Gender aspects in skin diseases

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Abstract

Gender differences in medicine have been recognized in anatomy, physiology, as well as in epidemiology and manifestations of various diseases. With respect to skin disorders, males are generally more commonly afflicted with infectious diseases while women are more susceptible to psychosomatic problems, pigmentary disorders, certain hair diseases, and particularly autoimmune as well as allergic diseases. Significantly, more female sex-associated dermatoses can be identified than the male sex-associated dermatoses. Dermatoses in the genital area differ between men and women. Gender differences also exist in the occurrence and prognosis of certain skin malignancies. The mechanisms underlying gender differences in skin diseases remain largely unknown. Differences in the skin structure and physiology, effect of sex hormones, ethnic background, sociocultural behaviour and environmental factors may interact to exert the influences. A better understanding of gender differences in human health and diseases will allow the development of novel concepts for prevention, diagnosis and therapy of skin diseases.

Introduction

There is growing interest in understanding the sexual dimorphism in medicine over the last decade, ranging from epidemiology, pathophysiology, clinical manifestation, to therapeutic response of various diseases. Gender differences in anatomy, physiology, immunity, genetics as well as geographical and sociocultural backgrounds may all interact contributing to the different disease manifestations between men and women. Sex hormones are the most well known and studied factors exerting the influence on gender development. All naturally existing oestrogens, oestrone, oestradiol (E2) and oestriol, are 18-carbon steroid compounds derived from 19-carbon androgens via irreversible catalysis of cytochrome P-450 19 aromatase.[1] The differences in sex steroid hormones between men and women depend on the amount of androgens made and the percentage of its conversion. The testes make approximately 7000 μg of testosterone (T) per day and convert 0.25% to E2, while the ovaries make only 300 μg of T per day but convert half of it to E2.[2] In other words, the androgen amount generated in men is at least 20 times of that in women, but the percentage of androgens converted to E2 is 200 times higher in women than in men, leading to a 1000-fold difference in quantity with oestrogen levels at picograms but androgen levels at nanograms.

Gender dimorphism in skin diseases

Based on clinical observations and epidemiological studies,[3–97] gender differences have been observed in diversifying spectra of skin diseases. In general, autoimmune dermatoses, allergic diseases, pigmentary disorders and hair diseases show female predominance, while infectious diseases and pre-cancerous/malignant skin diseases occur more often in men (Tables 1 and 2). In addition to pregnancy dermatoses, there are significantly more female-predominant than male-predominant skin diseases. It seems that the male-predisposed dermatoses mainly occur either in adolescence (e.g. juvenile spring eruption of the ears and acne

Table 1 Skin diseases with significant female predominance (except female genital or pregnancy diseases)

High (female/male ratio ≥9)	Moderate (female/male ratio 5–8)	Low (female/male ratio 2–4)
Autoerythrocyte sensitization syndrome	Lichen sclerosus et atrophicus	Rhematoid arthritis
Disseminated discoid lupus erythematosus	Chronic venous insufficiency/varicose vein/ulcus cruris venosum	Scleroderma
Lupus erythematosus (adult)	Morton interdigital neuroma	Antiphospholipid antibody syndrome
Sjögren syndrome	Verrucae planae juveniles	Temporal giant cell arteritis
Type III hereditary angioedema	Multiple eccrine hidrocystomas	Chronic immune thrombocytopenic purpura
Frontal fibrosing alopecia (Kossard)	Loose anagen hair syndrome	Chronic urticaria
Graham–Little syndrome		Cutaneous adverse drug reaction (including Stevens–Johnson-syndrome/toxic epidermal necrolysis)
Central centrifugal cicatricial alopecia		Erythromelalgia
Chronic telogen effluvium		Lichen planopilaris
Trichotillomania		Polymorphous light eruption
Fox–Fordyce disease		Actinic prurigo
Rosacea fulminans		Prurigo pigmentosa
Acne excoriée		Granuloma annulare
Lichen nuchae		Necrobiosis lipoidica
Perioral dermatitis		Sarcoidosis
Melasma		Erythema nodosum
Hori nevus		Partial lipodystrophy
Dercum's disease		Ota nevus
Angioma serpiginosum		Adult tinea capitis
Hidradenoma papilliferum		Trichilemmal cyst/proliferating trichilemmal cyst
Erosive adenomatosis of nipple		Pilomatricoma
Multiple dermatofibroma		Cylindroma
Mammary Paget's disease		Eruptive syringoma
		Subungual glomus tumour
		Angiokeratoma of Mibelli
		Subcutaneous panniculitis-like T-cell lymphoma
		Primary cutaneous large B-cell lymphoma, leg type
		Lentigo maligna

Table 2 Skin diseases with significant male predominance (except male genital diseases)

High (male/female ratio ≥9)	Moderate (male/female ratio 5–8)	Low (male/female ratio 2–4)
Male pattern baldness	Kimura disease	Infantile acne
Acne fulminans	Papuloerythroderma of Ofuji	Eosinophilic pustular folliculitis (Ofuji disease)
Perifolliculitis capitis abscedens et suffodiens	Kaposi sarcoma (iatrogenic and AIDS-associated)	Thromboangiitis obliterans (Buerger disease)
Juvenile xanthogranuloma		Cutaneous angiosarcoma of the scalp and face
Juvenile spring eruption of the ears		Folliculitis decalvans
Acne keloidalis nuchae		Chronic actinic dermatitis (actinic reticuloid)
Rhinophyma		Subcutaneous and systemic mycoses
Angiokeratoma scroti (Fordyce)		Langerhans cell histiocytosis
Madelung disease		Cutaneous T-cell lymphoma
Kaposi sarcoma (classic and endemic)		Primary cutaneous marginal zone lymphomas
		Primary cutaneous follicle centre lymphoma
		Melanoma of the trunk

fulminans)[3,19] or in senescence (e.g. papuloerythroderma of Ofuji, actinic reticuloid, angiosarcoma of the scalp and face of the elderly and Merkel cell carcinoma).[3,22,77,78] Moreover, there are some special clinical patterns regarding gender differences in skin diseases: (i) The disease activity may begin near puberty and is full-blown in reproductive age but then subside after menopause. For

example, systemic lupus erythematosus (LE) exhibits a female-to-male ratio of 3 : 1 before puberty, 10–15 : 1 during the reproductive years, and 8 : 1 after menopause.[98] (ii) There is no gender difference or even male preference before puberty, but females predominate afterwards and accentuate further in senile ages. Tinea capitis is more common in boys of school-age and adolescent ages but affects 3–4 folds more adult women than men, especially after menopause.[36,37] Trichotillomania affects slightly more boys in pre-school ages, but more girls in adolescent ages, and show distinct female preponderance in adult ages (4 : 1) and most extreme in the oldest group (15 : 1).[99] Atopic eczema in pre-school children shows insignificant gender difference or slightly male preponderance in different studies, with significantly more adult females suffering from atopic eczema.[27,28] (iii) Gender differences can alternate at different ages for the same disease. For instance, infantile acne is predominantly seen in boys,[16,18] while acne excoriée and acne of late onset are mostly seen in women.[3,100] (iv) The disease prevalence may not differ much but the disease severity is pronounced in men, e.g. androgenetic alopecia.[53] (v) Sexual dimorphism differs in various geographical areas and under ethnic backgrounds (see later). (vi) Gender preference may differ among the different types of the same dermatoses. Angiokeratoma of Fordyce involves mainly males but angiokeratoma of Mibelli is predominantly seen in young girls.[64] Multiple cutaneous lipomas (lipomatosis) such as Dercum's disease occur predominantly in women while benign symmetric lipomatosis (Madelung disease) occur mainly in men.[92,93] Cutaneous T-cell lymphomas generally affect more men than women,[79] especially follicular mycosis fungoides and Sezary syndrome,[80,81] with the exception of subcutaneous panniculitis-like T-cell lymphoma, in which females outnumber males.[82] In the new WHO–EORTC classification of cutaneous lymphomas, primary cutaneous marginal zone lymphomas and primary cutaneous follicle centre lymphoma occur more commonly in males, while primary cutaneous large B-cell lymphoma, leg type affects more women.[83,84] (vii) Gender effect has been also observed in disease prognosis. In primary cutaneous melanoma, increasing age and male gender are independently associated with thicker tumours (>2 mm) and histological ulceration.[85] Rapid tumour growth has been observed more frequently in males, especially in those above the age of 70 years.[86] Melanoma of the trunk showed a striking male predilection, especially in the old age group,[87] while lentigo maligna and acral lentiginous melanoma involve more females than males.[88–90] Worldwide, female melanoma patients have superior survival compared with males,[91] but this difference seems to disappear after the age of 65 years.[85] Younger melanoma patients have a more favourable prognosis than older patients, a difference being more pronounced in women.[85]

The aetiology and pathogenesis in causing gender differences in the development of skin disorders remain incompletely understood. To be considered are gender differences in the structure and function of the skin, hormonal influence, genetic predisposition, sociocultural background and geographical/environmental factors.

Gender differences in the structure and function of the skin

The thickness and mass of stratum corneum appear to be gender-independent in most studies.[101–103] No difference exists between men and women regarding the hydration and adhesion of stratum corneum. There are conflicting results about the gender difference in the values of trans-epidermal water loss (TEWL).

Studies on gender differences in skin surface pH show controversial results in different body regions, partly because of the lack of standardized methodology.[103] In a recent Korean study, men, as compared with women, exhibit significantly higher sebum casual levels but lower pH values on the facial sites.[104] Another recent French study shows no significant gender differences in sebum secretion rate, TEWL and stratum corneum hydration, but a higher skin pH value in the flexural side of forearm in women.[105] Although a higher incidence of irritant contact dermatitis has been reported in women than in men, the skin irritability as measured in experimental studies does not show gender preference.

Measurement of dermal thickness and collagen volume/density shows higher values in men than in women, while men demonstrate a gradual thinning with advancing age (12–93 years) but women have a constant skin thickness up to fifth decade, after which it decreases with age.[101,103] The skin elasticity, torsional extensibility and cutaneous extensibility do not differ between sexes, but it takes longer periods to induce artificially the suction blisters in women. Subcutaneous fat remains identical in thickness before puberty but thenceforth increases significantly more in women with elevated activity of lipoprotein lipase.

There are no functional differences between men and women in the cutaneous microvascular response to histamine. However, the sweating response to heat load appears to be lower in women than in men,[106] and females demonstrate a higher threshold in the onset of post-exercise sweating.[107] Qualitatively, gender-specific volatile compounds have been identified in the axillary sweat.[108] Women are more sensitive to small temperature changes and to pain induced by heat, cold or prick. Women tend to report greater pain sensitivity and severity, which, in addition to sociocultural factors, can also be explained by the gender-based difference in pain perception and central processing of pain.[109,110] On the other hand, women display greater pain tolerance than men on both behavioural and physiological levels.[111] Significant gender differences have been found in pruritogen-induced scratching behaviour in mice, with higher scratching scores in females.[112] The possibility of gender differences in the prevalence and severity of itch in humans deserves further attention.

The anatomical and physiological distinction between female and male genitalia predisposes to different dermatoses; Zoon's

plasma cell balanitis and erythroplasia of Queyrat are mostly observed in men with redundant prepuce, while pregnancy dermatoses occur exclusively in women. However, it remains largely unknown why lichen sclerosus et atrophicus, erosive adenomatosis of nipple,[113] eruptive syringoma,[63,114] hidradenoma papilliferum involve mostly female instead of male genitalia.

In vitro oestradiol has been demonstrated to directly induce melanogenesis[115] and to increase the expression of human melanocortin 1 receptor,[116] which may be partly responsible for the female predisposition to pigmentary dermatoses.

Gender differences in immune responses

In some experimental models, specific immune responses have been found to be more intense in females than in males.[117] Expression of both oestrogen and androgen receptors have been demonstrated on leucocytes and inflammatory cells such as dendritic cells,[118] macrophages, lymphocytes,[119] neutrophils,[120] and mast cells.[121] Membrane-bound androgen receptors and membrane-bound oestrogen receptors, which mediate rapid non-genomic effects, have been identified in many immune cells.[122] Physiological concentration of E2 can affect the differentiation and maturation of dendritic cells including epidermal Langerhans cells.[123,124] Antigen-presenting cells from females are more efficient in presenting peptides than those from males, and the phagocytic activity of neutrophils and macrophages is higher in females than in males.[125] On the other hand, E2 pre-treatment suppresses the antiviral response in dendritic cells.[126] In humans and mice, E2 at periovulatory to pregnancy levels stimulates interleukin (IL)-4, IL-10, and interferon-γ but inhibits tumour necrosis factor-α (TNF-α) from CD4 + T cells, leading to an overall effect of down-regulation of T-cell-mediated immunity.[127] Serum levels of E2 in adult women can also enhance antibody secretion but induce suppression of bone marrow B-cell lineage precursors.[128] In anti-DNA antibody transgenic mice, elevated levels of oestrogen or prolactin can promote the survival and activation of high-affinity autoreactive B cells.[128] Physiological concentrations of E2, alone or in combination with environmental oestrogens such as organochloride pesticides and polychlorinated biphenyls are able to cause a rapid non-genomic, ER-α-mediated IgE-dependent release of β-hexosaminidase and leucotriene C4 from mast cells.[121,129]

The influence of androgens on immune responses is less clearly defined. Androgens tend to exert rather immunosuppressive effects by: (i) limiting lymphocyte proliferation and reducing immunoglobulin production; (ii) inhibiting the synthesis of pro-inflammatory products like TNF-α and nitric oxide synthase; (iii) suppressing the synthesis of pro-inflammatory transcriptional regulators such as NF-κB and p38 MAP kinase; (iv) increasing the synthesis of anti-inflammatory cytokines such as IL-10;[130] and (v) reducing the leucotriene biosynthesis in stimulated whole blood or neutrophils from males.[130] The UV doses required for immunosuppression are three times lower in men in an experimental model.[131]

Gender differences in genetics and molecular biology

Recent studies suggest that sex-specific genetic architecture also influences human phenotypes, including reproductive, physiological and disease traits. The underlying mechanism may be caused by sex-biassed gene expression, sex-specific alternative pre-mRNA splicing,[132] sex-specific gene–environment interactions, and sex-specific changes in gene regulation with age, particularly in sex steroid-responsive genes.[133] In a mouse study on UVB-induced skin carcinogenesis, tumours in male mice developed earlier and tended to be larger in size with greater total tumour burden and advanced histological grade than in female mice. The tumour formation was more influenced by the extent of oxidative DNA damage and antioxidant capacities than by inflammatory response.[134]

Both the mitochondrial genome and the X chromosome are asymmetrically inherited in *Drosophila* and mammals. Age-related mitochondrial oxidative stress is highly gender dependent.[135] On the basis of the mitochondrial theory of ageing, mitochondria from female rats generate half the amount of hydrogen peroxide than those of males and have higher levels of mitochondrial reduced glutathione, while the oxidative damage of mitochondrial DNA is fourfold higher in males than in females. Higher levels of oestrogens in females can up-regulate the expression of longevity-related antioxidant genes, such as those of selenium-dependent glutathione peroxidase and Mn-superoxide dismutase to protect against ageing process.[136] The female benefit is also associated with polymorphism of X-linked genes and cellular mosaicism for X-linked parental alleles, which confers a more adaptive and balanced cellular machinery that is advantageous in the host response to injury and infection. Several genes encoding key metabolic and regulatory proteins reside on the X chromosome, including members of the apoptotic cascade, hormone homeostasis, glucose metabolic enzymes, superoxide-producing machinery, and the toll-like receptor/nuclear factor kappaB/c-Jun N-terminal kinase signalling pathway.[137] The fact of female longevity may also influence the gender prevalence in disease formation.

Gender differences in sociocultural backgrounds

Higher awareness and self-report may be one of the reasons to explain the much higher incidence of chronic telogen effluvium and loose anagen hair syndrome in female patients.[45,46] Allergic contact hypersensitivity to nickel, cobalt and cosmetics is obviously more common in females,[138,139] most likely due to a repeated contact history. Female preponderance is also seen in hand eczema, especially in the form of irritant contact dermatitis, while men exhibit more commonly the form of allergic contact dermatitis.[140] Traumatic hairstyling techniques are popular in African-American women, frequently leading to scarring alopecia.[141]

On the other hand, male predominance in skin and systemic infections is usually explained by the frequent outdoor activities and the higher exposure risk, such as systemic histoplasmosis,

blastomycosis and most strikingly paracoccidioidomycosis as well as subcutaneous mycoses such as chromoblastomycosis, sporotrichosis and mycetoma.[142–147] A significantly higher male-to-female ratio is found in the opportunistic systemic infection of cryptococcosis and pneumocystis carinii.[41] Men are more susceptible than women to invasive fungal infections after renal transplantation.[42] Gender difference in sporotrichosis, however, is region-dependent, in which more female cases are reported from Japan and India, probably because of the frequent involvement of women in the farming.[148] In addition to the exposure factor, there is experimental evidence indicating the protective role of oestrogen in inhibiting the transition of conidia-mycelial propagules to the yeast form, a critical step in the pathogenesis of the disease.[149]

However, among the infectious diseases, it remains unclear why *Verruca planae* juveniles occurs five times more frequently in females than in males,[35] but tinea capitis is more common in boys of school-age and adolescent ages but affects three- to fourfold more adult women than men, especially after menopause.[36,37] Males generally predominate in leprosy, including rare variants such as histoid leprosy,[38] in which multibacillary leprosy predominates in males while paucibacillary leprosy predominates in females.[39]

Gender differences in geographical aspects

Geographical differences in disease prevalence have been observed in extra mammary Paget's disease, in which females are mainly affected in Western countries but studies in Asian people display a male-predominant manifestation;[150,151] Winiwarter–Buerger disease (thromboangiitis obliterans) affects mostly young, male, heavy tobacco smokers of Indo–Asian descent.[57,58] Most cases of Hori naevus, Ota naevus, Kimura disease and prurigo pigmentosa have been reported from Asian countries, whereas acne fulminans, hidradenitis suppurativa, chronic actinic dermatitis, polymorphous light eruption and actinic prurigo seem to more commonly observed in Western populations. Central centrifugal cicatricial alopecia has so far been reported mostly in African-American women,[152] while acne keloidalis nuchae is commonly seen in African males. The female predisposition to chronic venous insufficiency/varicose vein/ulcus cruris venosum is less obvious in Asian people than in Western population and varies widely in Western countries according to different studies.[54–56] It is conceivable that geographical differences are partly affected by genetics, environmental factors, and the sociocultural differences in attitudes of doctor access and availability of medical care.

Conclusions

Oestrogens appear to affect mainly collagen synthesis, adipose tissues and cutaneous vessels while androgens influence more the function of hair follicles, sebaceous glands and eccrine/apocrine sweat glands. In addition to the hormonal effect that may be considered as 'initiator', the external environmental factors seem to act as 'promoter' to accelerate and enhance the disease development, such as ultraviolet irradiation in LE and melasma, smoking in acne inversa[153–155] and Buerger disease,[156] and irritants in perioral dermatitis. Psychosocial stress should also play a key role in the development of acne excoriée and trichotillomania. Increasing experimental data suggest an influence of oestrogens on the activation of immune responses, while more work is needed to clarify the role of androgens. Population-based studies are warranted to confirm the gender differences identified in hospital-based observations. Ethnic background should be considered in the analysis of the role of sex dimorphism in disease pathogenesis. Further observation is worthwhile to see whether behaviour change will modify disease occurrence, e.g. whether higher prevalence of smoking will lead to increased incidence of thromboangiitis obliterans in women.[156]

We are in an era of fast expanding awareness of the fundamental biological and sociocultural differences between men and women that affect health and development of physical or mental diseases. The impact of gender differences on the development and manifestation of disease is multidimensional, influenced by the interplay between genetic predisposition, hormonal regulation, environmental factors and sociocultural background. The goal is to advance the understanding of basic biology and thus elucidate the mechanisms through which sex or gender differences operate in humans in health and disease. On this basis, new preventive, diagnostic, and therapeutic concepts may be developed.

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