Ayello EA, Kirsner RS. Diabetic foot ulcers: part II. Management. J Am Acad Dermatol. 2014;70(1):21. e1–4.
48. Graham J, Song S, Engeland C. Acute pain speeds skin barrier recovery in healthy men and women. J Psychosom Res. 2012;73:452–8.
49. Mcguire L, Heffner K, Glaser R, Needleman B, Malarkey W, Dickinson S, Lemeshow S, Cook C, Muscarella P, Melvin WS, Ellison EC, Kiecolt-Glaser JK. Pain and wound healing in surgical patients. Ann Behav Med. 2006;31(2):165–72. doi:10.1207/s15324796abm3102_8.

50. Padgett DA, Marucha PT, Sheridan JF. Restraint stress slows cutaneous wound healing in mice. Brain Behav Immun. 1998;12(1):64–73. doi:10.1006/brbi.1997.0512.
51. Livingstone W, Mortel TF, Taylor B. A path of perpetual resilience: exploring the experience of a diabetes-related amputation through grounded theory. Contemp Nurse. 2011;39(1):20–30. doi:10.5172/conu.2011.39.1.20.
52. Alagiakrishnan K, Sclater A. Psychiatric disorders presenting in the elderly with type 2 diabetes mellitus. Am J Geriatr Psychiatry. 2012;20(8):645–52. doi:10.1097/jgp.0b013e31823038db.
53. Hood KK, Lawrence JM, Anderson A, Bell R, Dabelea D, Daniels S, Rodriguez B, Dolan LM, Diabetes in Youth Study Group. Metabolic and inflammatory links to depression in youth with diabetes. Diabetes Care. 2012;35(12):2443–6. doi:10.2337/dc11-2329.
54. Gouin J, Kiecolt-Glaser JK. The impact of psychological stress on wound healing: methods and mechanisms. Immunol Allergy Clin North Am. 2011;31(1):81–93. doi:10.1016/j.iac.2010.09.010.
55. Johnston M, Vogele C. Benefits of psychological preparation for surgery: a meta-analysis. Ann Behav Med. 1993;15:245–56.
56. Montgomery GH, David D, Winkel G, Silverstein JH, Bovbjerg DH. The effectiveness of adjunctive hypnosis with surgical patients: a meta-analysis. Anesth Analg. 2002;94(6):1639–45. doi:10.1213/00000539-200206000-00052.
57. Guex JJ, Myon E, Didier L, Nguyen LC, Taieb C. Chronic venous disease: health status of a population and care impact on this health status through quality of life questionnaires. Int Angiol. 2005;24(3):258–64.
58. Jone J, Barr W, Robinson J, Carlisle C. Depression in patients with chronic venous ulceration. Br J Nursing. 2006;15(Sup2). doi:10.12968/bjon.2006.15.sup2.21237.
59. Lebrun E, Tomic-Canic M, Kirsner RS. The role of surgical debridement in healing of diabetic foot ulcers. Wound Repair Regen. 2010;18(5):433–8. doi:10.1111/j.1524-475x.2010.00619.x.
60. Phillips T, Stanton B, Provan A, Lew R. A study of the impact of leg ulcers on quality of life: financial, social, and psychologic implications. J Am Acad Dermatol. 1994;31(1):49–53. doi:10.1016/s0190-9622(94)70134-2.
61. Cole-King A, Harding KG. Psychological factors and delayed healing in chronic wounds. Psychosom Med. 2001;63(2):216–20. doi:10.1097/00006842-200103000-00004.
62. Hareendran A, Bradbury A, Budd J, Geroulakos G, Hobbs R, Kenkre J, Symonds T. Measuring the impact of venous leg ulcers on quality of life. J Wound Care. 2005;14(2):53–7. doi:10.12968/jowc.2005.14.2.26732.
63. Wilson AB. Quality of life and leg ulceration from the patient's perspective. Br J Nursing. 2001;13(Sup2). doi:10.12968/bjon.2004.13.sup2.13235.
64. Franks PJ, Moffatt CJ, Doherty DC, Smithdale R, Martin R. Longer-term changes in quality of life in chronic leg ulceration. Wound Repair Regen. 2006;14(5):536–41. doi:10.1111/j.1743-6109.2006.00160.x.
65. Esterling BA, L'Abate L, Murray EJ, Pennebaker JW. Empirical foundations for writing in prevention and psychotherapy. Clin Psychol Rev. 1999;19(1):79–96. doi:10.1016/s0272-7358(98)00015-4.
66. Weinman J, Ebrecht M, Scott S, Walburn J, Dyson M. Enhanced wound healing after emotional disclosure intervention. Br J Health Psychol. 2008;13(1):95–102. doi:10.1348/135910707x251207.
67. Emery CF, Blumenthal JA. Effects of physical exercise on psychological and cognitive functioning of older adults. Ann Behav Med. 1991;13:99–107.
68. Emery CF, Kiecolt-Glaser JK, Glaser R, Malarkey WB, Frid DJ. Exercise accelerates wound healing among healthy older adults: a preliminary investigation. J Gerontol A Biol Sci Med Sci. 2005;60(11):1432–6. doi:10.1093/gerona/60.11.1432.
69. Keylock KT, Vieira VJ, Wallig MA, Dipietro LA, Schrementi M, Woods JA. Exercise accelerates cutaneous wound healing and decreases wound inflammation in aged mice. Am J Physiol Regul Integr Comp Physiol. 2007;294(1):R179–84. doi:10.1152/ajpregu.00177.2007.
70. House J, Landis K, Umberson D. Social relationships and health. Science. 1988;241(4865):540–5. doi:10.1126/science.3399889.
71. Glasper ER, Devries A. Social structure influences effects of pair-housing on wound healing. Brain Behav Immun. 2005;19(1):61–8. doi:10.1016/j.bbi.2004.03.002.

72. Detillion CE, Craft TK, Glasper ER, Prendergast BJ, Devries A. Social facilitation of wound healing. Psychoneuroendocrinology. 2004;29(8):1004–11. doi:10.1016/j.psyneuen.2003.10.003.
73. Kiecolt-Glaser JK, Loving TJ, Stowell JR, Malarkey WB, Lemeshow S, Dickinson SL, Glaser R. Hostile marital interactions, proinflammatory cytokine production, and wound healing. Arch Gen Psychiatry. 2005;62(12):1377. doi:10.1001/archpsyc.62.12.1377.
74. Rossi A, Barraco A, Donda P. Fluoxetine: a review on evidence based medicine. Ann Gen Hosp Psychiatry. 2004;3(1):2.
75. Farahani RM, Sadr K, Rad JS, Mesgari M. Fluoxetine enhances cutaneous wound healing in chronically stressed Wistar rats. Adv Skin Wound Care. 2007;20(3):157–65. doi:10.1097/01.asw.0000262710.59293.6b.
76. Sivamani RK, Shi B, Griffiths E, Vu SM, Lev-Tov HA, Dahle S, Chigbrow M, La TD, Mashburn C, Peavy TR, Isseroff RR. Acute wounding alters the beta2-adrenergic signaling and catecholamine synthetic pathways in keratinocytes. J Invest Dermatol. 2014;134(8):2258–66. doi:10.1038/jid.2014.137.
77. Denda M, Fuziwara S, Inoue K. β2-adrenergic receptor antagonist accelerates skin barrier recovery and reduces epidermal hyperplasia induced by barrier disruption. J Invest Dermatol. 2003;121(1):142–8. doi:10.1046/j.1523-1747.2003.12310.x.
78. Pullar CE, Rizzo A, Isseroff RR. Beta-adrenergic receptor antagonists accelerate skin wound healing: evidence for a catecholamine synthesis network in the epidermis. J Biol Chem. 2006;281(30):21225–35. doi:10.1074/jbc.m601007200.
79. Sivamani RK, Pullar CE, Manabat-Hidalgo CG, Rocke DM, Carlsen RC, Greenhalgh DG, Isseroff RR. Stress-mediated increases in systemic and local epinephrine impair skin wound healing: potential new indication for beta blockers. PLoS Med. 2009;6(1):e12. doi:10.1371/journal.pmed.1000012.
80. Pullar CE, Provost GS, O'leary AP, Evans SE, Baier BS, Isseroff RR. β2AR antagonists and β2AR gene deletion both promote skin wound repair processes. J Invest Dermatol. 2012;132(8):2076–84. doi:10.1038/jid.2012.108.
81. Pullar CE, Chen J, Isseroff RR. PP2A activation by 2-adrenergic receptor agonists: novel regulatory mechanism of keratinocyte migration. J Biol Chem. 2003;278(25):22555–62. doi:10.1074/jbc.m300205200.
82. Pullar CE. Beta2-Adrenergic receptor activation delays wound healing. FASEB J. 2006;20(1):76–86. doi:10.1096/fj.05-4188com.
83. Romana-Souza B, Nascimento AP, Monte-Alto-Costa A. Low-dose propranolol improves cutaneous wound healing of burn-injured rats. Plast Reconstr Surg. 2008;122(6):1690–9. doi:10.1097/prs.0b013e31818cbf67.
84. Romana-Souza B, Porto LC, Monte-Alto-Costa A. Cutaneous wound healing of chronically stressed mice is improved through catecholamines blockade. Exp Dermatol. 2010;19(9):821–9. doi:10.1111/j.1600-0625.2010.01113.x.
85. Broadbent E, Kahokehr A, Booth RJ, Thomas J, Windsor JA, Buchanan CM, Wheeler BR, Sammour T, Hill AG. A brief relaxation intervention reduces stress and improves surgical wound healing response: a randomised trial. Brain Behav Immun. 2012;26(2):212–7. doi:10.1016/j.bbi.2011.06.014.
86. Raghuram N, Vinay C, Chandrashekara S, Gopinath K, Srinath B, Rao R, Nagendra H. Influence of yoga on postoperative outcomes and wound healing in early operable breast cancer patients undergoing surgery. Int J Yoga. 2008;1(1):33. doi:10.4103/0973-6131.36795.
87. Holden-Lund C. Effects of relaxation with guided imagery on surgical stress and wound healing. Res Nurs Health. 1988;11(4):235–44. doi:10.1002/nur.4770110405.
88. Ginandes C, Brooks P, Sando W, Jones C, Aker J. Can medical hypnosis accelerate post-surgical wound healing? results of a clinical trial. Am J Clin Hypn. 2003;45(4):333–51. doi:10.1080/00029157.2003.10403546.
89. Moore LE, Kaplan JZ. Hypnotically accelerated burn wound healing. Am J Clin Hypn. 1983;26(1):16–9. doi:10.1080/00029157.1983.10404132.

90. Kiecolt-Glaser JK, Marucha PT, Atkinson C, Glaser R. Hypnosis as a modulator of cellular immune dysregulation during acute stress. J Consult Clin Psychol. 2001;69(4):674–82. doi:10.1037/0022-006x.69.4.674.
91. Patterson DR, Everett JJ, Burns GL, Marvin JA. Hypnosis for the treatment of burn pain. J Consult Clin Psychol. 1992;60(5):713–7. doi:10.1037/0022-006x.60.5.713.
92. Crepaz N, Passin WF, Herbst JH, Rama SM, Malow RM, Purcell DW, Wolitski RJ. Meta-analysis of cognitive-behavioral interventions on HIV-positive persons' mental health and immune functioning. Health Psychol. 2008;27(1):4–14. doi:10.1037/0278-6133.27.1.4.
93. Cruess DG, Antoni MH, Mcgregor BA, Kilbourn KM, Boyers AE, Alferi SM, Carver CS, Kumar M. Cognitive-behavioral stress management reduces serum cortisol by enhancing benefit finding among women being treated for early stage breast cancer. Psychosom Med. 2000;62(3):304–8. doi:10.1097/00006842-200005000-00002.
94. Penedo FJ, Dahn JR, Molton I, Gonzalez JS, Kinsinger D, Roos BA, Carver CS, Schneiderman N, Antoni MH. Cognitive-behavioral stress management improves stress-management skills and quality of life in men recovering from treatment of prostate carcinoma. Cancer. 2004;100(1):192–200. doi:10.1002/cncr.11894.
95. Antoni MH, Lutgendorf SK, Blomberg B, Carver CS, Lechner S, Diaz A, Stagl J, Arevalo JM, Cole SW. Cognitive-behavioral stress management reverses anxiety-related leukocyte transcriptional dynamics. Biol Psychiatry. 2012;71(4):366–72. doi:10.1016/j.biopsych.2011.10.007.

Chapter 20
Herpes and Stress

Bárbara Roque Ferreira and José Carlos Cardoso

Abbreviations

ACTH	Adrenocorticotropin hormone
AIDS	Acquired immune deficiency syndrome
cAMP	Cyclic adenosine monophosphate
CBT	Cognitive behavior therapy
CD3	Cluster of differentiation 3
CD8	Cluster of differentiation 8
CMV	Cytomegalovirus
CNS	Central nervous system
CRF	Corticotropin releasing factor
DFA	Direct fluorescent antibody
DHEA-S	Dehydroepiandrosterone sulfate
DNA	Deoxyribonucleic acid
EBER	EBV-encoded small RNA
EBV	Epstein-Barr virus
HHV	Human herpesviruses
HIV	Human immunodeficiency virus
HPA axis	Hypothalamic-pituitary-adrenal axis
HSV	Herpes simplex virus
IL-6	Interleukin 6

B.R. Ferreira, MD • J.C. Cardoso, MD (✉)
Dermatology Department, Coimbra Hospital and University Centre,
Praceta Mota Pinto, 3000-075 Coimbra, Portugal
e-mail: barbara.roqueferreira@gmail.com; jose.c.cardoso@gmail.com

K. França, M. Jafferany (eds.), *Stress and Skin Disorders*,
DOI 10.1007/978-3-319-46352-0_20

LAK cell	Lymphokine activated killer cell
LAT	Latency-associated transcript
NK cell	Natural Killer cell
PCR	Polymerase chain reaction
SAM axis	Sympathetic-adrenal-medullary axis
VZV	Varicella–zoster virus

Human Herpesviruses and Psychodermatology

Hippocrates, the father of Medicine, was the first who mentioned the mind-body relationship [1]. At an embryological level, the brain and the skin have the same ectodermic origin and they also share biochemical mechanisms, as it would be expected. More precisely, the neuro-immuno-cutaneous-endocrine model was suggested by O'Sullivan et al. (1998) to explain the mind and body connection. This means that there is a link between skin, central nervous system (CNS), endocrine system and immunity. This model intends to explain how many dermatoses are triggered or exacerbated by stress factors, including psychological stress [2]. The skin is the interface between the inner and the outer environment and, thereby, from physical agents to psychosocial stress factors, all are linked with the natural history of several skin diseases. Besides, skin diseases have a high impact on the patients' health-related quality of life, with high levels of psychological morbidity.

Human herpesviruses (HHV) include eight different viruses with double-stranded DNA (herpes simplex virus types 1 and 2 (HSV-1, HSV-2), varicella–zoster virus (VZV), Epstein–Barr virus (EBV), cytomegalovirus (CMV), human herpesvirus type 6 (HHV-6), human herpesvirus type 7 (HHV-7) and human herpesvirus type 8 (HHV-8)). Because viruses require host cells to replicate their genetic component, the etiopathogenesis and clinical presentation is closely related to the host's biopsychosocial dimensions [3]. The pathogenesis of herpesvirus infections includes a primary infection, latency and reactivation. All HHV may have longstanding latency in the host after the primary infection and their reactivation is correlated with the host's immune response [4]. In the last years, several studies have pointed out psychoneuroimmunological evidence for the role of psychological stress in the development of skin lesions due to the different HHV [5], stressing this as an emerging topic in Psychodermatology. Moreover, as we could find for other skin diseases, patients with skin manifestations of HHV may also have feelings of shame and stigma, with impact on relationships. Thus, as well as the medical treatments, these patients should be given psychological assessment and intervention to treat mental health problems that worsen or that result from having the skin lesions. A critical analysis on this matter is the purpose of this text.

Human Herpesviruses: Classification and Clinical Features

HHV include eight members of double-stranded DNA viruses. The pathogenesis of HHV infections follows the sequence of primary infection, latency and reactivation.

The family *Herpesviridae* consists of three subfamilies and they are categorized into three groups: alpha, beta and gamma herpesvirinae [6]. Herpes simplex virus types 1 (HSV-1 or HHV-1) and 2 (HSV-2 or HHV-2) and varicella–zoster virus (VZV or HHV-3) are classified as *Alphaherpesvirinae*. Cytomegalovirus (CMV or HHV-5), human herpesvirus type 6 (HHV-6) and human herpesvirus type 7 (HHV-7) are classified as *Betaherpesvirinae*. Epstein–Barr virus (EBV or HHV-4) and human herpesvirus type 8 (HHV-8) are classified as *Gammaherpesvirinae*. Another important point concerning the classification of the HHV is the predominant cell type infected during the lytic or the latent infection [4].

During the lytic infection, HHV-1, HHV-2, HHV-3 and HHV-4 can infect epithelial cells. HHV-4 can also infect B cells. On the other hand, HHV-5 can infect lymphocytes, macrophages and endothelial cells. HHV-8 also infects lymphocytes. Finally, HHV-6 and HHV-7 infect T cells. In turn, the latent infection occurs in neurons for HHV-1, HHV-2 and HHV-3. It occurs in B cells for HHV-4 and T cells for HHV-7. HHV-5 can have the latent infection either in lymphocytes and macrophages, HHV-6 in lymphocytes and monocytes and HHV-8 in lymphocytes and endothelial cells [4]. Basically, the neuron is the cell involved in latency for the *Alphaherpesvirinae*, the monocyte lineage for the *Betaherpesvirinae*, and lymphocytes for the *Gammaherpesvirinae* [6].

HHV-1 (HSV-1) and HHV-2 (HSV-2)

These HHV have a worldwide distribution. Orolabial HSV is more often due to HSV-1 while genital HSV commonly results from HSV-2. Nevertheless the contrary can be possible and has become much more frequent in the last decades [7]. Indeed, in developed countries, half of new cases of genital herpes are now due to HSV-1 [8]. However, up to now HSV-2 has been considered the first cause of genital ulcers worldwide [9].

The transmission of HSV can occur during symptomatic and asymptomatic periods of viral shedding. The initial infection can be primary or non-primary and clinically they can be both symptomatic and asymptomatic: it is a primary initial infection when the patient is experiencing a first HSV infection and it is a non-primary initial infection when there was a previous infection with a HSV, but at that moment the patient was infected with another HSV [4]. Afterwards, the virus remains in latency (non-infectious state) in sensory ganglia (trigeminal in the case of orolabial HSV and sacral in the case of genital HSV) and the reactivation can occur due to several factors

such as physical stress factors (for example, fever or trauma) and psychological stress [4, 7]. The reactivation can occur with asymptomatic viral shedding or clinical manifestations. The production of memory CD8+ T cells, specific for HSV, is critical to control the infection and to prevent symptomatic recurrences [4].

As previously mentioned, HSV-1 is commonly transmitted by direct contact with saliva or other infected secretions and HSV-2 by sexual contact [3]. An asymptomatic presentation is highly common and the clinical features are varied. When the patient has a primary infection, the onset of symptoms is generally from 3 to 7 days after the exposure. Before the onset of mucocutaneous lesions there is a generalized prodrome of fever and malaise and sometimes localized dysesthesia. Subsequently, the patient will have the initial skin lesions characterized by grouped vesicles on an erythematous base which might become umbilicated and progress to pustules, erosions and/or ulcerations [4]. The lesions usually resolve in 2–3 weeks [3]. When the patient has a reactivation of HSV, the clinical presentation is similar, but the severity of symptoms tends to be milder and the duration of the disease is shorter [4].

Orolabial HSV can also be clinically expressed by a gingivostomatitis in children or, for example, as pharyngitis in young adults. The reactivation is usually on vermilion border of lips, but it can appear, for example, on cheek, nasal mucosa or hard palate as well. Genital HSV can cause a painful balanitis or vulvitis and vaginitis in the context of a primary infection. Commonly a reactivation is subclinical. Apart from what was described above, HSV infections can have other cutaneous and extracutaneous manifestations, such as: eczema herpeticum, herpetic whitlow, herpes gladiatorum, ocular and neonatal HSV and encephalitis [3].

Frequently, the diagnosis of a HSV infection is based on the clinical presentation. However, a Tzanck smear can be easily performed, with results in minutes. Polymerase chain reaction (PCR), direct fluorescent antibody (DFA), viral culture and a skin biopsy for hematoxylin and eosin are other possibilities. For epidemiologic studies and to establish serostatus, Western blot is useful [4].

HHV-3 (VZV)

HHV-3 or VZV is the HHV which causes varicella and herpes zoster. VZV has a worldwide distribution and 98 % of the population could be seropositive. The peak incidence for varicella is between 10 and 14 years [3]. The incidence as well as the severity of herpes zoster increase throughout adulthood and represent the reactivation of latent VZV infection. It is estimated that approximately 20 % of healthy adults and 50 % of immunocompromised patients will develop herpes zoster [4]. Risk factors are still under research, but they include psychological and physical stress (such as, trauma, fever or radiation therapy), immunosuppression, cellular immune dysfunction as well as a family history of zoster [3, 4].

Regarding the way of transmission of varicella, the major route is through the respiratory tract (airborne droplets) but the contact with vesicular fluid can also transmit the disease. The incubation period may last about 15 days and the infected patient can transmit the disease 2 days before the appearance of the skin lesions and until all

the vesicles have disappeared [3]. VZV can replicate in the liver, in the spleen and it also invades the epidermis. It remains latent in the cells of the dorsal root ganglia. When the reactivation occurs (herpes zoster), the virus replicates in the affected dorsal root ganglion causing a neuronal inflammation and painful neuralgia [4].

After the incubation period, the primary infection (varicella) may clinically begin with a prodrome of fever and myalgia. This prodrome tends to be more common in adults than in children. Afterwards, there is an eruption of erythematous and pruritic macules and papules which start on the scalp and face and then progress to the trunk and extremities (the absence of lesions on the lower extremities is usual). Hours later, the patient will develop vesicles surrounded by an erythematous halo [3]. The lesions evolve to pustules and crusts after 1–2 weeks. The oral mucosa may also be involved. All things considered, the presence of lesions in the different stages of development described above is characteristic of varicella. The disease is generally self-limited and benign, but complications can occur. Varicella in adolescents and adults is often more severe than that in children, having a higher risk for complications, especially pneumonia. In the immunocompetent host, the most common complication is secondary bacterial infection of the skin. Occasionally, other complications, such as thrombocytopenia, hepatitis, glomerulonephritis, myocarditis or vasculitis can develop. Rarely, CNS complications can occur, such as Reye's syndrome and encephalitis. CNS complications are far more frequent in immunocompromised patients, as is the involvement of other organs. Furthermore, the skin lesions of immunocompromised patients may have atypical features [4].

Clinically, herpes zoster starts with a prodrome of severe pain or dysesthesia in the dermatome affected. Thereafter, commonly, painful grouped vesicles on erythematous base appear on that dermatomal distribution, more often on the trunk. Some patients will not develop the skin lesions. Usually, in young patients without immune compromise the disease has a benign course. Nevertheless, older patients as well as those with immune compromise will experience a more severe disease. Postherpetic neuralgia (dysesthesia that persists after the resolution of the skin lesions) is the most common complication and its incidence is directly related to older age, affecting 50 % of patients older than 60 years [10]. In the immunocompetent patient, other complications can occur, namely: pneumonitis, ophthalmic zoster or Ramsay-Hunt syndrome. In turn, in the immunocompromised patient, unusual clinical features are common as well as a disseminated cutaneous disease and more severe visceral involvement.

Usually, the diagnosis is based on the recognition of the typical clinical features. However, as it was described for HSV, Tzanck smear, DFA or PCR can help in the diagnosis. DFA and PCR can differentiate between HSV and VZV. Serology is only useful in retrospect [4].

HHV-4 (EBV)

EBV, the etiologic agent of infectious mononucleosis, was the first human virus isolated from a neoplastic disorder [11]. The reactivation of EBV can be responsible for several diseases, namely hydroa vacciniforme, lymphoproliferative diseases and

nasopharyngeal carcinoma. Infectious mononucleosis caused by EBV usually occurs between 15 and 25 years old after a long incubation period (30–50 days). The peak incidence is between 1–6 and 14–20 years of age. The transmission generally occurs through infectious saliva and hence the primary infection is in the oropharyngeal epithelium. After the resolution of the disease, B cells can maintain a latent infection. A prodrome of fatigue and headache may occur. After that period, the majority of patients exhibit pharyngitis, fever and cervical lymphadenopathy. Exsudative tonsillitis may also be observed. Half of the patients can also have splenomegaly and, eventually, hepatomegaly. The cutaneous eruption begins 5 days after the beginning of the disease. It is a non-specific exanthema that starts on the trunk and proximal extremities and then appears on the face and forearms. Rarely, patients may develop genital ulcers, Gianotti-Crosti syndrome and other skin conditions. Serious complications are uncommon. They include splenic rupture, airway compromise and CNS complications such as encephalitis. More frequently, hepatitis or thrombocytopenia can be found. Some patients may also develop a generalized rash after the administration of penicillin or cephalosporin in this context. Patients with infectious mononucleosis may exhibit a moderate elevation of hepatic transaminase levels, thrombocytopenia and lymphocytosis with atypical lymphocytes. The diagnosis could be done by a high titer of heterophile antibodies (>1:40) but this does not happen in the majority of young children, so commonly specific serologies are required. Different antibodies can help to differentiate between a primary infection, a latent one and reactivation. PCR and i*n situ* hybridization for EBV-encoded small RNA (EBER) can also make the diagnosis. Primary EBV infection is not associated with any pathognomonic histologic finding [4].

HHV-5 (CMV)

CMV infects 60–95 % of adults worldwide and it is frequently acquired during childhood and reproductive years. In adults, sexual contact is an important way of transmission but blood transfusion, breast-feeding, transplanted organs and hematopoietic stem cell transplantation are other important ways. Transplacental transmission is also possible especially when the mother has a primary infection and it causes severe clinical problems to the fetus namely congenital deafness and mental retardation [12]. The incubation period ranges between 4 and 8 weeks. In immunocompetent patients, the primary infection is frequently asymptomatic but, sometimes, the patient may exhibit a mononucleosis-like syndrome, similar to what happens with EBV. Nevertheless, there is no exsudative tonsillitis, but hepatosplenomegaly can develop. Symptomatic disease is more common in children. The clinical course is usually self-limited but some complications such as CNS sequelae and myocarditis have already been described. In immunocompromised patients, a mononucleosis-like syndrome can also be seen but atypical cutaneous

manifestations are also common. Besides, patients with acquired immune deficiency syndrome (AIDS) may have chorioretinitis and other systemic complications. Patients who received an organ transplant can also develop severe systemic complications. After the primary infection, the virus remains latent and when the host is immunocompetent reactivation rarely occurs. The clinical features of a reactivation are similar to a primary infection. Several laboratorial tests can diagnose a CMV infection, namely culture, serology or PCR. In histology, the "owl's eye" feature resulting from the infection of endothelial cells is considered characteristic of CMV [4].

HHV-6

Infection by HHV-6 commonly occurs during the first 2 years of life. Transmission of HHV-6 is commonly through saliva but other ways, such as transplanted organs, have also been reported. After the infection, HHV-6 remains in latency in CD4+ T cells. The clinical presentations may include: exanthema subitum, also called "roseola infantum" and "sixth disease", which is frequent in spring; a febrile syndrome; a mononucleosis-like syndrome. The "sixth disease" is characterized by an incubation period of 1–2 weeks followed by high fever that persists during approximately 4 days. Thereafter, the fever diminishes and, as this happens, a cutaneous eruption appears. This lasts from 1 to 2 days and is composed of erythematous macules and papules on the trunk and proximal extremities. The involvement of soft palate (with Nagayama's spots) is also common. Periorbital edema can occur later. Sometime the "sixth disease" can complicate with seizures. Reactivation is much more common in immunocompromised patients. Clinically, it can present with fever, exanthema or systemic involvement (hepatitis, pneumonitis, encephalitis and others). It has also been suggested a role of HHV-6 in pityriasis rosea. The diagnosis of a HHV-6 is usually clinical. However, laboratorial tests can also help, namely serology, PCR and viral culture. The histological features are not specific [4].

HHV-7

Similarly to HHV-7, the peak incidence of infection by HHV-7 is during the first 2 years of life. The transmission mainly occurs through infected saliva. Little is known regarding the etiopathogenesis of this virus. A primary infection is usually subclinical but some cases of exanthema subitum were linked with HHV-7. It has been suggested that some cases of pityriasis rosea can occur as a clinical manifestation of HHV-7 reactivation. The laboratorial diagnosis may include serology, PCR, culture and immunohistochemistry [4].

HHV-8

The pathogenesis of HHV-8, the etiologic agent of Kaposi's sarcoma, as well as the route of HHV-8 transmission are currently unclear. Both sexual and non-sexual (through saliva) routes were described. Besides HHV-8 endemic places (such as African countries), high prevalence of HHV-8 antibody was reported in men who have sex with men. The presence of HHV-8 is not sufficient to develop Kaposi's sarcoma. Other cofactors, such as immunosuppression, may be important [13]. The replication (and reactivation) of the virus is easier upon an immunocompromised host especially in the setting of HIV-1 co-infection. The primary infection is non-specific. Children may have a morbiliform eruption and adults may present diarrhea or lymphadenopathy, for example. Patients with human immunodeficiency virus (HIV+) and other immunocompromised hosts may experience a more severe disease with, for instance, pancytopenia. Reactivation can present in several ways and the pathogenic mechanisms behind them are not fully understood. The patient can present Kaposi's sarcoma, multicentric Castleman's disease or primary effusion lymphoma. There are four subtypes of Kaposi's sarcoma, with different clinical features, considering the region or the age affected and the co-existence of HIV infection or organ transplant. The diagnosis can be confirmed by skin biopsy for histology and immunohistochemistry [4].

Herpes and Psychological Stress

It has been mentioned that, apart from the psychological impact and mental health problems as a result of having a skin manifestation of HHV infections, psychological stress can also cause or exacerbate skin diseases caused by HHV. Thereby, similarly to other psychodermatologic conditions, the connection between herpes and stress both at a biological and clinical levels should be analysed in two ways: mental health problems as a result of having skin disease and mental health problems (psychological stress) that trigger skin lesions.

Mental Health Problems as a Result of Having Skin Disease

Similar to other skin diseases, patients with skin lesions due to HHV report mental health problems as a consequence of having skin manifestations of the disease. The role of social stigma is of utmost importance in this context too. For example, Hamil and Goldmeier (2005) mentioned that genital herpes, one of the most common sexually transmitted infections, is associated with stigmatization and consequent psychosexual morbidity, poor self-esteem and depressive symptoms [14, 15]. These mental health problems seem to be worse in women than in men [15]. Nevertheless, some authors suggest that social support and cognitive coping

strategies may have a critical role in the prevention of mental health problems in these patients [15, 16].

Psychosocial problems may be expected for patients with other herpes lesions, such as orofacial herpes, considering the disfigurement and, consequently, the stigma of skin lesions especially on visible areas. Moreover, previous studies have also shown that herpes zoster and postherpetic neuralgia were positively correlated with anxiety, depression and insomnia. Furthermore, in a study conducted by Chen et al. (2014) herpes zoster was an independent risk factor for depression (including major depression), after adjusting for demographic data and comorbid medical conditions [17]. On the other hand, the impact on quality of life is really high for patients with postherpetic neuralgia, with difficulties in work and disruption of the family homeostasis. This then increases anxiety and depression symptoms. Moreover, a prevalence of 50 % was reported for suicidal ideation in the setting of postherpetic neuralgia. Thereby, it is important to bear in mind that severe mental health problems can affect these patients and their assessment and treatment is of high importance [18].

Psychological Stress and Mental Health Problems Trigger/ Worsen Skin Lesions

In the last decades, scientists have identified stress as an important factor to modulate the CNS, endocrine and immune systems, with strong implications in the pathogenesis of many diseases. Stressors can be both psychological and physical and they can similarly interfere in the CNS, with both emotional and molecular changes. CNS, endocrine and immune systems communicate through neurotransmitters, hormones and cytokines. After the effect of a stressor, the normal concentration and effect of those molecules can be changed, changing, in turn, all the systems. For example, stress can increase the levels of corticotropin releasing factor (CRF) and adrenocorticotropin hormone (ACTH). ACTH can stimulate the hypothalamic-pituitary-adrenal (HPA) axis to suppress T cells. Then, the immune system is modified and becomes more susceptible to infections [19].

The determinants of severity for the different HHV are still not completely clarified. For example, many studies have reported the risk factors for herpes zoster, but their results are controversial. Nevertheless, the role of psychosocial factors and psychological stress seems to be consistent as a risk factor for herpes zoster and postherpetic neuralgia in different studies [5, 20–22]. The pathogenesis of postherpetic neuralgia is complex, involving the CNS and the peripheral nervous system and can be understood through the “vulnerability-diathesis-stress model”. In this model, vulnerability includes psychosocial and neurobiologic factors such as, respectively, psychopathology and age. Diathesis includes, for example, the absence of antiviral treatment during acute infection or the severity of the acute infection and neuronal damage. Stress includes both the psychological and social dimensions. Psychological stress and inadequate social support increase the risk for postherpetic

neuralgia and exacerbate the pain. Stressful information in the limbic system and cognitions about the pain placed in the cortex difficult the patient's ability to deal with the pain [18].

There is also evidence that cell-mediated immunity has a critical role in limiting the clinical manifestation of zoster. Moreover, major depression has been associated with a marked decline in varicella-zoster virus-specific cellular immunity, in similar levels to those observed in normal people with more than 60 years of age, in whom the incidence of herpes zoster is higher [23]. In the same line of thought, psychosocial stress seems to be linked with reduced immunologic control of other latent herpesviruses, namely, HSV, EBV and CMV, as proved by the high antibody titers [23, 24].

Clinically, there has been strong evidence for the relationship between psychosocial stress and symptomatic HSV (oral and genital) recurrence [25, 26]. Regarding the link between psychological stress and HSV-2 infection, in a prospective longitudinal study, it was found that psychological stress was temporally associated with the onset of HSV-2 lesions (high levels of anxiety and depression 5 days before and 3 days after the episode) [27]. At a biochemical level, Elftman et al. showed that psychological stress experienced at the onset of HSV-infection impairs the ability of dendritic cells from HSV-infected mice to induce proliferation of $CD8^+$ T cells. Thereafter, HSV-specific $CD8^+$ T cell functions, which are dependent on signals from dendritic cells, were then disturbed, promoting a more aggressive disease with earlier onset and delayed resolution of skin lesions [28]. The lower levels of CD8+ T cells due to psychological stress and the subsequent loss of control of latent herpes simplex virus were shown by other studies as well [29]. Because mucosal tissues are clinically important places for infection with HSV, other authors studied their changes in response to psychological stress. It was observed that psychological stress might suppress both innate and adaptive immune responses, thus making difficult the ability to control mucosal (nasal and vaginal) HSV infection [30, 31].

Moreover, chronic stress modifies hypothalamic-pituitary-adrenal axis (HPA) and the sympathetic-adrenal-medullary (SAM) system as well as immune-mediated pathways, compromising the host's cellular immune response and triggering HSV reactivation. More precisely, the role of cellular signaling molecules induced by stress, namely catecholamines, cyclic adenosine monophosphate (cAMP), proinflammatory cytokines such as interleukin 6 (IL-6), glucocorticoids and prostaglandins may be critical in HSV reactivation. Catecholamines are released by the endocrine system after psychological stress and they can bind adrenergic cell membrane receptors on neuronal cells where the virus is latent. Afterwards, the production of cAMP is stimulated, activating a cascade that leads to the latency-associated transcript (LAT), which is the only intensively transcribed gene during the latent period, transcription and HSV activation. Glucocorticoids levels increase after psychological stress and suppress immune function and activate cAMP adrenergic receptors [19].

In turn, EBV reactivation was also seen to be correlated with psychological stress and high levels of stress hormones (urinary epinephrine and norepinephrine) [32]. As to other HHV, psychological stress can modulate the cellular immune response to latent EBV [33]. Interestingly, it was shown recently that people with high attachment anxiety have elevated EBV IgG antibody titers, suggesting a dysfunction on cellular immunity over the latent EBV [34].

As described to other HHV, in a recent study it was also observed that higher CMV-IgG was linked with increased anxiety or depressive symptoms, thus pointing out the causal link with psychological stress [35, 36].

Finally, disruption of the immune system related to circulatory cortisol levels in the context of psychological stress may also lead to a reactivation of a latent HHV-6 with correlated increase of antibody titers [37].

Medical Treatment

Some examples of the most consensual medical treatment considerations are listed in the Table 20.1. This table also lists some topics under discussion and research.

Psychological Intervention

Some studies have reported that psychological interventions modulate psychological variables connected with skin diseases, including those caused by HHV, with correlated immune changes and therapeutic relevance. Cellular immunity plays a critical role in HHV infection. The assessment of the severity of depressive symptoms and their treatment is correlated with normalization in NK cell activity and lymphocyte proliferation (altered in depressed subjects), improving immune function [23].

Although the studies on psychological interventions for skin diseases due to HHV are still scarce, according to the literature, there has been some evidence for the benefit of cognitive behavior therapy (CBT) and medical hypnosis in patients with skin diseases due to HHV. Both have been suggested as effective for several skin diseases [47].

The core of CBT is a problem-focused psychotherapy about the connection between thoughts, emotions, physical symptoms and behaviors. The disfigurement caused by having a skin disease may lead to stigma and, thereby, to negative thoughts, which are the starting point for depression and anxiety, to unhelpful feelings and behaviors. Additionally, variations of CBT have been successfully used. Therefore, an initial psychological assessment is crucial and even simple CBT can be offered in clinical practice, with proved benefits, for people with low or moderate levels of distress/depression [48]. Thus, with CBT we may stop the vicious cycle commonly seen in patients with psychodermatologic conditions, which is the following: the negative thoughts that people construct about the disease trigger negative feelings, which lead to physical changes (in biological functions, such as altered sleep) and, thereafter, to unhelpful behaviors. Some studies have also found evidence for a biological mechanism behind the clinical benefits. A case-control study performed by Lutgendorf et al. (1997) showed that CBT improved mood disorders and anxiety symptoms in symptomatic HIV-seropositive men and that was correlated with lower herpes simplex virus-type 2 antibody titers [49]. Later, Cruess et al. (2000) showed in a similar case-control study that HSV-2 antibody titers decreased after CBT

Table 20.1 Medical treatment options for HHV infections

Virus	Medical treatment	
HSV	Topical treatment: Aciclovir cream (5 %) five times daily (3–4 hourly intervals) during waking hours for 4 days [7].	
	Examples of systemic treatment schemas [3, 4]:	Orolabial herpes and genital herpes – primary infection: valacyclovir 1 g orally twice daily during 10 days
		Orolabial herpes – recurrence: valacyclovir 2 g orally twice daily only 1 day [7]
		Genital herpes – recurrence: valacyclovir 1 g orally daily during 5 days or 500 mg orally twice daily during 3 days
		Immunocompromised patient: valacyclovir 1 g orally twice daily until all the lesions have resolved
		Eczema herpeticum: valacyclovir 1 g orally twice daily or, in severe cases, acyclovir 5 mg/kg iv, if patient >12 years, or 10 mg/kg, if patient <12 years, every 8 h during at least 10–14 days and until all lesions have resolved
		Neonatal: acyclovir 20 mg/kg iv every 8 h during 14–21 days
		Resistant HSV and immunocompromised patient: foscarnet 40 mg/kg iv every 8–12 h during 2–3 weeks and all the lesions have resolved
	There is no vaccine or drug to prevent or cure [9].	
VZV	Gold standards for the treatment of VZV are acyclovir and valacyclovir [38]. Examples of schemas of treatment are [3, 4]:	Varicella in immunocompetent patient: valacyclovir 20 mg/kg with the maximum of 1 g orally every 8 h during 5 days.
		Zoster in immunocompetent patient: valacyclovir 1 g orally every 8 h during 7 days
		Immunocompromised (varicella and zoster): acyclovir 10 mg/kg iv every 8 h during 7–10 days and up to the lesions have resolved (in severe cases); valacyclovir 1 g orally every 8 h for 7–10 days (in mild cases); foscarnet 40 mg/kg iv every 8 h until total resolution (in resistant cases)
	Varicella-vaccines are efficacious. Different recommendations worldwide [39]. Herpes zoster vaccine is considered safe and effective to reduce the burden and severity of the disease in older adults. It is cost-effective when administered to immunocompetent adults >60 years [10].	
	For postherpetic neuralgia, a multidisciplinary approach is the best option: prevention strategies including zoster vaccine, antiviral therapy within 72 h of rash onset and pain control. Besides, anticonvulsants, antidepressants, topical lidocaine, capsaicin and opioids can be combined [40].	
EBV	Supportive care.	
	Corticosteroids for complicated cases associated with, for example, severe thrombocytopenia [4].	
	In patients with lymphoproliferative disease prophylactic use of antiviral drugs to prevent EBV reactivation may decrease the occurrence of EBV+ lymphoproliferative disease post-transplant. Cellular therapy targeting EBV on this context is being analysed [11].	

(continued)

Table 20.1 (continued)

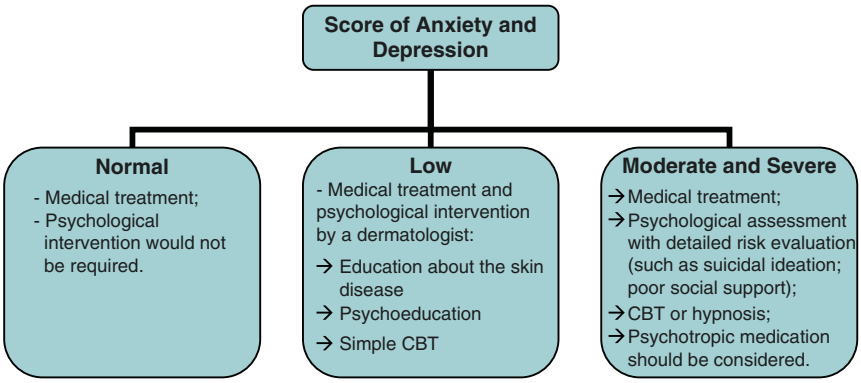
Virus	Medical treatment
CMV	Supportive care of CMV-induced mononucleosis in immunocompetent patients.
	CMV-seronegative donors for seronegative recipientes.
	For treatment and prophylaxis of CMV infections in immunocompromised patients, the first line options are: ganciclovir iv and valganciclovir oral 14–28 days [41]. Foscarnet, cidofovir and sirolimus are second-line options for resistant cases [42]. Anti-CMV immunoglobulins may be another option for the resistant cases [41–43].
	CMV vaccine is not still available [12].
	Cellular immunotherapy studies on adaptive immunity, in particular T cells and natural killer (NK), are being conducted [44].
HHV-6	Supportive care.
	In the setting of complications in immunocompromised patients, some studies point out foscarnet and ganciclovir but dosages are not consensual [45].
	Autologous T cell immunotherapy to prevent post-transplantation viral reactivation is under research [45].
HHV-7	Supportive care.
	No consensual treatment strategies.
HHV-8	Several treatment options exist: cryotherapy, radiotherapy, topical alitretinoin, intralesional interferon-α, intralesional and systemic vinblastine, other systemic agents, anti-retroviral therapy for patients with AIDS and even liposomal anthracyclines [46]. Other treatments are still under research.

and this was correlated with a decrease in cortisol/dehydroepiandrosterone sulfate (DHEA-S) ratio levels, reinforcing the knowledge that had been previously suggested by the neuro-immuno-cutaneous-endocrine model by O'Sullivan et al. (1998) [2, 50].

On the other hand, hypnosis is a psychological intervention that explores inner concentration and focused attention. Neurophysiological studies have shown that hypnosis modifies self-awareness as well as environmental consciousness, involving therefore internal and external brain networks [51]. In a study performed by Fox et al. (1999) psychological and immunological parameters were measured prior and after hypnotherapy in a group of patients with recurrent genital herpes simplex virus. They saw a significant reduction in the number of reported episodes of recurrent genital herpes simplex virus as well as an increase in the numbers of CD3 and CD8 lymphocytes after hypnosis. Moreover, the patients showed significant rises in natural killer (NK) cell counts and HSV specific lymphokine activated killer (LAK) cells activity. Furthermore, there was a correlation between those findings and lower anxiety scores [52]. More recently, through a case-control study with patients suffering from recurrent orofacial herpes infections, Pfitzer et al. (2005) concluded that with a hypnosis program, disease severity could be significantly reduced. They could also conclude that, in patients with recurrent orofacial herpes infections, a treatment only targeted to the physical changes was not enough. There was an important correlation between a deep analysis of psychological factors, such as person's sensuality, and treatment success

Table 20.2 Psychodermatologic approach of the patient with skin conditions due to HHV

Initial assessment by a dermatologist
The scores of anxiety and depression should be determined. Several scales are available. For example: "The Hospital Anxiety and Depression Scale" [55];
If normal, no psychological intervention is required (only medical treatment);
If low, moderate or severe, a psychological intervention should be considered.
For patients with low levels of anxiety and depression, the psychodematologic approach can be conducted by the dermatologist.
Patients with moderate and severe levels of anxiety and depression would ideally require a psychodermatology team (dermatologist, psychiatrist, psychologist and nurse).



[53]. This last point highlights the relevance of a deep analysis of the patient's life history in psychodermatologic diseases. This had been already suggested by Herman Musaph [54], one of the fathers of psychodermatology, and it is an important issue crossing all psychological interventions.

All in all, a truly biopsychosocial approach for patients suffering from skin manifestations of HHV should explore psychosocial factors and psychopathology. For example, as it was mentioned, postherpetic neuralgia has a multidimensional mechanism, having sensory and affective elements. Because psychological interventions can affect cortisol release, they also influence the course of chronic pain. CBT has evidence to support its use in the treatment of chronic pain conditions, including postherpetic neuralgia. It helps to manage anxiety, depression, feelings of hopelessness and it also provides pain management strategies. The patient learns how to cope with stress, helping to relax and control the pain. Through CBT the pain-tension-anxiety cycle is then stopped, with correlated biochemical beneficial changes [18].

Thereby, as for other skin diseases, a psychological examination should be included in clinical practice. This would help to select the best psychological intervention (evidence-based) to treat mental health problems related to the skin disease. Dermatologists can take psychosocial history, determine the scores of anxiety or depression, the impact of the skin diseases on quality of life and start the process of engagement with psychological treatment. Table 20.2 suggests an algorithm outlining psychodermatologic approach to the patient with skin disease and cutaneous

symptoms due to HHV. Some psychological interventions can be conducted in dermatologic practice (such as simple CBT) while others may need a referral to a psychiatrist or a psychologist [48].

References

1. Hunter H, Griffiths C, Kleyn C. Does psychosocial stress play a role in the exacerbation of psoriasis? Br J Dermatol. 2013;169(5):965–74.
2. O'Sullivan R, Lipper G, Lerner E. The neuro-immuno-cutaneous-endocrine network: relationship of mind and skin. Arch Dermatol. 1998;134(11):1431–5.
3. Goldsmith L, Katz S, Gilchrest B, Paller A, Leffell D, Wolff K. Fitzpatrick's dermatology in general medicine. 8th ed. New York: McGraw-Hill Professional; 2012.
4. Bolognia J, Jorizzo J, Schaffer J. Dermatology. 3rd ed. Philadelphia: Elsevier; 2012.
5. Brănişteanu DE, Stoleriu G, Oanţă A, Dorobăţ CM, Petrariu FD, Anchidin DM, Ciubotaru FM, Brănişteanu DC. Clinical-epidemiological trends of herpes zoster: a 5-year study. Rev Med Chir Soc Med Nat Iasi. 2014;118(3):817–22.
6. Arvin A, Campadelli-Fiume G, Mocarski E, et al., editors. Human herpesviruses: biology, therapy, and immunoprophylaxis. Cambridge: Cambridge University Press; 2007.
7. Cunningham A, Griffiths P, Leone P, Mindel A, Patel R, Stanberry L, Whitley R. Current management and recommendations for access to antiviral therapy of herpes labialis. J Clin Virol. 2012;53(1):6–11.
8. Gupta R, Warren T, Wald A. Genital herpes. Lancet. 2007;370(9605):2127–37.
9. Suazo PA, Tognarelli EI, Kalergis AM, González PA. Herpes simplex virus 2 infection: molecular association with HIV and novel microbicides to prevent disease. Med Microbiol Immunol. 2015;204(2):161–76.
10. Shapiro M, Kvern B, Watson P, Guenther L, McElhaney J, McGeer A. Update on herpes zoster vaccination: a family practitioner's guide. Can Fam Physician. 2011;57(10):1127–31.
11. Tse E, Kwong YL. Epstein Barr virus-associated lymphoproliferative diseases: the virus as a therapeutic target. Exp Mol Med. 2015;47:e136.
12. Wu SJ, Villarreal DO, Shedlock DJ, Weiner DB. Synthetic DNA approach to cytomegalovirus vaccine/immune therapy. Adv Exp Med Biol. 2015;848:131–48.
13. Rohner E, Wyss N, Trelle S, Mbulaiteye SM, Egger M, Novak U, Zwahlen M, Bohlius J. HHV-8 seroprevalence: a global view. Syst Rev. 2014;3:11.
14. Hamill M, Goldmeier D. Patients support innovative models of care in recurrent genital herpes clinics: results from a patient satisfaction study. Int J STD AIDS. 2005;16(9):615–7.
15. Mindel A. Psychological and psychosexual implications of herpes simplex virus infections. Scand J Infect Dis Suppl. 1996;100:27–32.
16. Fraley S. Psychosocial outcomes in individuals living with genital herpes. J Obstet Gynecol Neonatal Nurs. 2002;31(5):508–13.
17. Chen M, Wei H, Su T. Risk of depressive disorder among patients with herpes zoster: a nationwide population-based prospective study. Psychosom Med. 2014;76(4):285–91.
18. Livengood JM. The role of stress in the development of herpes zoster and postherpetic neuralgia. Curr Rev Pain. 2000;4(1):7–11.
19. Sainz B, Loutsch JM, Marquart ME, Hill JM. Stress-associated immunomodulation and herpes simplex virus infections. Med Hypotheses. 2001;56(3):348–56.
20. Lasserre A, Blaizeau F, Gorwood P, Bloch K, Chauvin P, Liard F, Blanchon T, Hanslik T. Herpes zoster: family history and psychological stress-case-control study. J Clin Virol. 2012;55(2):153–7.
21. Katz J, McDermott MP, Cooper EM, Walther RR, Sweeney EW, Dworkin RH. Psychosocial risk factors for postherpetic neuralgia: a prospective study of patients with herpes zoster. J Pain. 2005;6(12):782–90.

22. Schmader K, Studenski S, MacMillan J, Grufferman S, Cohen HJ. Are stressful life events risk factors for herpes zoster? J Am Geriatr Soc. 1990;38(11):1188–94.
23. Irwin M, Costlow C, Williams H, Artin KH, Chan CY, Stinson DL, Levin MJ, Hayward AR, Oxman MN. Cellular immunity to varicella-zoster virus in patients with major depression. J Infect Dis. 1998;178 Suppl 1:S104–8.
24. Kiecolt-Glaser JK, Glaser R. Psychoneuroimmunology and health consequences: data and shared mechanisms. Psychosom Med. 1995;57:269–74.
25. Chida Y, Mao X. Does psychosocial stress predict symptomatic herpes simplex virus recurrence? A meta-analytic investigation on prospective studies. Brain Behav Immun. 2009;23(7):917–25.
26. Pereira DB, Antoni MH, Danielson A, Simon T, Efantis-Potter J, Carver CS, Durán RE, Ironson G, Klimas N, Fletcher MA, O'Sullivan MJ. Stress as a predictor of symptomatic genital herpes virus recurrence in women with human immunodeficiency virus. J Psychosom Res. 2003;54(3):237–44.
27. Strachan E, Saracino M, Selke S, Magaret A, Buchwald D, Wald A. The effects of daily distress and personality on genital HSV shedding and lesions in a randomized, double-blind, placebo-controlled, crossover trial of acyclovir in HSV-2 seropositive women. Brain Behav Immun. 2011;25(7):1475–81.
28. Elftman MD, Hunzeker JT, Mellinger JC, Bonneau RH, Norbury CC, Truckenmiller ME. Stress-induced glucocorticoids at the earliest stages of herpes simplex virus-1 infection suppress subsequent antiviral immunity, implicating impaired dendritic cell function. J Immunol. 2010;184(4):1867–75.
29. Freeman ML, Sheridan BS, Bonneau RH, Hendricks RL. Psychological stress compromises CD8+ T cell control of latent herpes simplex virus type 1 infections. J Immunol. 2007;179(1):322–8.
30. Ashcraft KA, Bonneau RH. Psychological stress exacerbates primary vaginal herpes simplex virus type 1 (HSV-1) infection by impairing both innate and adaptive immune responses. Brain Behav Immun. 2008;22(8):1231–40.
31. Wonnacott KM, Bonneau RH. The effects of stress on memory cytotoxic T lymphocyte-mediated protection against herpes simplex virus infection at mucosal sites. Brain Behav Immun. 2002;16(2):104–17.
32. Stowe RP, Pierson DL, Barrett AD. Elevated stress hormone levels relate to Epstein-Barr virus reactivation in astronauts. Psychosom Med. 2001;63(6):891–5.
33. Glaser R, Pearson GR, Bonneau RH, Esterling BA, Atkinson C, Kiecolt-Glaser JK. Stress and the memory T-cell response to the Epstein-Barr virus in healthy medical students. Health Psychol. 1993;12(6):435–42.
34. Fagundes CP, Jaremka LM, Glaser R, Alfano CM, Povoski SP, Lipari AM, Agnese DM, Yee LD, Carson 3rd WE, Farrar WB, Malarkey WB, Chen M, Kiecolt-Glaser JK. Attachment anxiety is related to Epstein-Barr virus latency. Brain Behav Immun. 2014;41:232–8.
35. Rector JL, Dowd JB, Loerbroks A, Burns VE, Moss PA, Jarczok MN, Stalder T, Hoffman K, Fischer JE, Bosch JA. Consistent associations between measures of psychological stress and CMV antibody levels in a large occupational sample. Brain Behav Immun. 2014;38:133–41.
36. Sarid O, Anson O, Yaari A, Margalith M. Human cytomegalovirus salivary antibodies as related to stress. Clin Lab. 2002;48(5–6):297–305.
37. Vivoli R, Rovesti S, Borella P, Cermelli C. Relation between psychoneuroendocrine profile in stressful conditions and antibodies to herpesvirus 6 and 7. J Biol Regul Homeost Agents. 2008;22(4):239–45.
38. Andrei G, Snoeck R. Advances in the treatment of varicella-zoster virus infections. Adv Pharmacol. 2013;67:107–68.
39. Carrillo-Santisteve P, Lopalco PL. Varicella vaccination: a laboured take-off. Clin Microbiol Infect. 2014;20 Suppl 5:86–91.
40. Philip A, Thakur R. Post herpetic neuralgia. J Palliat Med. 2011;14(6):765–73.
41. Kotton CN. CMV: prevention, diagnosis and therapy. Am J Transplant. 2013;13 Suppl 3:24–40.

42. Requião-Moura LR, deMatos AC, Pacheco-Silva A. Cytomegalovirus infection in renal transplantation: clinical aspects, management and the perspectives. Einstein (Sao Paulo). 2015;13(1):142–8.
43. Ohlin M, Söderberg-Nauclér C. Human antibody technology and the development of antibodies against cytomegalovirus. Mol Immunol. 2015;67(2 Pt A):153–70.
44. Boeckh M, Murphy WJ, Peggs KS. Recent advances in cytomegalovirus: an update on pharmacologic and cellular therapies. Biol Blood Marrow Transplant. 2015;21(1):24–9.
45. Becerra A, Gibson L, Stern LJ, Calvo-Calle JM. Immune response to HHV-6 and implications for immunotherapy. Curr Opin Virol. 2014;9:154–61.
46. Robey RC, Bower M. Facing up to the ongoing challenge of Kaposi's sarcoma. Curr Opin Infect Dis. 2015;28(1):31–40.
47. Shenefelt PD. Biofeedback, cognitive-behavioral methods, and hypnosis in dermatology: is it all in your mind? Dermatol Ther. 2003;16(2):114–22.
48. Williams C, Garland A. A cognitive–behavioral therapy assessment model for use in everyday clinical practice. Adv Psychiatr Treat. 2002;8(3):172–9.
49. Lutgendorf S, Antoni M, Ironson G, et al. Cognitive-behavioral stress management decreases dysphoric mood and herpes simplex virus-type 2 antibody titers in symptomatic HIV-seropositive gay men. J Consult Clin Psychol. 1997;65(1):31–43.
50. Cruess S, Antoni M, Cruess D, et al. Reductions in herpes simplex virus type 2 antibody titers after cognitive behavioral stress management and relationships with neuroendocrine function, relaxation skills, and social support in HIV-positive men. Psychosom Med. 2000;62(6): 828–37.
51. Vanhaudenhuyse A, Laureys S, Faymonville M. Neurophysiology of hypnosis. Neurophysiol Clin. 2014;44(4):343–53.
52. Fox P, Henderson D, Barton S, et al. Immunological markers of frequently recurrent genital herpes simplex virus and their response to hypnotherapy: a pilot study. Int J STD AIDS. 1999;10(11):730–4.
53. Pfitzer B, Clark K, Revenstorf D. Medical hypnosis in cases of herpes labialis improves resistance for recurrence. A pilot study. Hautarzt. 2005;56(6):562–8.
54. Musaph H. Itching and scratching. Philadelphia: F.A. Davis Company; 1964.
55. Zigmond AP, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67:361–70.

Chapter 21
Psoriasis

Katlein França and Mohammad Jafferany

Introduction

Psoriasis is a chronic inflammatory multi organ disease that affects 1–3 % of the general population [1]. It is a T-cell mediated autoimmune inflammatory skin disease characterized by cutaneous inflammation, hyperkeratosis, increased epidermal proliferation, angiogenesis and abnormal keratinization [2]. Among patients affected by psoriasis, 5–40 % are affected by psoriatic arthritis. Classic psoriasis treatments include topicals, such as vitamin D, calcipotriol, corticosteroids, dithranol, retinoids, systemic therapy that includes methotrexate, retinoid, cyclosporine and phototherapy with UV-B, Psoralen plus ultraviolet therapy and excimer laser. These therapies have a limited efficacy and may not always provide clearance of the lesions [2]. More recent therapies include biologics, enzyme inhibitors and small molecules inhibitor [3]. Developing countries still prefer conventional treatments, due the expensive cost and unavailability of the more recent therapies cited above. This disease has different characteristics, clinical presentations and pathognomonic features, but there are no established diagnostic criteria as well as no unified classification for the clinical spectrum of the disease [4]. Most commonly the disease presents as chronic, erythematous, symmetrical, scaling papules and plaques. In darker skinned individuals erythema may be more difficult

K. França, MD, PhD (✉)
Centro Studi per la Ricerca Multidisciplinare e Rigenerativa, Università Degli Studi "G. Marconi", Rome, Italy

Department of Dermatology and Cutaneous Surgery, Department of Psychiatry and Behavioral Sciences, Institute for Bioethics and Health Policy, University of Miami Miller School of Medicine, Miami, FL, USA
e-mail: k.franca@med.miami.edu

M. Jafferany, MD, FAPA
Department of Psychiatry and Neurosciences, Central Michigan University, College of Medicine, Saginaw, MI 48603, USA
e-mail: m.jafferany@cmich.edu

K. França, M. Jafferany (eds.), *Stress and Skin Disorders*,
DOI 10.1007/978-3-319-46352-0_21

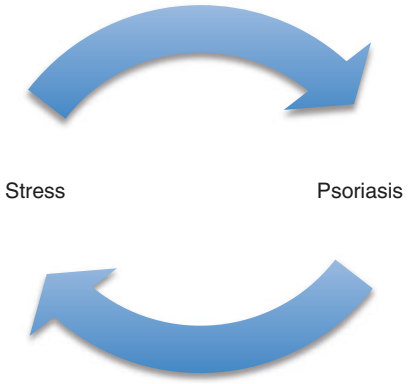


Fig. 21.1 Vicious cycle: stress responsible for the onset and exacerbation of psoriasis and psoriasis causes psychological stress

to be detected. The lesions may have a dark brown or violaceous hue instead of the red color observed in patients with lighter skin color [5] (Figs. 21.1, and 21.2).

Patients with psoriasis may experience different symptoms that include itching, irritation, burning and stinging, sensitivity, pain and bleeding [6]. The etiology of psoriasis is not fully understood. It is considered a multifactorial disease that involves both genetic environmental influences. Among these factors, stress has been considered as an important role in the onset and exacerbation of psoriasis [7]. Psychological stress may be also a consequence of psoriasis. The psychosocial impact of this disease is greatest among women, young people and minorities [8, 9] (Fig. 21.1).

Stress and Psoriasis

Stress has been reported to be a trigger for many dermatologic conditions including acne, urticaria, atopic dermatitis among others [10–12]. Patients with these conditions usually report a close chronologic association between the stressful event and the exacerbation of the skin condition. Like many other dermatological diseases, psoriasis can also worsen with stress [7].

A study performed with a large sample of Nordic patients investigated the perceived influence of stress on psoriasis onset and disease severity and compared stress reactors and non-reactors with respect to psoriasis-related stress, disease severity, family history of psoriasis and socio-demographic factors. Seventy-one percent of 5795 members of the Nordic psoriasis association and 66 % of 702 patients recruited from Nordic dermatologists or university clinics reported that their psoriasis was exacerbated by stress, and 35 % in both groups reported that the onset of their psoriasis occurred during a stressful period. Patients experiencing higher levels of stress also reported greater disease severity, psoriasis-related stress and impairment of disease-related quality of life. Interestingly, these patients also

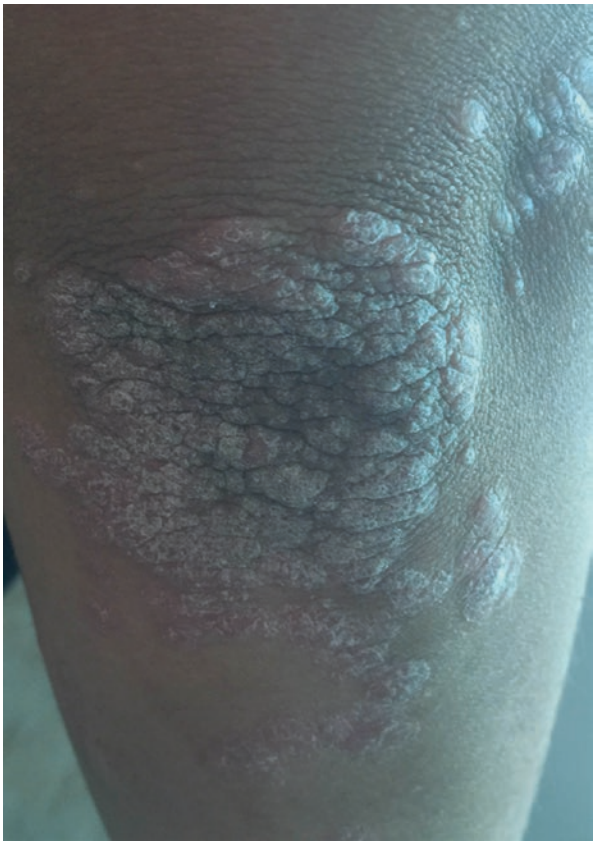


Fig. 21.2 Erythematous and violaceous scaly plaque of psoriasis over the elbow in a skin of color patient

reported more frequent use antidepressants, tranquillizers and tobacco. And they were more likely to have a family history of psoriasis [13]. Two prospective studies performed by Verhoeven et al. and Evers et al. showed that higher level of stress experienced by patients modulated the disease course. Daily stressors were associated with increased Psoriasis Area and Severity Index (PASI) scores as well as more complain of itch [14, 15]. Malhotra et al. [16] evaluated the stressful life events within 1 year preceding onset or exacerbation lesions in 50 patients of psoriasis vulgaris and 50 patients chronic urticaria. These patients were examined clinically and administered Gurmeet Singh's presumptive stressful life events scale. The researchers found the presence of Stressful life in 26 % of the patients in the psoriasis vulgaris group and 16 % of the patients in the chronic urticaria group within 1 year preceding onset or exacerbation of skin disease. Among patients with psoriasis, the most common stressful life event reported was financial loss or problems (8 %), followed by death of close family member (4 %), sexual problems (4 %), family

conflict (2%), major personal illness or injury (2%), and transfer or change in working conditions (2%), failure in examinations (2%), family member unemployed (2%), illness of family member (2%), getting married or engaged (2%), miscellaneous (2%). It is interesting to observe, that the experience of a stressful event is subjective. An event like getting married or engaged can be positive for some individuals but cause a significant amount of stress to others.

Immune regulation plays an important role in the development of psoriatic lesions. Early studies focused on understanding of psoriasis as a T lymphocyte mediated autoimmune condition with the production of cytokines, T helper (Th1) cells, interferon (IFN)-γ and tumor necrosis factor (TNF)-α [17]. More recently studies focus on the Th17 cytokine network including interleukin (IL) 17 and IL23, as a central role for the deployment of this disease [18]. Maese, explains that in genetically predisposed individuals, internal or external factors that include biomechanical stress and or immunologic dysregulation increased the expression of IL23 and this stimulates the differentiation and activation of Th17, and induces their production of IL-22, which regulates proliferation and differentiation of keratinocytes. Activated Th17 cells leads to increased levels of IL-17 and these are responsible for attracting neutrophils to the tissue site [17, 19, 20]. The hypothalamic-pituitary-adrenal axis (HPAA), which may be dysregulated in these patients, is one potential mediator of the stress and psoriasis [21]. Loite et al. have performed gene expression analysis studies and found an increased expression of HPAA mediators in lesional and non-lesional psoriasis skin samples compared to normal skin samples [21, 22]. Richards et al. performed a study with forty patients and found that stress responsive patients exhibit an altered HPAA response to acute social stress [23]. Karanikas et al. performed a study with the objective of investigating any alteration of the neuroendocrine profile of psoriatic patients through stimulation of the hypothalamic-pituitary-adrenal axis with corticotropin releasing hormone in 40 patients with psoriasis comparing to a control group of also 40 patients. Contrary to previous studies they found no particular neuroendocrine profile of HPAA axis responsiveness [24]. More studies are needed to clarify the role of the HPPA axis as a mediator of stress and psoriasis.

Oxidative Stress

In the recent years, studies have been suggesting that compromised function of antioxidant system and increased reactive oxygen species (ROS) production are involved in the pathogenesis of psoriasis. Kadam et al. performed a study with 90 psoriasis patients and compared with 30 healthy controls. The researchers investigated serum levels of malondialdehyde, nitric oxide end products and the activities of antioxidant enzymes such as erythrocyte-superoxide dismutase, catalase and

total antioxidant status. They found increased serum malondialdehyde, nitric oxide end products with decrease in erythrocyte-superoxide dismutase activity, catalase activity and total antioxidant status in patients with psoriasis. This study showed a possible relation of psoriasis and the enhancement of Reactive Oxygen Species production and a decreased antioxidant potential [25].

The relationship between smoking-induced oxidative stress and the clinical severity of psoriasis was investigated by Attwa et al. [26] These researchers found that smoking-induced oxidative damage that results from increased reactive oxygen species production along with insufficient capacity of antioxidant mechanisms could be involved in the pathogenesis of psoriasis. Urinary biopyrrin levels have been studied as an indicator of oxidative stress in patients with psoriasis. A study published in 2016 involving 85 patients, being 55 cases with chronic plaque psoriasis and a control group with 30 age, gender and body mass index-matched normal subjects measured urinary biopyrrin levels using enzyme immunoassay. The study found increased levels of biopyrrins in patients with psoriasis, and this level was correlated with the disease severity. Further studies are needed to validate this finds as well to understand the clinical usefulness of antioxidants for patients with psoriasis [27].

Psychological Stress as a Result of Psoriasis

Psoriasis is probably the most widely studied psychodermatological disorder due to its association with stress and having strong psychosocial impact on patients' lives. Psoriasis has higher associations with psychiatric illness than do other dermatologic conditions. Despite the visible evidence for psychiatric morbidity in patients with psoriasis, most guidelines for the treatment of psoriasis do not include screening for anxiety and depression and other psychosocial parameters. Numerous instruments could be used to evaluate psychiatric comorbidity among psoriasis patients. Skindex-29, particularly its emotions and functioning scale, general health questionnaire and dermatological HRQoL (health related quality of life) are the most common instruments used in the evaluation of psychosocial impairment in psoriasis and many other psychodermatologic disorders.

Social stigmatization, rejection by the family and friends with consequent profound effect on self-confidence, self-image and sense of well being are most commonly seen in psoriasis patient. Sampogna et al. [28] conducted a study on 936 patients to evaluate the psychosocial functioning of psoriasis patients. The authors concluded the most common psychosocial problems experienced by psoriasis were shame, anger, worry, difficulties in daily activities and social life. Patients with psoriasis suffer from depression frequently and it is estimated to be up to 30 % [29]. Various studies have demonstrated significant depression, worries and suicidal ideations in psoriasis patients. A United Kingdom based cohort study of

patients with psoriasis demonstrated increased incidence of diagnoses of depression, anxiety and suicidal ideations. The authors estimated that over 7 % diagnoses of depression, about 5 % diagnoses of anxiety and 0.3 % diagnoses of suicidality are attributable to psoriasis each year [30]. A recent Danish study found limited evidence to suggest an increased risk of self-harm and non-fatal suicide attempts in psoriasis patients [31].

Generally psychiatric comorbidity in psoriasis patients runs parallel with disease severity, however many studies have demonstrated that although psoriatic lesions were cleared by various treatment approaches, anxiety, depression, persistent worrying remained either same or decreased to some extent but not completely. This lack of correlation between psychological impact and physical severity has been explained by Kimball et al. [32] They suggest that the lack of correlation in some patients may be due to the cumulative impact of living with psoriasis. Some authors suggest that the maintenance of distress is related to maladaptive coping responses and schemas [33]. On the other hand lower levels of distress have been reported with longer disease duration indicating psychological acceptance or reflecting long-term adaption [34]. Kleyn et al. [35] conducted a FMRI study which demonstrated reduced signal responses to disgusted faces in psoriasis patients compared with controls. The authors hypothesize that patients with psoriasis develop a coping mechanism to protect them from stressful emotional responses by blocking the processing of disgusted facial expressions. A recent prospective cross-sectional study [36] on Singaporean patients demonstrated significant psychiatric comorbidity in psoriasis patients. The authors reported anxiety disorder in 17 %, while a depressive disorder was suggested in 15 % of the study population.

Besides stigmatization and social isolation and rejection, patient with psoriasis have also difficulties with relationships. The family members of patients with psoriasis were interviewed by Eghlileb et al. 57 % of family members reported psychological distress, 55 % social disruption, 44 % limitations to leisure activities and 37 % reported deterioration of close relationships [37]. Sexual functioning in psoriasis has been studied in many cross-sectional surveys. Gupta and Gupta [38] conducted a cross sectional survey on 120 inpatients. 40 % reported decline in sexual activity since the onset of psoriasis. In another study conducted by Sampogna et al. [39] reported about 35 % of patients with psoriasis confirmed impaired sexual life secondary to psoriasis. Increased prevalence of erectyl dysfunction was reported in study of 92 patients. The psoriasis patients were matched with controls with other skin conditions. The authors reported prevalence of erectly dysfunction in 58 % of patients with psoriasis as compared to 49 % of patients with other skin diseases [40]. Substance abuse is fairly common but under-reported in patients with psoriasis impairing social life and affecting treatment. Mills et al. [41] reported that twice as many patients with psoriasis smoked compared to controls. Another study [42] found that alcohol exacerbated psoriasis severity and pruritus and impaired treatment response.

Conclusion

Psychiatric comorbidity in psoriasis patients is well documented in the literature. It is highly recommended that every patient of psoriasis should be thoroughly evaluated for the psychosocial percussions of the disease. Treatment guidelines should incorporate screening instruments for anxiety, depression and other psychosocial functioning. Psychiatric consult at the beginning and on periodic basis should be advised to patient for better functioning and treatment compliance in these patients.

References

1. Weger W. Current status and new developments in the treatment of psoriasis and psoriatic arthritis with biological agents. Br J Pharmacol. 2010;160(4):810–20.
2. Rahman M, Alam K, Ahmad MZ, Gupta G, Afzal M, Akhter S, Kazmi I, Jyoti, Ahmad FJ, Anwar F. Classical to current approach for treatment of psoriasis: a review. Endocr Metab Immune Disord Drug Targets. 2012;12(3):287–302.
3. Ritchlin CT, Krueger JG. New therapies for psoriasis and psoriatic arthritis. Curr Opin Rheumatol. 2016;28(3):204–10.
4. Raychaudhuri SK, Maverakis E, Raychaudhuri SP. Diagnosis and classification of psoriasis. Autoimmun Rev. 2014;13(4–5):490–5. doi:10.1016/j.autrev.2014.01.008. Epub 2014 Jan 13.
5. Alexis AF, Blackcloud P. Psoriasis in skin of color: epidemiology, genetics, clinical presentation, and treatment nuances. Desai SR, Alexis A, eds. J Clin Aesthet Dermatol. 2014;7(11):16–24.
6. Sampogna F, Gisondi P, Melchi CF, Amerio P, Girolomoni G, Abeni D. Prevalence of symptoms experienced by patients with different clinical types of psoriasis. Br J Dermatol. 2004;151(3):594–9.
7. Heller MM, Lee ES, Koo JY. Stress as an influencing factor in psoriasis. Skin Therapy Lett. 2011;16(5):1–4.
8. Sathyanarayana Rao TS, Basavaraj KH, Das K. Psychosomatic paradigms in psoriasis: psoriasis, stress and mental health. Indian J Psychiatry. 2013;55(4):313–5.
9. Gupta MA, Gupta AK, Ellis CN, Voorhees JJ. Some psychosomatic aspects of psoriasis. Adv Dermatol. 1990;5:21–30.
10. Yosipovitch G, Tang M, Dawn AG, Chen M, Goh CL, Huak Y, Seng LF. Study of psychological stress, sebum production and acne vulgaris in adolescents. Acta Derm Venereol. 2007;87(2):135–9.
11. Arndt J, Smith N, Tausk F. Stress and atopic dermatitis. Curr Allergy Asthma Rep. 2008;8(4):312–7.
12. Chung MC, Symons C, Gilliam J, Kaminski ER. Stress, psychiatric co-morbidity and coping in patients with chronic idiopathic urticaria. Psychol Health. 2010;25(4):477–90.
13. Zachariae R, Zachariae H, Blomqvist K, Davidsson S, Molin L, Mørk C, Sigurgeirsson B. Self-reported stress reactivity and psoriasis-related stress of Nordic psoriasis sufferers. J Eur Acad Dermatol Venereol. 2004;18(1):27–36.
14. Verhoeven EW, Kraaimaat FW, Jong EM, Schalkwijk J, van de Kerkhof PC, Evers AW. Effect of daily stressors on psoriasis: a prospective study. J Invest Dermatol. 2009;129:2075–7.
15. Evers AW, Verhoeven EW, Kraaimaat FW, de Jong EM, de Brouwer SJ, Schalkwijk J, et al. How stress gets under the skin: cortisol and stress reactivity in psoriasis. Br J Dermatol. 2010;163(5):986–91.

16. Malhotra SK, Mehta V. Role of stressful life events in induction or exacerbation of psoriasis and chronic urticaria. Indian J Dermatol Venereol Leprol. 2008;74:594–9.
17. Moynihan J, Rieder E, Tausk F. Psychoneuroimmunology: the example of psoriasis. Giornale italiano di dermatologia e venereologia : organo ufficiale, Societa italiana di dermatologia e sifilografia. 2010;145(2):221–8.
18. Elloso MM, Gomez-Angelats M, Fourie AM. Targeting the Th17 pathway in psoriasis. J Leukoc Biol. 2012;92(6):1187–97. doi:10.1189/jlb.0212101. Epub 2012 Sep 7.
19. Mease PJ. Inhibition of interleukin-17, interleukin-23 and the TH17 cell pathway in the treatment of psoriatic arthritis and psoriasis. Curr Opin Rheumatol. 2015;27(2):127–33.
20. Zheng Y, Danilenko DM, Valdez P, Kasman I, Eastham-Anderson J, Wu J, Ouyang W. Interleukin-22, a T(H)17 cytokine, mediates IL-23-induced dermal inflammation and acanthosis. Nature. 2007;445(7128):648–51.
21. Brunoni AR, Santos IS, Sabbag C, Lotufo PA, Benseñor IM. Psoriasis severity and hypothalamic-pituitary-adrenal axis function: results from the CALIPSO study. Braz J Med Biol Res. 2014;47(12):1102–6.
22. Loite U, Kingo K, Reimann E, Reemann P, Vasar E, Silm H, Kõks S. Gene expression analysis of the corticotrophin-releasing hormone-proopiomelanocortin system in psoriasis skin biopsies. Acta Derm Venereol. 2013;93(4):400–5.
23. Richards HL, Ray DW, Kirby B, Mason D, Plant D, Main CJ, Fortune DG, Griffiths CE. Response of the hypothalamic-pituitary-adrenal axis to psychological stress in patients with psoriasis. Br J Dermatol. 2005;153(6):1114–20.
24. Karanikas E, Harsoulis F, Giouzepas I, Griveas I. Stimulation of the hypothalamic-pituitary-adrenal axis with corticotropin releasing hormone in patients with psoriasis. Hormones (Athens). 2007;6(4):314–20.
25. Kadam DP, Suryakar AN, Ankush RD, Kadam CY, Deshpande KH. Role of oxidative stress in various stages of psoriasis. Indian J Clin Biochem. 2010;25(4):388–92.
26. Attwa E, Swelam E. Relationship between smoking-induced oxidative stress and the clinical severity of psoriasis. J Eur Acad Dermatol Venereol. 2011;25(7):782–7.
27. Bakry OA, El Hefnawy S, Mariee AH, El Gendy Y. Urinary biopyrrins: a new marker of oxidative stress in psoriasis. Indian J Dermatol. 2016;61(2):169–73.
28. Sampogna F, Tabolli S, Abeni D. Living with psoriasis prevalence of shame, anger, worry and problems in daily activities and social life. Acta Derm Venereol. 2012;92:299–303.
29. Weiss SC, Kimball AB, Liewehr DJ, et al. Quantifying the harmful effects of psoriasis on health-related quality of life. J Am Acad Dermatol. 2002;47:512–8.
30. Kurd SK, Troxel AB, Critis-Christoph P, et al. The risk of depression, anxiety and suicidality in patients with psoriasis: a population based cohort study. Arch Dermatol. 2010;146:891–5.
31. Egeberg A, Hansen PR, Gislason GH, et al. Risk of self-harm and non-fatal suicide attempts, and completed suicide in patients with psoriasis – a population-based cohort study. Br J Dermatol. 2016. doi: 10.1111/bjd.14633 [Epub ahead of Print].
32. Kimball AB, Gieler U, Linder D, et al. Psoriasis: Is the impairment to a patient's life cumulative? J Eur Acad Dermatol Venereol. 2010;24:989–1004.
33. Mizara A, Papadoupolos I, McBride SR. Core beliefs and psychological distress in patients with psoriasis and atopic eczema attending secondary care: the role of schemas in chronic skin disease. Br J Dermatol. 2012;166:986–93.
34. Devrimici-Ozguven H, Kundakci TN, Kumbasar H, et al. The depression, anxiety, life satisfaction and affective expression levels in psoriasis patients. J Eur Acad Dermatol Venereol. 2000;14:267–71.
35. Kleyn CE, McKie S, Ross R, et al. Diminished neural and cognitive responses to facial expressions of disgust in patients with psoriasis: a functional magnetic resonance imaging study. J Invest Dermatol. 2009;129:2613–9.
36. Tee SI, Lim ZV, Theng CT, et al. A prospective cross sectional study of anxiety and depression in patients with psoriasis in Singapore. J Eur Acad Dermatol Venereol. 2016;30(7):1159–64. doi:10.1111/jdv13615.

37. Eghlileb AM, Davies EEG, Finlay AY. Psoriasis has a major secondary impact on the lives of family members and partners. Br J Dermatol. 2007;156:1245–50.
38. Gupta MA, Gupta AK. Psoriasis and sex: a study of moderately to severly affected patients. Int J Dermatol. 1997;36:259–62.
39. Sampogna F, Gisondi P, Tabolli S, et al. Impairment of sexual life in patients with psoriasis. Dermatology. 2007;214:144–50.
40. Goulding JM, Price CL, Defty CL, et al. Erectyl dysfunction in patients with psoriasis: increased prevalence, an unmet need, and a chance to intervene. Br J Dermatol. 2011;164:103–9.
41. Mills CM, Srivastava ED, Harvey IM. Smoking habits in psoriasis: a case controlled study. Br J Dermatol. 1992;127:18–21.
42. Gupta MA, Schork NJ, Gupta AK, et al. Alcohol intake and treatment responsiveness of psoriasis: a prospective study. J Am Acad Dermatol. 1993;28:730–2.

Chapter 22
Stress Management Techniques in the "Stressed" Skin Disorder Patient

Philip D. Shenefelt

Introduction

Stress from an engineering standpoint is force applied to a material, while strain is what occurs within the material as a result of the stress. When the stress is more than the material can endure, the material can deform or break as a result of the excess strain. For people, stress can be external or internal and the strain if chronic or excessive can also cause physical, emotional, mental, or spiritual deformation or breakage. Excess stress and strain on a physical, emotional, mental, or spiritual level can impair the patient's response to treatment for many skin disorders. The skin and the nervous system form adjacent to each other in the ectoderm of the fetus and remain interconnected physically and biochemically and interact throughout life. The skin-nervous system interactions result in significant psychosomatic or behavioral influences on many dermatologic conditions. Skin disorder patients can often benefit from nonpharmacological interventions for stress and strain with minimal if any side effects. Psychoneuroimmunology elucidates the biological basis of how the brain and nerves alter immune responses in common skin disorders such as atopic dermatitis, psoriasis, and urticaria [1]. These interactions and influences allow non-pharmacologic interventions to produce positive effects on many dermatologic diseases through stress and strain reduction. Accompanying that shift is usually an emotional shift in polyvagal autonomic state [2] from sympathetic to parasympathetic with an accompanying shift in body chemistry from sympathetic fight or flight to dorsal vagal complex rest, digest, repair, and heal and to ventral vagal emotional feeling and expression with social engagement. The shifts in emotional and autonomic states are often required to facilitate and unblock physical healing of the skin. Age and culturally appropriate modifications permit tailoring

P.D. Shenefelt, MD
Department of Dermatology and Cutaneous Surgery, MDC 79, College of Medicine, University of South Florida, 12901 Bruce B. Downs Blvd, Tampa, FL 33612, USA
e-mail: pshenefe@health.usf.edu

K. França, M. Jafferany (eds.), *Stress and Skin Disorders*,
DOI 10.1007/978-3-319-46352-0_22

the interventions to individual patients. Adding elements of age and culturally appropriate fun and storytelling often will motivate the patient to cooperate. Shifts in spiritual aspects to facilitate physical healing of skin disorders has been discussed elsewhere [3].

Nonpharmacologic interventions include acupuncture and acupressure, aromatherapy, autogenic training, biofeedback, breathing rate slowing techniques, brief dynamic psychotherapy, cognitive-behavioral therapy (CBT) methods, energy acupressure techniques such as emotional freedom techniques (EFT), eye movement desensitization and reprocessing (EMDR), guided imagery, hypnosis, meditation, music, placebo, shamanic drumming, and suggestion. Acupressure and aromatherapy can be used at any age. Autogenic training requires language skills. Biofeedback can often incorporate a video or audio game-like age-appropriate approach to engage the patient. CBT must also be age-appropriate starting at about age 8 years and can incorporate storytelling as well as straight talk. EFT can be done for the patient on infants, toddlers, and preschoolers and taught to elementary school age and adolescent patients as well as adults and the elderly. EMDR can be used with older preschoolers, elementary school age, adolescent, and adult patients. Hypnoidal techniques such as rocking can be used with infants and toddlers. Older preschoolers and elementary school age patients generally shift into imaginative trance quite easily, with a peak of hypnotizability between ages 8 and 12 years old. Adolescents and adults may have more difficulty shifting into trance, depending on their innate genetic abilities and prior experiences. Elementary school age and adolescent and adult patients can be taught self-hypnosis as well. For low hypnotizables, distraction will likely be the most important element, while for moderate hypnotizables sensory or time distortion will be more useful, and for high hypnotizables dissociation or fantasy will predominate. Meditation can help to relax and calm older children and adults. Music can calm anxious children and adults. Placebo can be used when age and ethically appropriate. Avoidance of nocebo is equally important. Some patients benefit from shamanic drumming for relaxation. Appropriately phrased suggestions can benefit older preschoolers, elementary school age, adolescent patients, and adults.

Non-pharmacological Modalities for Stress Reduction

Acupuncture and Acupressure

Needle acupuncture focal stimulation of cutaneous nerves at specified sites has been reported to be helpful in stress reduction [4] in the Chinese literature. The treatment sites correspond to specific numbered acupuncture points on the 12 lateral and 2 midline meridians. In traditional Chinese medicine, a complex system relating the lateral meridians to specific hollow and solid organs is described. Nonsterile acupuncture needles carry a risk of blood-borne pathogen infection. Use in some patients may be limited by aversion to needles. Non-needle acupuncture methods

include moxibustion, cupping, acupressure, and more recently laser acupuncture. Acupressure for stress reduction, relaxation and calming can be self-administered holding firm pressure to the point of mild discomfort for about 3 min each at one or more of Yintang (Governing Vessel 24) on the glabellum between eyebrows, Anmian (Ext head neck 21) over mastoid process, Hoku (Large Intestine 4) in mid web between thumb and index finger, Shenmen (Heart 7) at ventral ulnar crease of wrist, or Neikuan (Pericardium 6) on ventral mid forearm 2½ fingerbreadths from wrist crease [5]. Tapping at acupuncture sites will be discussed below under the heading of emotional freedom techniques.

Aromatherapy

Stress reduction through direct contact massage aromatherapy with application of a fragrant essential oil diluted in a carrier oil has been used successfully as a relaxer. While some topical pharmacological effect cannot be excluded, the olfactory stimulation activates nerves that extend directly adjacent to the limbic system in the brain. According to reports, oil of Bergamont (caution—photosensitizer) has been reported to have antiseptic and antidepressant properties. Geranium oil is reported to be antiseptic and antidepressant. Jasmine oil is said to have antidepressant, sedative, and relaxant properties. Lavender oil reportedly has analgesic, antiseptic, bactericidal, anti-inflammatory, and sedative effects. Lemon balm (Melissa) is said to be antidepressant. Sandalwood oil is reported to be antiseptic and antidepressant. Other essential oils that have been used include benzoin, chamomile, frankincense, myrrh, sweet marjoram, and thyme. The carrier oils such as avocado oil, coconut oil, evening primrose oil, sweet almond oil, and wheat germ oil also may have some topical pharmacologic activities [6]. These are based on case reports and case series. Massage with carrier oil with or without essential oil added resulted in significant improvement with atopic dermatitis resistant to other treatments in a case series [7]. As an adverse effect, allergic contact dermatitis has been reported from direct contact aromatherapy [8].

Noncontact aromatherapy coupled with relaxation can link a specific fragrance with the relaxation response. That specific fragrance can then be used as a conditioned stimulus to induce the relaxation response. In a study 6–12 year old children smelled fragrances of the essential oils of ginger, lavender, lemon, peppermint, spearmint, and sweet orange and noted the effects on their mood and energy. Preference ranking by non-Latino Caucasian males of which one oil to take home in descending order were lemon, sweet orange, peppermint, spearmint, lavender, and ginger. Non-Latino Caucasian females preferred the same order. Latino males noted as preferences in descending order spearmint, sweet orange, lemon, and lavender. Latino females preferred sweet orange, spearmint, and lemon. Some of the fragrances evoked memories in some of the participants [9]. For all patients, choices of relaxing fragrances can be offered and individual preferences will vary.

Autogenic Training

Autogenic training is a specialized form of hypnosis developed by Johann Heinrich Schultz, a German who first trained in dermatology and then in neurology. He became fascinated with hypnosis and developed a formula for relaxation in trance that became known as autogenic training [10]. It may be performed lying supine or sitting. The formula is to close the eyes, find a comfortable body position, and allow yourself to concentrate on what is going on inside of you. First concentrate on your arms and legs and repeat six times that "my arms and legs are very heavy" (muscular relaxation). Next concentrate on your hands and feet and repeat six times that "my hands and feet are very warm" (vasodilation). Then repeat six times that "my heartbeat is calm and strong" (regulation and slowing of heartbeat). Next repeat six times that "it breathes me" (shift from thoracic to abdominal breathing). Then repeat six times that "warmth radiates over my abdomen" (calming of visceral gut activity). Finally, repeat six times that "my forehead is cool" (mental relaxation). Research has shown autogenic training to be helpful for stress reduction. Autogenic training was shown to be superior to standard dermatological care for treatment of atopic dermatitis [11].

Biofeedback

Biofeedback involves the use of instruments to provide real time visual or auditory feedback about specifically measureable biological activities. Relaxation is generally accompanied by less sweating and warmer finger temperatures. Biofeedback training can that have an autonomic nervous system component such as biofeedback of galvanic skin resistance (GSR) for sweating and biofeedback of skin temperature can be used to help with relaxation training [12]. Children 7–16 years old have proven to be especially adept at skin temperature biofeedback [13]. Incorporating a game or some play aspect into the biofeedback can help to maintain the person's interest and motivation. Relaxation biofeedback may result in some improvement in atopic dermatitis [14]. Hypnosis may enhance the effects obtained by biofeedback [15, 16]. Heart rate variability biofeedback with handheld electronic devices such as the emWave Personal Stress Reliever or StressEraser can promote relaxation, improving skin conditions worsened by stress. An inexpensive and simple biofeedback device for finger temperature is a temperature-sensitive color changing card that Barrios [17] used to promote relaxation in school children. He is the inventor of the Stress Control Card that has a heat sensitive color changing biofeedback thermometer placed on a credit card sized card having color indications from colder black through red and green to warmer blue, similar in function to the well known mood ring. It measures ranges of finger temperatures, giving biofeedback of vasoconstriction versus vasodilatation associated with autonomic activity. Colder finger temperatures are a result of sympathetic nervous system vasoconstriction, which when the person is in an environment of normal room

temperature often reflects stress. The higher finger temperature is associated with relaxation. Relaxation can benefit most inflammatory skin disorders, including atopic dermatitis and psoriasis.

Breathing Rate Slowing Techniques

Slowing the breathing rate from anxious 20 breaths per minute shallow chest breaths through normal 12 per minute breaths to slow 6 per minute abdominal breaths shifts the stressed or anxious patient from sympathetic dominant fight, flight, or freeze response to parasympathetic rest, digest, and heal mode. See Table 22.1. This can be done by using a phone app to time the breathing such as Breathe2Relax or by watching the second hand on a watch and breathing in for 5 s and out for 5 s repeatedly, producing 6 breaths per minute. Activities involving breath such as singing, chanting, or blowing a musical instrument also slow the breathing rate. Breath is an important aspect of the healing process in traditional Chinese medicine and in yogic traditions as well [18].

Brief Dynamic Psychotherapy

Stress reduction with individual brief dynamic psychotherapy in children as young as 5 years old was found to significantly benefit children with atopic dermatitis in a randomized control trial [19]. A total of 11–18 sessions were required over a 6

Table 22.1 Correlation of breathing rate with feeling relaxed versus anxious

Breaths per minute	Blood pCO_2	Blood pH	Autonomic nervous system	Dominant brain wave (Hz)	Mental state
4				Theta (4–8)	Trance
6	Higher	Lower	Parasympathetic (relax, heal, digest)		
8				Alpha (8–12)	Relaxed
10					
12	Moderate	Moderate	Mixed	Beta (12–18)	Alert
14					
16					
18					
20					
22	Lower	Higher	Sympathetic (fight, flight)	High beta (18–38)	Hyperalert, anxious
24					

month period. This can also help stressed adults with skin disorders, especially those with a psychosomatic overlay on their skin disorder.

Cognitive-Behavioral Therapy Methods

Stress reduction can also occur through cognitive-behavioral therapy (CBT) methods that help to alter dysfunctional thought patterns (cognitive) or actions (behavioral) [20]. These methods include habit reversal therapy. Adding hypnosis to cognitive-behavioral therapy can facilitate virtual aversive therapy and enhance desensitization and other cognitive-behavioral methods [16]. A randomized controlled trial using CBT for atopic dermatitis aimed to reduce scratching frequency and stress [11]. The subjects maintained scratching diaries and were instructed in habit reversal techniques, relaxation techniques, distraction techniques, positive self talk, and applying ice to itchy skin. Assessments at 1 year for CBT showed significantly improved atopic skin conditions with significantly decreased topical corticosteroid use compared with standard dermatological treatment or education groups [11].

Emotional Freedom Techniques (EFT)

Emotional freedom techniques (EFT) [21] are related to acupressure. EFT starts with selecting a negatively emotionally charged memory or problem area, focusing intently on that thought or memory or condition, pressing on the subclavicular "sore spot", and repeating an affirmation such as "Even though I have this problem with _____, I deeply and completely accept myself" while progressively tapping with the combined index and middle fingers on a series of up to 14 specific acupuncture sites on the head, chest, and hand. For infants, toddlers, and preschoolers, this tapping process can be done for them, either directly on them or on a surrogate. Older children, adolescents and adults can be taught to use the technique themselves. EFT can neutralize negative emotional charged memories or problem areas, reducing anxiety and stress and enhancing performance [21]. Anecdotally reported improvements or resolution of skin conditions on www.EFTuniverse.com include acne, allergic contact dermatitis, atopic dermatitis, lupus erythematosis, needle phobia, procedure anxiety, psoriasis, and warts. A controlled comparison of EFT with EMDR (see below) in a study that included older adolescents and adults showed that for post traumatic stress disorder (PTSD) both produced significant therapeutic gains [22]. Some patients do develop PTSD as a result of life events that were overwhelmingly traumatic to them, including hospitalizations and medical procedures. Reducing emotional distress often results in improvement of inflammatory skin conditions such as acne, atopic dermatitis, and psoriasis.

Eye Movement Desensitizing and Reprocessing (EMDR)

Eye movement desensitizing and reprocessing (EMDR) also involves selecting a negatively emotionally charged memory or problem area, focusing on that thought, and doing an alternating bilateral activity such as following a finger from side to side with the eyes [23], hearing alternating left and right tones through headphones, feeling alternating left and right vibrations in handheld paddles, or alternately tapping left and right distal thighs or upper arms. It is slightly more effective than EFT in producing positive benefits in PTSD [22]. The efficacy of EMDR has been evaluated in a meta-analysis. The post treatment effect size was medium and significant [24]. When combined with the EFT affirmations it becomes a hybrid known as Wholistic Hybrid derived from EMDR and EFT (WHEE), reducing anxiety and stress and enhancing performance [25]. EMDR has been reported effective for improving atopic dermatitis and psoriasis [26].

Guided Imagery

Guided imagery involves trance induction often through progressive relaxation followed by deepening, guided imagery of a scenario, and re-alerting. It is a form of hypnosis. The scenario often vividly describes suggested sensory experiences during the deepening phase followed by a journey, story, or other relaxing or therapeutic script. While guided imagery is commonly used to help induce relaxation and stress reduction and there are many available scripts and recordings, there has not yet been appreciable scientific study of its effectiveness related to patients with skin disorders.

Hypnosis

Hypnosis consists of guiding the patient into a trance state of narrowed awareness, focused attention, selective wakefulness, and heightened suggestibility for a specific purpose such as relaxation, pain or pruritus reduction, or habit modification. Autogenic training and guided imagery are considered to be forms of hypnosis. Autogenic training is discussed above. Guided imagery intentionally involves trance induction, while story-telling often induces spontaneous trance. Meditation is a close cousin to hypnosis. Both hypnosis and meditation involve the use of trance phenomena. Hypnosis is a western concept and focuses more on fixing something, while meditation is more of an eastern concept and focuses more on centering and balance. Both can reduce psychological roadblocks to healing. The hypnotic trance has objectively documented differences in regional cerebral blood flow [27] and EEG [28] patterns compared with the usual waking state. The use of hypnosis may

improve or clear numerous skin disorders. Examples include acne excoriée, alopecia areata, atopic dermatitis, congenital ichthyosiform erythroderma, dyshidrotic dermatitis, erythromelalgia, furuncles, glossodynia, herpes simplex, hyperhidrosis, ichthyosis vulgaris, lichen planus, neurodermatitis, nummular dermatitis, postherpetic neuralgia, pruritus, psoriasis, rosacea, trichotillomania, urticaria, verruca vulgaris, and vitiligo [29, 30]. Most children ages 4 and above are good hypnotic subjects, with hypnotic ability reaching a peak at around age 8–12 years [31]. Thereafter there is some mild decline in hypnotizablity into adulthood. A randomized controlled trial showed hypnosis to result in significantly greater resolution of verrucae than controls [32]. A small pilot study randomized controlled trial with psoriasis demonstrated significant improvement in high hypnotizables [33]. Similarly a non-randomized controlled trial utilizing hypnotic suggestions showed that atopic patients had significant improvement and significantly less use of topical corticosteroids by 6 weeks and maintained up to 2 years compared with controls [34]. Hypnosis is most useful in high and medium hypnotizables, and should generally not be used with schizophrenics or others who are not mentally intact. Relaxation with hypnosis can reduce anxiety and pain associated with dermatologic procedures. Hypnosis has been shown in a randomized control trial to significantly reduce anxiety during dermatological procedures [35]. Psychosomatic hypnoanalysis has been successful in reducing erythema nodosum, herpes simplex reactivation, neurodermatitis, neurotic excoriations, rosacea, urticaria, and verrucae [36, 37]. Hypnoanalysis of 41 consecutive cases of verrucae resistant to prior hypnotic suggestion, including 11 prepubertal children and 5 adolescents, resulted in the warts resolving in 31 cases [38]. The psychosomatic hypnoanalysis appears to remove psychological obstacles to healing.

Meditation

Various forms of meditation have been used since antiquity. They are an efficient and effective means of reducing stress. The various types of meditation may broadly be divided into concentrative meditation where the focus is on one object such as a candle flame or mandala, image, sound, word, or mantra and mindfulness meditation where the focus is on emotional nonattachment but broad awareness of many objects, sounds, other sensations, or thoughts. For concentrative meditation, the focus is on a single item, while for mindfulness meditation the focus is open to the flow of all stimuli. Both may involve entering a trance. The concentrative trance reduces external awareness, while the mindfulness trance maintains external awareness while remaining calmly centered. There are parallels of concentrative meditation to internally focused hypnotic trance and of mindfulness meditation to alert awake hypnotic trance.

Mindfulness meditation has also been used extensively for stress reduction. Originally associated with Buddhism and in particular Zen, it has been adapted for medical use. Jon Kabat-Zinn [39, 40] has been a major proponent of this methodology,

employing mindfulness meditation and hatha yoga stretching. He developed the Mindfulness-Based Stress Reduction program. The 8 week course had weekly 2 h classes where techniques of breath, awareness of body sensations, and stretching yoga combined with at half day of meditation and daily homework of 45 min taped guided meditation or 30 min of meditation on their own helped them to develop nonjudgmental, moment to moment awareness, attention monitoring, and acceptance. He also performed a study [41] with randomization of psoriasis patients undergoing ultraviolet B (UVB) or psoralen plus ultraviolet A (PUVA) light treatments into two groups, those listening to mindfulness meditation tapes and those who were controls. Patients in the mindfulness meditation tape group reached the halfway point in clearing and the clearing point significantly more rapidly than the controls for both UVB and PUVA treatments.

Music

Slow calming music such as classical music with a tempo of 60–70 beats per minute has been demonstrated to reduce anxiety in children in a waiting room in an emergency department setting [42]. This technique can also be used for relaxation of children and adults prior to and during skin procedures. The slower tempo helps to shift the patient out of sympathetic into parasympathetic dominance with its ensuing relaxation. Another approach has been to loan an MP-3 player (iPod Nano) to individual children while in the pediatric emergency department. The MP-3 players were color coded with different kinds of music for infants/toddlers, preschoolers, school-aged children, and adolescents [43]. This method is more expensive but allows provision of age-appropriate music. A systemic review of randomized control trials using music therapy for children listed and assessed the various studies and their generally favorable results [44]. In a randomized control trial, music was shown to reduce adult patient anxiety significantly during Mohs micrographic surgery [45].

Placebo

Positive expectations and a positive doctor-patient relationship can affect the child's experience of treatment, can reduce pain, and may influence outcome. Negative expectations can produce negative nocebo results [46]. Care must be taken in selecting language that will have a positive rather than negative effect on the patient. Research on the placebo effect illustrates that the natural healing capacities of individuals can be enhanced and nurtured [47]. The placebo effect for some common dermatologic conditions such as acne and urticaria is about 30 % [48]. The Griesemer index [49] rates dermatologic disorders on a percentage scale from 100 % to zero percent based on emotional triggering of the condition. Those disorders higher on

the Griesemer scale are more likely to have a significant placebo effect. Younger children are often easily influenced, while adolescents may resist influence by physicians and parents. Adults vary in their responsiveness. Ethical considerations often limit the application of the placebo in clinical practice.

Progressive Relaxation

Progressive muscular relaxation was developed by Edmund Jacobson [50]. He also developed biofeedback instrumentation and found that excess muscular tension was present in many psychosomatic disorders. Intentionally tensing and then relaxing the muscles decreased emotional distress and the resulting calmness and relaxation reduced psychosomatic symptoms. The basic method is to sit or lie recumbent and start at the hands, head, or toes with intentional muscle tensing followed by relaxation. The adjacent body part muscles are then tensed and relaxed, followed by those of the next adjacent body area until all areas of the body have been covered. Progressive muscular relaxation can be used by itself for treatment and prophylaxis of psychosomatic components of skin disorders. It may induce a meditative trance and is a frequently used method of hypnotic trance induction. The relaxation should be maintained for 5–25 min for optimal benefit. The sitting position is preferred if the patient desires to re-alert after the progressive muscular relaxation, while the recumbent position is preferred if the patient desires to drift off to sleep for a nap or at bedtime.

The relaxation response, a form of generic concentrative meditation, was introduced by Herbert Benson [51]. It involves sitting in a quiet place, closing your eyes, letting your muscles loosen and relax, starting at your feet and working upward (progressive muscular relaxation trance induction), breathing evenly through your nose and becoming aware of the breath (breath relaxation trance induction). With each exhalation, say the word "one" to yourself (concentrative mantra meditation trance induction). Maintain a passive attitude. Let any distracting thoughts or sensations drift away ignored like clouds in the sky. Maintain the concentrative meditation for 10–15 min. When you finish, remain sitting quietly for a few minutes, first with your eyes closed, then with your eyes open. The health benefits of the relaxation response have been extensive researched with positive results in areas such as cardiovascular health.

Shamanic Drumming

The earliest spiritual-religious practitioners were shamans. Among other activities, shamans practiced healing of spirit, mind, emotions, and body, including skin disorders. Shamanic techniques still have relevance today to promote healing of some

skin disorders resistant to conventional approaches. Many shamans in diverse cultures shift into altered states of consciousness (ASC) intentionally, often using auditory driving of drumming at 180–420 beats per minute, most commonly at 205–220 beats per minute but varying from one culture and individual to another [52]. At this rate of about 3.5 cycles per second with a first overtone of about 7 cycles per second, brain wave entrainment in the theta range can occur, enhancing shift into the ASC. Alternatively, shamanic auditory driving may be done using clicking sticks or rattles [52]. Repetitive chanting and singing may also induce ASC in shamans and other participants in the ceremony. In some cultures hallucinogenic or otherwise mind altering plant materials may be used to assist the shaman in attaining ASC. Dancing and fasting are other methods for attaining ASC. The shaman enters the ASC with special training and experience and for specific purposes, and in a specific cultural setting with expectations for specific content. This mode is termed by the author as the shamanic state of consciousness and content (SSCC) and corresponds with what Rock and Krippner call shamanic patterns of phenomenal properties [53]. Again, the individual may be in one of several possible altered shamanic states of consciousness, which should be kept in mind whenever there is reference to the SSCC. The shamanic state of consciousness and the content are two separate aspects that are combined in the SSCC. Required contents for the SSCC include a visual mental image or its equivalent in another sensory system such as auditory or kinesthetic, the outward appearance of that image must be consistent with a shamanic cosmology, the image must be consistent with the purpose of the shamanic journey, and the function of the vision must be consistent with the vision [53]. For the shaman, the nonphysical world encountered in the SSCC may be considered equally as real as the physical world [53]. Shamans were among the first psychotherapists, physicians, magicians, performing artists, storytellers, and weather forecasters [53]. Some could also locate game animals, enemy positions, or lost objects. Typical shamanic spiritual treatment elements include suggestion and imagery, discovery of the cause, removal or release of the cause, followed by subconscious relearning. These treatments can be directed when needed toward healing skin conditions, with positive results reported for atopic dermatitis and psoriasis.

Suggestion

Suggestion in the usual alert conscious state can be used to change subjective perceptions, to reduce pain, and may influence outcome. Reports the efficacy of suggestion in treating verruca vulgaris have since been confirmed numerous times to a greater or lesser degree [54]. Younger children often are in a hypnoidal state of consciousness as they play imaginatively and often readily accept suggestions. Resistant toddlers can sometimes be directed to do the opposite to get the desired effect. Resistant adolescents are more difficult to reach except through peers. Adults again respond variably to suggestion.

Conclusion

Skin disorders can have a significant effect on the psyche, and the psyche can have a significant effect on skin disorders through psychoneuroimmunoendocrine and behavioral mechanisms. Since many inflammatory skin disorders are triggered or aggravated by stress, it is important to teach patients to practice safe stress using non-pharmacological methods. Psychocutaneous treatments such as acupuncture, aromatherapy, autogenic training, biofeedback, breathing rate slowing techniques, brief psychodynamic therapy, cognitive-behavioral therapy methods, EFT, EMDR, guided imagery, hypnosis, meditation, music, placebo, shamanic drumming, or suggestion are safe non-pharmacological methods for improving skin disorders that have a significant psychological component. Further robust research is needed to reappraise and clarify the utility of some of these techniques for stress reduction and skin disorder improvement in patients.

References

1. Tausk F, Elenkov I, Moynihan J. Psychoneuroimmunology. Dermatol Ther. 2008;21:22–31.
2. Porges SW. The polyvagal theory: neurophysiological foundations of emotions, attachment, communication, and self-regulation. New York: Norton; 2011.
3. Shenefelt PD, Shenefelt DA. Spiritual and religious aspects of skin and skin disorders. Psychol Res Behav Manag. 2014;7:201–12.
4. Chen CJ. Acupuncture, electrostimulation, and reflex therapy in dermatology. Dermatol Ther. 2003;16(2):87–92.
5. Muenke M, Draeger-Muenke R. Acupressure and hypnosis: healer, heal thyself (and thy patients). Contemp Hypn Integ Ther. 2011;28(3):224–34.
6. Walsh D. Using aromatherapy in the management of psoriasis. Nurs Stand. 1996;11:53–6.
7. Anderson C, Lis-Balchin M, Kirk-Smith M. Evaluation of massage with essential oils on childhood atopic eczema. Phytother Res. 2000;14:452–5.
8. Weiss RR, James WD. Allergic contact dermatitis from aromatherapy. Am J Contact Dermat. 1997;8:250–1.
9. Fitzgerald M, Culbert T, Finkelstein M, Green M, Johnson A, Chen S. The effect of gender and ethnicity on children's attitudes and preferences for essential oils, a pilot study. Explore (NY). 2007;3:378–85.
10. Linden W. Autogenic training: a clinical guide. New York: Guilford Press; 1990.
11. Ehlers A, Stangier U, Gieler U. Treatment of atopic dermatitis: a comparison of psychological and dermatological approaches to relapse prevention. J Consult Clin Psychol. 1995;63:624–35.
12. Sarti MG. Biofeedback in dermatology. Clin Dermatol. 1998;16:711–4.
13. Delaney DC, Olson K, Labbe EE. Skin temperature biofeedback: evaluation of non-clinical children's responses. J Behav Ther Exp Psychiatry. 1992;23:37–42.
14. Haynes SN, Wilson CC, Jaffe PG, Britton BT. Biofeedback treatment of atopic dermatitis: controlled case studies of eight cases. Biofeedback Self Regul. 1979;4:195–209.
15. Dikel W, Olness K. Self-hypnosis, biofeedback, and voluntary peripheral temperature control in children. Pediatrics. 1980;66:335–40.
16. Shenefelt PD. Biofeedback, cognitive-behavioral methods, and hypnosis in dermatology: is it all in your mind? Dermatol Ther. 2003;16:114–22.
17. Barrios AA. Towards greater freedom and happiness. Los Angeles: SPC Press; 1985.

18. Draeger-Muenke R, Muenke M. The healing energy of breath in traditional Chinese medicine and other eastern traditions. In: Anbar RD, editor. Functional respiratory disorders: when respiratory symptoms do not respond to pulmonary treatment. New York: Humana Press/ Springer; 2012. p. 301–23.
19. Linnet J, Jemec GBE. Anxiety level and severity of skin condition predicts outcome of psychotherapy in atopic dermatitis patients. Int J Dermatol. 2001;40:632–6.
20. Levenson H, Persons JB, Pope KS. Behavior therapy & cognitive therapy. In: Goldman HH, editor. Review of general psychiatry. 5th ed. New York: McGraw-Hill; 2000. p. 472.
21. Craig G. The EFT manual. Santa Rosa: Energy Psychology Press; 2008.
22. Karatzias T, Power K, Brown K, McGoldrick T, Begum M, Young J, Loughran P, Chouliara Z, Adams S. A controlled comparison of the effectiveness and efficiency of two psychological therapies for posttraumatic stress disorder: eye movement desensitization and reprocessing vs. emotional freedom techniques. J Nerv Ment Dis. 2011;199:372–8.
23. Shapiro F. Eye movement desensitization and reprocessing (EMDR): basic principles, protocols, and procedures. 2nd ed. New York: Guilford Press; 2001.
24. Rodenburg R, Benjamin A, de Roos C, Meijer AM, Starns GJ. Efficacy of EMDR in children: a meta-analysis. Clin Psychol Rev. 2009;29:599–606.
25. Benor DJ, Ledger K, Toussaint L, Hett G, Zaccaro D. Pilot study of emotional freedom techniques, wholistic hybrid derived from eye movement desensitization and reprocessing and emotional freedom technique, and cognitive behavioral therapy for treatment of test anxiety in university students. Explore (NY). 2009;5:338–40.
26. Gupta MA, Gupta AK. Use of eye movement desensitization and reprocessing (EMDR) in the treatment of dermatologic disorders. J Cutan Med Surg. 2002;6:415–21.
27. Rainville P, Hofbauer RK, Bushnell MC, et al. Hypnosis modulates activity in brain structures involved in the regulation of consciousness. J Cogn Neurosci. 2002;14(6):887–901.
28. Freeman R, Barabasz A, Barabasz M, Warner D. Hypnosis and distraction differ in their effects on cold pressor pain. Am J Clin Hypn. 2000;43:137–48.
29. Shertzer CL, Lookingbill DP. Effects of relaxation therapy and hypnotizability in chronic urticaria. Arch Dermatol. 1987;123(7):913–6.
30. Shenefelt PD. Hypnosis in dermatology. Arch Dermatol. 2000;136:393–9.
31. Morgan AH, Hilgard ER. Age differences in susceptibility to hypnosis. Int J Clin Exp Hypn. 1973;21:78–85.
32. Spanos NP, Stenstrom RJ, Johnston JC. Hypnosis, placebo, and suggestion in the treatment of warts. Psychosom Med. 1988;50:245–60.
33. Tausk F, Whitmore SE. A pilot study of hypnosis in the treatment of patients with psoriasis. Psychother Psychosom. 1999;495:1–9.
34. Stewart AC, Thomas SE. Hypnotherapy as a treatment for atopic dermatitis in adults and children. Br J Dermatol. 1995;132:778–83.
35. Shenefelt PD. Anxiety reduction using hypnotic induction and self-guided imagery for relaxation during dermatologic procedures. Int J Clin Exp Hypn. 2013;61(3):305–18.
36. Shenefelt PD. Psychocutaneous hypnoanalysis: detection and deactivation of emotional and mental root factors in psychosomatic skin disorders. Am J Clin Hypn. 2007;50:131–6.
37. Shenefelt PD. Hypnoanalysis for dermatologic disorders. J Altern Med Res. 2010;2(4):439–45.
38. Ewin DM. Hypnotherapy for warts (verruca vulgaris): 41 consecutive cases with 33 cures. Am J Clin Hypn. 1992;35:1–10.
39. Kabat-Zinn J. Full catastrophe living: using the wisdom of your body and mind to face stress, pain and illness. New York: Delacorte; 1990.
40. Kabat-Zinn J. Wherever you go, there you are: mindfulness meditation in everyday life. New York: Hyperion; 1994.
41. Kabat-Zinn J. Influence of a mindfulness meditation-based stress reduction intervention on rates of skin clearing in patients with moderate to severe psoriasis undergoing phototherapy (UVB) and photochemotherapy (PUVA). Psychosom Med. 1998;60:625–32.
42. Holm L, Fitzmaurice L. Emergency department waiting room stress: can music or aromatherapy improve anxiety scores? Pediatr Emerg Care. 2008;24(12):836–8.

43. Young T, Griffin E, Phillips E, Stanley E. Music as distraction in a pediatric emergency department. J Emerg Nurs. 2010;33:472–3.
44. Mrazova M, Celec P. A systemic review of randomized control trials using music therapy for children. J Altern Complement Med. 2010;16:1089–95.
45. Vachiramon V, Sobanko JF, Rattanaumpawan P, Miller CJ. Music reduces patient anxiety during Mohs surgery: an open-label randomized controlled trial. Dermatol Surg. 2013;39(2):298–305.
46. Spiegel D. Placebos in practice (editorial). BMJ. 2004;329:927–8.
47. Di Blasi Z, Reilly D. Placebos in medicine: medical paradoxes need disentangling. (Letter). BMJ. 2005;330:45.
48. Gupta MA, Gupta AK. Psychodermatology: an update. J Am Acad Dermatol. 1996;34:1030–46.
49. Griesemer RD. Emotionally triggered disease in a dermatological practice. Psychiatr Ann. 1978;8:49–56.
50. Jacobson E. Progressive relaxation. Chicago: University of Chicago Press; 1929.
51. Benson H. The relaxation response. New York: Morrow; 1975.
52. Harner M. Cave and cosmos: shamanic encounters with another reality. Berkeley: North Atlantic Books; 2013.
53. Rock AJ, Krippner S. Demystifying shamans and their world: an interdisciplinary study. Charlottesville: Imprint Academic; 2011.
54. Ullman M. On the psyche and warts: I. Suggestion and warts: a review and comment. Psychosom Med. 1959;21:473–88.

Index

K. França, M. Jafferany (eds.), *Stress and Skin Disorders*,
DOI 10.1007/978-3-319-46352-0