Gender Differences in Skin: A Review of the Literature

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ABSTRACT

Background: There has been increasing interest in studying gender differences in skin to learn more about disease pathogenesis and to discover more effective treatments. Recent advances have been made in our understanding of these differences in skin histology, physiology, and immunology, and they have implications for diseases such as acne, eczema, alopecia, skin cancer, wound healing, and rheumatologic diseases with skin manifestations.

Objective: This article reviews advances in our understanding of gender differences in skin.

Methods: Using the PubMed database, broad searches for topics, with search terms such as gender differences in skin and sex differences in skin, as well as targeted searches for gender differences in specific dermatologic diseases, such as gender differences in melanoma, were performed. Additional articles were identified from cited references. Articles reporting gender differences in the following areas were reviewed: acne, skin cancer, wound healing, immunology, hair/alopecia, histology and skin physiology, disease-specific gender differences, and psychological responses to disease burden.

Results: A recurring theme encountered in many of the articles reviewed referred to a delicate balance between normal and pathogenic conditions. This theme is highlighted by the complex interplay between estrogens and androgens in men and women, and how changes and adaptations with aging affect the disease process. Sex steroids modulate epidermal and dermal thickness as well as immune system function, and changes in these hormonal levels with aging and/or disease processes alter skin surface pH, quality of wound healing, and propensity to develop autoimmune disease, thereby significantly influencing potential for infection and other disease states. Gender differences in alopecia, acne, and skin cancers also distinguish hormonal interactions as a major target for which more research is needed to translate current findings to clinically significant diagnostic and therapeutic applications.

Conclusions: The published findings on gender differences in skin yielded many advances in our understanding of cancer, immunology, psychology, skin histology, and specific dermatologic diseases. These advances will enable us to learn more about disease pathogenesis, with the goal of offering better treatments. Although gender differences can help us to individually tailor clinical management of disease processes, it is important to remember that a patient's sex should not radically alter diagnostic or therapeutic efforts until clinically significant differences between males and females arise from these findings. Because many of the results reviewed did not originate from randomized controlled clinical trials, it is difficult to generalize the data to the general population. However, the pressing need for additional research in these areas becomes exceedingly clear, and there is already a strong foundation on which to base future investigations. (Gend Med. 2007;4:308–328) Copyright © 2007 Excerpta Medica, Inc.

Key words: gender differences, skin, sex steroids, immunology and autoimmune diseases, wound healing, skin cancer.
INTRODUCTION
Over the past 25 years, there has been increasing interest in studying gender differences to learn more about disease pathogenesis and to discover more effective treatments, if not cures. However, in a MEDLINE search from 1975 to 2004 for publications on gender-specific dermatologic research, Holm et al. found few pertinent articles. In our review of gender-specific differences in skin, we found statistically significant results pertinent to gender differences in skin that were not always clearly obvious from reading the abstracts only. Our search for articles examining gender differences in skin yielded many advances in our understanding of immunology, skin histology/physiology, specific dermatologic diseases, and quality of life. Skin histology and physiology are frequently altered in dermatologic skin conditions, and gender differences in skin structure can be used as a strategy for learning about the pathogenesis of certain skin diseases, such as atopic dermatitis. Furthermore, gender differences in the immune system can offer insight into the pathogenesis of a multitude of diseases with cutaneous manifestations as well as the process of wound healing. Lastly, differences in response to skin conditions, partly influenced by societal expectations and responses to ideals of attractiveness, can significantly alter the quality of life among individuals coping with similar severities of identical dermatologic conditions. The purpose of this article was to highlight these recent advances in our understanding and consider the implications of this knowledge in helping us to better prevent, manage, and possibly cure, skin diseases.

METHODS
A PUBMED search of relevant articles was conducted. General searches for topics, such as gender differences in skin and sex differences in skin, as well as targeted searches for gender differences in specific dermatologic diseases, such as gender differences in melanoma, were performed. Additional articles were identified from cited references. Articles reporting gender differences in the following areas were reviewed: acne, skin cancer, wound healing, immunology, hair/alopecia, histology and skin physiology, disease-specific gender differences, and psychological responses to disease burden. Published results were considered to be statistically significant if $P \leq 0.05$.

HISTOLOGY/SKIN PATHOLOGY
As the largest organ in the body, skin is the primary protective barrier between an individual and his or her environment. Gender differences in skin structure can be used as a strategy for learning about the pathogenesis of certain skin diseases, such as atopic dermatitis, that are characterized by derangements in skin structure and function. Sex steroids influence skin thickness, thereby influencing susceptibility to infection and potential for wound healing. We also examined other differences, such as skin pH, that may alter skin flora and thus vary thresholds for skin infections in susceptible patients.

Differential Effects of Sex Steroids in Murine Skin Layers
Animal studies have noted gender differences in skin. Male mice have a 190% thicker dermis, but a thinner epidermis and hypodermis, than do female mice, resulting in male skin that is 40% thicker than female skin. Data collected from performing gonadectomies and testing the effects of androgen and estrogen treatments on mouse skin suggest that estrogen plays a major role in regulating epidermal thickness, and that estrogen's effects in regulating epidermal thickness are mainly via estrogen receptor-α (ERα) and not estrogen receptor-β (ERβ). After gonadectomy, female murine dermal thickness increased, whereas male murine dermal thickness did not significantly change, suggesting that androgens play a major role in regulating dermal thickness. Moreover, treatment with the androgens dihydrotestosterone and dehydroepiandrosterone significantly increased murine dermal thickness by 22% and 19%, respectively.
Susceptibility to Dermatologic Diseases Due to Gender Differences in Human Skin Physiology

In humans, male skin is thicker than female skin,\(^4\) and females have thicker subcutaneous tissues than do males.\(^5\) With aging, female skin becomes thinner than male skin,\(^6\) and postmenopausal women especially experience a decrease in skin thickness, suggesting that estrogens play a role in maintaining skin.\(^7\) Sex steroids can change skin thickness; ovariectomy is associated with thinning of the skin whereas estrogen therapy thickens skin.\(^8\)

Conflicting results have been published about gender differences in the physiology of human skin. Skin pH is believed to influence the stratum corneum layer (ie, the skin's barrier function) and the flora of organisms living in the skin.\(^9\)-\(^11\) Indeed, males may carry more aerobic flora and biotypes than may females, without any observed qualitative differences in the flora.\(^12\) Studies of skin pH in different areas of the body may offer valuable insight to the poorly understood pathogenesis of some diseases resistant to current standards of treatment, such as hidradenitis suppurativa, which tends to affect women in the axillae and men in perianal areas.\(^13\) Even small differences in pH may significantly change the structure of skin,\(^14\) and increasingly basic skin surfaces may allow for skin colonization of pathologic microorganisms.\(^9\),\(^14\) An interesting clinical correlation is a study that suggested an association between elevated intertriginous pH and the increased incidence of candidal intertrigo in patients with diabetes.\(^15\)

One study found no significant gender differences in skin surface pH, transepidermal water loss, stratum corneum hydration, or casual sebum content.\(^16\) However, 4 other studies found that women had higher skin surface pH levels than did men,\(^17\)-\(^20\) and yet another study reported the opposite finding.\(^21\) What may be confounding these results is that different areas of the body were sampled among the studies. Also, the use of cosmetics may have increased pH\(^22\) and prevented consistent results. To mitigate the effect of cosmetics on skin pH, Jacobi et al\(^19\) instructed participants to avoid all cosmetic products for 7 days before measurement of skin pH, but it is still conceivable that cosmetics may have longer-lasting effects on skin pH that need to be considered when analyzing results. A further strength of the study is that participants were permitted time to become acclimated to standard room temperature and humidity before study measurements were taken,\(^19\) which accounted for the fact that overall sweat rates and total lactate secretion are greater in males than in females.\(^23\) Williams et al\(^24\) found that women have more acidic axillary skin surface pH than men have, and after washing with tap water, the axillary skin surface pH decreases significantly in women, whereas it slightly increases in men. In the future, better understanding of the skin's response to cleansing with water and different types of soaps in different regions of the body will result in gender-specific recommendations for skin care, especially in relation to specific dermatologic diseases characterized by deranged skin pH.

What clinical significance can be attributed to gender differences in skin lipid and protein content remains to be fully elucidated. In a study of skin friction in 11 anatomical regions, skin surface lipid content was found to be statistically lower on the forehead, dorsal forearm, and postauricular areas in females, but the dynamic friction coefficient (μ) showed no gender difference.\(^25\) With age, there was a significant change in ceramide ratios in females but not in males, and it was suggested that female hormones played a possible role in the makeup of stratum corneum sphingolipids.\(^26\) Gender differences in cutaneous protein composition have also been observed and are hypothesized to result from different protein makeup between males and females, which is influenced by differing hormone statuses.\(^19\)

Gender Differences in Immunology

The immune system protects against foreign antigens to prevent disease while maintaining a level of self-tolerance to prevent autoimmune disease. Sex steroids influence many different
immune responses, and changing levels of sex steroids with aging and other disease states have been implicated in a variety of gender differences observed in wound healing, infectious and autoimmune diseases, and many other dermatologic conditions. Subsequently, an elaborate and complex interaction between different sex steroids and their receptors has been uncovered. The underlying basis for these gender differences in immunology, however, has not been clarified.

**Basis for Disease Expression**

A vast amount of literature explores gender differences in the immune system, with sex steroids commonly implicated in causing these differences. In general, estrogen stimulates the immune system whereas testosterone inhibits it. However, this statement is far too simplistic, as revealed after the discovery of the novel ERβ in 1996. The 2 types of estrogen receptors, ERα and ERβ, are differentially expressed in different cell lineages and have different functions. For example, ERβ signaling mediates the apoptosis of undifferentiated monocytes via the Fas/Fas ligand system, and signaling via ERα decreases proinflammatory cytokine levels in mice models of autoimmune diseases. Targeted treatments with selective ER modulators have great potential in treating autoimmune diseases more selectively while decreasing adverse effects.

At least before menopause, it is believed that women are better able than men to cope with infectious diseases because they have higher CD4 lymphocyte levels and a higher propensity to develop a Th1 response, express more inflammatory cytokines, develop a more robust antibody titer in response to vaccination, and generate higher immunoglobulin levels in response to antigenic challenges. Whereas estrogens stimulate the humoral immune response, androgens enhance the cellular immune response. As a result, diseases characterized by robust humoral immune responses that lead to counterproductive levels of Th2 lymphocytes are highly female dominant compared with diseases due to Th1 dysfunction. Unfortunately, there is a price to pay for an enhanced immune response. Estrogens encourage the development of autoreactive B cells and are believed to inhibit apoptosis to permit the survival of autoreactive T cells. As a result, autoimmune diseases are found much more commonly in females.

Despite mounting evidence that sex steroids contribute to gender differences in immunology, the underlying pathogenesis has yet to be made clear. Defects in the X chromosome, which normally contains genes that influence sex hormone levels and immune tolerance, may be potential culprits. Evidence in favor of this proposition includes the fact that diseases involving changes to the X chromosome, such as Turner’s syndrome, in which an X chromosome is missing, are more commonly associated with the development of autoimmune diseases. Another potential contributor to gender differences in immunology are Langerhans’ cells (LCs), which are derived from the bone marrow and play an important role as antigen presenting cells in the cutaneous immune response. LC density has been found to correlate with T-cell response, lending support to the idea that LCs play a role in immune reactions in the skin. However, gender differences in human LC density or structure have not been described.

**Lyme Borreliosis: Disease Expression Influenced by Gender Differences**

Lyme borreliosis is a vector-borne disease with a characteristic cutaneous manifestation known as erythema migrans. From 1992 to 1998, males aged 5 to 19 and ≥60 years had a higher incidence of Lyme borreliosis infection than did females in the same age range. In a 5-year follow-up study of individuals in Sweden who were diagnosed with erythema migrans and treated with antibiotics, 31 of 708 people were reinfected, with the overwhelming majority of those (27 of 31) being women aged >44 years. When lymphocytes were collected from reinfected individuals and stimulated in vitro with a variety of antigens, women had substantially more spontaneous production of total cytokines than...
did men; however, women also had substantially greater Th2 ratios, suggesting that they may have had a Th2 dominant response and a decreased inflammatory response even though they had a larger absolute secretion of cytokines. Further research needs to focus on how women’s immune systems adapt to decreasing estrogen levels after menopause.

AUTOIMMUNE DISEASES

There is a striking gender difference in the prevalence and incidence of autoimmune diseases. Precipitous changes in some of these ratios with aging have directed much research toward the possible roles of sex hormones and their receptors, as well as inherent differences in sex chromosomes and the immune system between the sexes.

Chronic Immune Thrombocytopenic Purpura

Chronic immune thrombocytopenic purpura (ITP) occurs especially in women in their 30s and 40s, with a female-to-male ratio of 3–4:1 which suggests that sex hormones may play a role in its pathogenesis. It is believed that megakaryocyte and platelet generation is controlled via “thrombopoietic” cytokines, whose production may be influenced by sex hormones. Although a study examining gender-related differences in the thrombopoietic cytokine pattern in patients with ITP failed to find any gender differences in cytokine levels regulating thrombopoiesis in these patients, people with chronic ITP may have higher levels of estradiol than may patients without chronic ITP, suggesting that sex hormones play a role in ITP susceptibility, independent of sex.

Systemic Lupus Erythematous

Systemic lupus erythematous (SLE) is an autoimmune disease with a female-to-male ratio of 3:1 before puberty, 10–15:1 during the reproductive years, and 8:1 after menopause. This gender difference in incidence suggests that sex hormones play a key role in the pathogenesis of SLE. Postmenopausal women taking estrogen have increased risks of developing SLE, with the risk being proportional to the duration of treatment. Both males and females with SLE have increased activity of the cytochrome P450 enzyme CYP1B1 that preferentially converts estradiol to more potent serum estrogens such as 16-α-hydroxyestrone, resulting in a 20-fold increase in the fraction of high- to low-potency estrogens in patients with SLE versus healthy individuals. It has been suggested that increased prolactin levels may partly be responsible for decreased androgen levels, which have been associated with SLE.

Scleroderma

Scleroderma, also known as systemic sclerosis (SSc), is an autoimmune connective tissue disease that can lead to fibrosis of multiple organ systems. Involvement in scleroderma may be limited to the skin (limited cutaneous or CREST syndrome) or include many internal organs (diffuse cutaneous systemic sclerosis or progressive systemic sclerosis). Overall female-to-male incidence ratios of scleroderma have been reported to be 2.9:1 and 3:1. In the reproductive years, the female-to-male SSc ratio is as high as 15:1 before plummeting to 1.8:1 in those aged ≥45 years. The rate of monosomy X is 2-fold higher in females with SSc than in healthy women, suggesting that haploinsufficiency of X-linked genes may be a contributor to the female predominance of SSc and other autoimmune diseases. One recent meta-analysis involving 1291 patients and 3435 controls from 11 case-control studies found SSc to be associated with occupational exposure to solvents (odds ratio = 2.4), and men had a statistically significant higher relative risk of developing SSc when exposed to solvents than women did (odds ratio = 3.0 vs 1.8), though the 95% CIs did overlap slightly.

A prospective study of 91 patients with SSc found only 2 clinical differences between men and women: whereas myositis was 7-fold more common in men than in women, men had a lower prevalence of arthralgias. One study in a cohort of patients found that men had shorter
mean disease duration than did women, though this finding was not observed in another study. Gender differences in age at disease onset or diagnosis have not been reported, and no consensus exists concerning sex as a prognostic factor in SSc. Some studies have concluded that men have worse survival rates than do women, yet other studies have found no statistically significant gender differences in morbidity or mortality in SSc.

**Rheumatoid Arthritis**

Rheumatoid arthritis (RA) is characterized by a chronic inflammatory synovitis and affects more females than males, with an incidence 4 to 5 times higher in females than in males younger than age 50 that decreases to a ratio of ~2:1 after 60 to 70 years of age. A significant decline in the incidence of RA has been observed over the past decades especially in females, who showed the largest decrease in incidence. It has been suggested that oral contraceptive use may account for some of this decline. Smoking in men, but not in women, has been associated with a 2-fold higher risk of developing RA. Females usually develop RA earlier in life than do males, and a study of male and female patients matched for duration of disease found no differences in disease activity or severity, with the exception that women had Sjögren's syndrome more frequently than did men. Another study observed gender differences in the clinical presentation of RA, with men developing erosive disease earlier and more frequently and also more commonly developing nodules and rheumatoid lung disease, whereas women usually manifested with sicca syndrome.

It now appears that women have 2 major factors increasing their susceptibility to autoimmune diseases. During their reproductive years, women have to cope with the immune-inducing effects of increased estrogen levels, and after menopause, women have to contend with decreases in estrogen that may thereby increase autoreactive monocyte survival resulting from decreased activation of the Fas/Fas ligand system.

**HAIR/ALOPECIA**

**Complex Interplay Between Estrogen, Androgen, and Progesterone**

ERs have been implicated in modulating hair growth. Very little gender difference has been found in the expression of the 2 ERs (i.e., ERα and ERβ) in nonbalding scalp skin, but it is not known whether there is a gender difference in ERs in balding skin. ERβ has widespread localization in the hair follicle, especially in the dermal papilla cells and the specialized bulge region of the outer root sheath, and appears to be the main receptor for estrogen's effect on hair growth. The mechanism behind male pattern hair loss is poorly understood because it has been observed to correlate with androgen levels in at-risk individuals, although it has been suggested that scalp hair growth does not require androgen receptors (ARs). A complex interplay between estrogen and ARs may regulate the skin and its appendages, as suggested by the antagonistic nature between estrogens and androgens in other tissues, such as ERβ's inhibition of dihydrotestosterone in the prostate by decreasing levels of AR. Even less understood is the role of progesterone receptor (PR) in hair growth.

**Androgenetic Alopecia**

Androgenetic alopecia occurs most prominently in men and usually involves the frontal and temporal scalp areas; adult male plasma androgen levels are believed to be necessary for this process, which begins after puberty and continues throughout adult life. In the dermal papilla of hair follicles, PR has stained positive in the nucleus and cytoplasm in 30% of cases of androgenetic alopecia. However, Pelletier and Ren did not find PRs in hair follicles. Further research is needed to determine what role PRs play in modulating hair growth in skin. Limited evidence stems from one study which found that chronic progesterone treatment decreased ER concentration in monkey skin.

**Female Pattern Hair Loss**

In contrast to male pattern hair loss, female pattern hair loss usually occurs independently of...
androgen levels and begins after 30 years of age, involving the frontal and parietal scalp areas in a more diffuse pattern. It has been suggested that females may be protected from developing androgenetic alopecia because they have less 5α-reductase and AR activity in the frontal and occipital scalp hair follicles. Women also have more aromatase expression in scalp hairs, especially on the occiput, suggesting that estrogen formation from testosterone is a protective factor against developing androgenetic alopecia.

Potential for Gender-Tailored Treatment of Hair Loss

Currently, topical 17β-estradiol is used in some countries to treat female pattern hair loss, possibly by prolonging anagen. Conrad et al cultured anagen VI follicles from frontotemporal scalp skin in the presence of estrogen and documented significant gender differences in the response of human scalp hair follicles to estrogen stimulation. In males, ERβ predominantly stains in the nuclei of matrix keratinocytes, whereas in females, ERβ stains predominantly in dermal papilla fibroblasts of hair follicles. In response to estrogen treatment, males showed significantly increased immunoreactivity of ERβ in dermal papilla fibroblasts, whereas females failed to show any change in ERβ immunoreactivity. Furthermore, in response to estrogen treatment, transforming growth factor-β immunoreactivity increased significantly in the lower outer root sheath in females but decreased in males. Other genes were found to be regulated differently depending on sex, and further advances in our understanding of estrogen-dependent gene regulation will help us develop gender-tailored treatments for male versus female pattern balding. ER modulators that promote catagen can also be used to treat hirsutism, but gender differences in the response to estrogen need to be elucidated.

ACNE

Hyperresponsive Sebum Production: One Step in Acne Pathogenesis

It is believed that sebum production plays a role in the development of acne and may be increased by androgens and decreased by estrogens. Acne is believed to result from the hyperresponsive reaction of sebocytes and keratinocytes to androgens, which lead to follicular plugging, thus promoting the inflammatory response to Propionibacterium acnes, which flourishes in follicular ducts, especially in skin with elevated surface pH. It is poorly understood why some sebocytes are hyperresponsive to androgens; one possibility is that the ratio of hormones may be more important than actual hormonal levels.

Though increased levels of androgens have been associated with increased sebum production, this observation has not been reproduced in vitro. Recently, the synergistic and catalytic effect of increasing sebaceous lipids when using linoleic acid (which acts as a ligand at the peroxisome proliferator-activated receptor (PPAR)) with testosterone has been demonstrated. Whether or not differences in dietary habits (thereby influencing linoleic acid levels) or gender differences in these receptors exist remains unknown. What is exciting is the future potential for local PPAR modulation in acne treatment.

Gender Differences in Murine Sebaceous Glands

Male mice have 45% larger sebaceous glands than do their female counterparts, a finding that, if true in humans, could account for men being more likely to have refractory acne. Sex steroid stimulation may be one cause for this difference; gonadectomy in male mice resulted in a 46% atrophy of sebaceous gland size, whereas gonadectomy in female mice increased sebaceous gland size by 19%. There are significant gender differences in AR and ERα expression in male versus female sebocytes. AR is expressed almost exclusively in sebocyte nuclei of male mice but is decreased in sebocyte cytoplasm and nuclei of female mouse. ERα is not found in intact male mouse sebaceous glands, but females have strong ERα expression in basal cell nuclei, consistent with the fact that androgens increase sebum production.
Gender Differences in Human Sebaceous Glands

Sex hormones are produced locally in human skin, and their varying levels of expression reflect differential expression of sex steroid-producing enzymes in different skin cell types, of which sebaceous glands are prominent. However, it is not known whether there are human gender differences in sebaceous gland sex steroid receptor expression, although androgens may influence cell proliferation and lipo genesis in the sebaceous gland. Basal cells and sebocytes in sebaceous glands have more positive immunostaining for ERβ than for ERα. and ERβ is the overwhelmingly predominant ER expressed in the epidermis. Moreover, melanocortin-1 receptor expression in sebocytes and keratinocytes of acne-involved skin was recently found to be increased compared with normal skin and has been implicated in acne pathogenesis. Further studies are needed to detect any potential gender differences in these receptors in the skin and its appendages, but even if these studies do not yield results, differing hormonal levels between the sexes likely contribute to the higher rate of sebum production in adult men versus adult women. Isotretinoin is a potent systemic treatment for severe acne and serves to decrease sebaceous gland production and size, whereas other acne treatments mainly address *P. acnes* and follicular keratinization.

Pediatric Eczema

In newborns, no gender differences in the development of eczema have been found. However, in the first 6 months of life, boys have a higher propensity to develop eczema than do girls. In contrast, there is a higher prevalence of eczema in girls than in boys in the preschool ages, and this trend continues into adolescence. Eczema without concomitant respiratory allergies may be more common in girls than in boys (female-to-male ratio of 1.4:1), whereas males more commonly have eczema with concomitant respiratory allergies. These findings suggest that girls have atopic eczema less frequently than do boys. Indeed, non-atopic eczema has been noted to occur twice as commonly in girls (5.9%) than in boys (3.1%), and this difference accounts for the larger numbers of girls than of boys with eczema. Compared with 5- to 7-year-old boys, girls in this same age group have been shown to have a higher skin surface pH and decreased stratum corneum hydration, factors that have been associated with an increased propensity in children for developing acute atopic eczematous lesions. Girls with eczema also have substantially higher transepidermal water loss than do boys with eczema. Another reason for late-onset eczema without atopy has also been hypothesized to be related to gender differences in indoor versus outdoor activity. It has been reported that girls play indoors more frequently than do boys, and children who play more indoors than outdoors have an almost 2-fold greater prevalence of eczema.

WOUND HEALING

Sex Steroid Influences in the Epidermal Permeability Barrier in Animals

Animal studies have demonstrated significant roles for sex steroid actions in the development of the permeability barrier. Barrier development in fetal rat skin is accelerated by estrogens and is retarded by testosterone, and male rat fetuses have slower epidermal barrier formation than do female rat fetuses, suggesting that androgens are responsible for the observed gender differences in cutaneous barrier function. Accelerated cutaneous wound healing, associated with decreased AR stimulation on macrophages causing in vivo downregulation of tumor necrosis factor-α (TNF-α), occurs after castration in male mice or AR blockade with flutamide. Not all types of androgens are solely associated with decreased inflammatory responses and impaired wound healing; androgens have also been associated with both pro- and anti-inflammatory states. In vitro macrophage production of TNF-α and interleukin-1 has been inhibited by androstenediol, emphasizing that...
much remains to be understood about the complexity of sex steroid actions.

**Skin Grafts in Animals: Associations with Langerhans’ Cells and the H-Y Antigen**

Skin allografts are rejected more frequently and quickly in females than in males, and orchiectomy in males results in quicker rejection of skin allografts. Koyama et al. hypothesized that if LCs did play a role in the immune reaction in the skin and were involved in skin graft rejection, they would be found in differing amounts in males versus females. Male mice had substantially lower LC density in the hind limb and ear skin than did female mice; castration substantially increased LC density in male mice whereas ovariectomy had no effect on LC number in female mice. Androgens made in the testes may suppress LC density in males, contributing to more rejection of skin allografts in females than in males.

However, other studies of epidermal LC density in humans, mice, and guinea pigs have not found any differences in LC density between males and females. A unique aspect of Koyama’s study not found in the previous research was that age-matched mice were used; it is known that LC density decreases gradually over time, potentially confounding data if age-matched subjects are not used. Subcutaneous and topical application of testosterone propionate substantially decreases LC density both in castrated males and normal female mice, providing further evidence that sex differences in LC density may be a result of higher androgen levels in males.

Recent studies have been undertaken to learn more about a male-specific minor histocompatibility antigen, the histocompatibility Y (H-Y) antigen, which is located on the long arm of sex chromosome Y. The H-Y antigen was first described in 1968 as a transplantation antigen in mice that potentially caused male mice skin grafts to be rejected in female mice recipients, whereas female mice skin grafts were tolerated in male mice recipients. Another study involving rats had similar results, finding that male skin grafts were rejected within 6 weeks after grafting, whereas all female skin grafts were accepted in male recipients, providing further evidence that the H-Y antigen may play a role in skin graft rejection.

**Implications for Sex Steroids in Human Wound Healing**

Abnormal wound healing in the elderly results in significant morbidity, mortality, and costs in health care. Being male is considered a risk factor for abnormal healing in the elderly, and men have an altered inflammatory response and take longer than women to heal acute wounds. In response to trauma, hemorrhage, and sepsis, women have substantial survival advantages over men. For example, women fare significantly better than men after challenge with surgical sepsis, with a mortality rate of 26% versus 70%, respectively.

Trauma is associated with alterations in sex steroid concentrations, with higher estrogen concentrations in both sexes and decreased testosterone levels in males. Patients with delayed wound healing resulting from abnormalities in sex steroid levels (eg, patients with decreased testicular function leading to androgen deficiency, patients with renal failure, patients’ status post-ovariectomy, and those in their elderly years) stand to benefit greatly from increased understanding of the role of sex steroids in wound healing. Physiological levels of 5-α-dihydrotestosterone decrease wound immune function and impair wound healing after trauma and hemorrhage, in a milieu of increased proinflammatory cytokines and decreased tumor growth factor-β at the wound site. Gender differences in the human epidermal permeability barrier have not been demonstrated, but understanding such a difference, if it exists, would help clinicians to recognize the poorly understood influence that sex plays in the severity of diseases associated with abnormal skin barrier function, such as atopic dermatitis and severe psoriasis, that occur more frequently in males than in females.

Decreased estrogen levels, leading to decreased stimulation of cutaneous ERs, may lead to significant downstream effects that can interfere with wound healing, such as impaired cytokine
signal transduction, destructive levels of inflammation, and an altered protein balance.\textsuperscript{129} Indeed, estrogen treatment accelerates cutaneous wound healing,\textsuperscript{162} and topical estrogens have been used in elderly patients to promote quicker and more effective wound healing.\textsuperscript{145} However, elderly males respond substantially less to estrogen treatment than do their female counterparts;\textsuperscript{129} this may be a result of testosterone's antagonism of wound healing, because increasing testosterone levels in elderly men are positively correlated with increased delays in wound repair.\textsuperscript{129} Counterproductively, high proinflammatory responses in the skin inhibit proper wound healing, and the elderly may lack sufficient anti-inflammatory responses. In contrast, young adults may have sufficient levels of systemic and local estrogen that play a role in reducing inflammation via influencing cell adhesion molecule expression.\textsuperscript{129}

\section*{CANCER}
\subsection*{Influence of Sex Steroids: Evidence from Animal Studies and Cultures}

The bulge region of the hair follicle is believed to be a source of hair follicle stem cells.\textsuperscript{163} Skin carcinomas may stem from this bulge region and be triggered by estradiol,\textsuperscript{163} and 17β-estradiol has been shown to induce squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) in mice and rats, an effect that is reversed after gonadectomy.\textsuperscript{164} High levels of ERβ, and not ERα, have been discovered in human SCC tissues and cell lines.\textsuperscript{165} Treatment with tamoxifen, an estrogen antagonist, significantly interfered with SCC invasion, in part by decreased intracellular focal adhesion kinase signaling, inhibition of epidermal growth factor receptor, and derangements in actin.\textsuperscript{165} 17β-estradiol also stimulates melanocyte division in culture,\textsuperscript{166} even though a study conducted before the discovery of the novel ERβ reported that there were no ERs in malignant melanoma.\textsuperscript{167}

\subsection*{Melanoma}

Before 1995, studies failed to find ERα in melanomas, but after the discovery of ERβ in 1996,\textsuperscript{29} ERβ was found to be the predominant ER type in melanocytic lesions, suggesting that estrogen and estrogen-like ligands play roles in melanocyte physiology via ERβ.\textsuperscript{168} ERβ was most immunoreactive in dysplastic nevi with severe atypia and lentigo malignas, and its immunoreactivity varied depending on the microenvironment, with melanocytes in invasive melanomas showing less reactivity than melanocytes that were still in proximity to keratinocytes.\textsuperscript{168} Furthermore, ERβ immunoreactivity decreased with increasing Breslow depth, suggesting that the loss of ERβ expression in melanomas may be a significant stage in which melanomas become independent of estrogen.\textsuperscript{168} In addition, in nonmelanoma melanocytic lesions, there was a trend toward women having more ERβ immunoreactivity in melanomas than men did, but the trend was not statistically significant, possibly because the study size was not large enough.\textsuperscript{168}

From birth until death, the probability of developing melanoma is 1.72\% (1 in 58) in men and 1.22\% (1 in 82) in women, and men have a 2-fold higher probability of developing melanoma compared with women between 60 and 79 years of age.\textsuperscript{169} Sex is also a prognostic factor in cutaneous melanoma,\textsuperscript{170–173} with women having better prognoses compared with men.\textsuperscript{174,175} Indeed, between 1973 and 1997, the rate of death from melanoma in the United States was 2-fold greater in males than in females.\textsuperscript{176,177}

Studies searching for relationships between sex and melanoma tumor thickness, one of the most important factors in predicting outcomes, have found conflicting results. One study did not find sex to be significantly associated with prognosis in intermediate- to-thick melanomas,\textsuperscript{174} whereas 2 other studies showed that males had decreased survival compared with women when matching for tumor thickness.\textsuperscript{172,178} Furthermore, men with positive sentinel lymph node (SLN) biopsies may have worse prognoses than women with positive SLNs.\textsuperscript{174,178}

However, sex has not been associated with SLN status.\textsuperscript{178–185} A prospective study, involving 1829 patients aged 18 to 70 years with melanomas ≥1.00 mm Breslow thickness who were
treated with wide excision and SLN biopsy, found that male sex was associated with thicker melanomas, an increased tendency to have tumor ulceration, and a greater likelihood of being older than 60 years of age at melanoma diagnosis. Even when taking these associations into account, sex was still determined to be an independent factor affecting survival in cutaneous melanoma. Future study directions in this area include investigating whether there is any delay in seeking or obtaining medical care in men versus women, because men were more likely to present with melanoma at an advanced age of >60 years.

Sex steroids may play a role in melanoma. In women, malignant melanoma is rare before puberty but sharply increases in incidence from puberty until about 50 years of age, when the incidence decreases after menopause. Also, the risk of females developing cutaneous malignant melanoma is increased by ~16% for every 5 years of delayed childbearing, and multiparity reduces the risk of developing cutaneous malignant melanoma by ~8% for each additional birth; a pooled analysis has also demonstrated similar benefits of an earlier age at first birth and of multiparity in decreasing the risk of developing cutaneous melanoma. However, the myth that nevi may grow or change during pregnancy is not true and should not delay diagnostic evaluation by a health professional. Learning more about gender differences in melanoma can suggest new treatment modalities, one possibility being the use of sex steroids and hormonal therapy.

Nonmelanoma Skin Cancer

Two studies (n = 1711 and n = 5044) have found that BCCs had higher male-to-female ratios of 1.17 and 1.42, respectively, but another study (n = 10,245) reported a male-to-female ratio of 0.92. Although incidence rates of nonmelanoma skin cancer (NMSC) vary by location, men have consistently been found to have higher incidence rates than do women in studies based in Germany (100.2/100,000 for men vs 72.6/100,000 for women), North America (309/100,000 for men vs 165.6/100,000 for women), and Australia (2058/100,000 for men vs 1194/100,000 for women). It has been observed that women are significantly younger than men when receiving a diagnosis of BCC (aged 63.5 years vs 64.9 years, respectively, with a 95% CI of -2.4 to -0.4). In Sweden, males have been noted to have an ~20-fold higher incidence of skin cancer of the ear, compared with females. Other studies have also found striking gender differences in the locations of NMSC, and whereas BCC tumors occur more often on the ears and scalp in males, they occur more often on the lips, neck, and legs in females. It has been speculated that the reason for higher frequency of BCC on the upper lip in women may be due to the lack of mustache hairs protecting the underlying skin from sun exposure, as also observed in another study reporting a female-to-male ratio of 3.5:1 for upper-lip BCCs that increases to 16:1 in younger women 30 to 39 years of age. Other factors influencing these gender differences in BCC include the use of carcinogenic cosmetics, earlier referral in females, and a more conscientious attitude of females toward their skin. It has also been hypothesized that hair follicles play a role in the development of BCC. Human papilloma virus DNA has been found in plucked hair, implicating gender differences in hair follicle density in accounting for the observed gender differences in BCC location.

A very large series of 10,245 patients with BCCs found that these malignancies of the head and neck occurred more frequently in women (85.2%) than in men (81%). When analyzed by subtype, superficial BCCs showed the largest gender difference in distribution, occurring more predominantly on the head in women (44.5% in women vs 34.7% in men) but more predominantly on the trunk in men (49.9% in men vs 42% in women). Women more frequently had the morpheiform type (7.2% in women vs 5.2% in men). Overall male-to-female ratios were 1.02 in nodular BCCs, 0.96 in superficial BCCs, and 0.73 in morpheiform BCCs. Women more commonly were younger than men when undergo-
ing excision of nodular and superficial BCCs of the trunk, contrasting with the observation that women tended to be older than men when undergoing excision of both superficial and nodular BCCs of the head and neck.

QUALITY OF LIFE
Engaging the patient in an active discussion of their emotional reaction toward their dermatologic condition is crucial in understanding how their lives are affected—the number of complaints cannot be simply correlated with quality of life. Gender differences in psychology are partly influenced by cultural expectations as well as by the surrounding environment, and these differences help determine patients' responses to their dermatologic conditions as well as the degree to which they may become functionally impaired in society. The response and the degree of impairment do not always correlate with each other.

With psoriasis, men may be more afraid than women of losing their jobs when taking time off from work for medical appointments. However, women with psoriasis experience more stigmatization than do men. A study of patients aged ≥15 years with atopic dermatitis found no significant gender differences in age, duration of disease, or disease severity; however, women more frequently reported their atopic dermatitis in all locations of the body except for the feet. Similarly, another study in healthy volunteers noted that women tended to have more subjective complaints of dry skin than did men (P < 0.001), despite there being no clinical or objective differences in any measurements taken during the study. The largest gender difference was in reported location of atopic dermatitis in visible areas such as the head, neck, and hands: 78.3% of women versus 55.7% of men reported disease activity in these areas, and lesions in visible areas diminished quality of life more in women than in men. Although a heightened sensitivity for disease may decrease quality of life more in women than in men with skin disease in visible areas, it partly helps to explain the previously mentioned fact that, compared with men, women tend to be treated earlier and have better prognoses for skin cancers.

CONCLUSIONS
Our search for articles examining gender differences in skin yielded many advances in our understanding of skin histology, immunology, specific dermatologic diseases, and quality of life. These advances will enable us to learn more about disease pathogenesis, with the goal of offering better treatments and compassionate care.

A recurring theme encountered in many of the articles referred to a delicate balance between normal and pathogenic conditions. One of the most studied delicate balances is the complex interplay between estrogens and androgens in men and women, and how changes and adaptations with aging affect the disease process. Sex steroids modulate epidermal and dermal thickness as well as immune system function, and changes in these hormonal levels with aging and/or disease processes alter skin surface pH, quality of wound healing, and propensity to develop autoimmune disease, thereby significantly influencing potential for infection and other disease states. The discussed gender differences in alopecia, acne, and skin cancers also distinguish hormonal interactions as a major target for which more research is needed to translate current findings to clinically significant applications.

Although many significant gender differences were found that can help us individually tailor clinical management of disease processes, it is important to remember that a patient's sex should not radically alter diagnostic or therapeutic efforts until clinically significant differences between males and females arise from these findings. Furthermore, because many of the results reviewed did not originate from randomized controlled clinical trials, it is difficult to generalize the data to the general population. However, the pressing need for additional research in these areas becomes exceedingly clear, and there is already a strong foundation on which to base future investigations.
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