Clinical Interventions in Aging

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PERSPECTIVES

Improvement in Cutaneous Conditions Can Benefit Some Health Conditions in the Elderly

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Abstract: As we are aging, a number of cutaneous and extracutaneous disorders will be developed. Although the pathogenesis of these aging-associated disorders is not clear yet, abnormalities in the skin are linked to some aging-associated disorders at least to some extent. Inflammatory dermatoses such as psoriasis and atopic dermatitis predispose to the development of cardiovascular diseases, obesity and type 2 diabetes. In addition, both chronologically aged skin and individuals with some aging-associated systemic conditions display altered epidermal function, such as reduced stratum corneum hydration levels, which can provoke cutaneous inflammation. Because aged skin exhibits higher expression levels of inflammatory cytokines, which play a pathogenic role in a variety of aging-associated health condition, the association of the skin with some aging-associated disorders is likely mediated by inflammation. This postulation is supported by the evidence that improvement in either epidermal function or inflammatory dermatoses can mitigate some aging-associated disorders such as mild cognitive impairment and insulin sensitivity. This perspective discusses the association of the skin with aging-associated disorders and highlights the potential of improvement in cutaneous conditions in the management of some health conditions in the elderly.

Keywords: aging, stratum corneum hydration, inflammaging, epidermis, diabetes, obesity, cardiovascular diseases

Introduction

Chronologically aged humans often suffer from multiple cutaneous and extracutaneous disorders, including xerosis, pruritus, type 2 diabetes, atherosclerotic cardiovascular disease, etc. Over 20% of individuals aged ≥60 years suffer from pruritus and eczematous dermatitis.[1,2] Xerosis was found in 96% of individuals aged >65 years,[3] and 60% of individuals aged >50 years.[4] Similarly, prevalence of type 2 diabetes is over 20% in individuals aged ≥60 years.[5] The prevalence of cardiovascular diseases is over 70% in individuals aged 65–74 years, with an increase with age.[6] Etiologies of these disorders have been widely speculated, including oxidative stress, gut microbiome, air pollution, diets and lifestyle.[7–13] These speculations hold some truth. For example, gut microbiota with high capability to obtain energy from diet increase body fat in mice.[14] While microbial dysbiosis induces obesity and inflammation,[15] administration of probiotic attenuates high-fat diet-induced gain in body weight.[16] Correspondingly, reductions in gut microbiota by antibiotic treatment prevent the development of insulin tolerance and body weight gain induced by high-fat diet in mice.[17] Oxidative stress is another factor, which is assumed to be associated with aging and aging- associated diseases. Plasma oxidized low-density lipoprotein levels correlate positively with arterial stiffness.[18] Moreover, reactive oxygen species can negatively regulate insulin signaling pathway, leading to the development of insulin resistance and obesity.[19] Collectively, this line of evidence suggests the contribution of a variety of factors to the pathogenesis of aging-associated disorders. However, a wealth of evidence also indicates a link of aging-associated disorders to inflammatory dermatoses and altered epidermal function. For instance, the prevalence of aging-associated disorders such cardiovascular and metabolic diseases is higher in individuals with inflammatory dermatoses, including psoriasis, atopic dermatitis, hidradenitis suppurativa and seborrheic dermatitis.[20–23] Additionally, recent studies suggest a link of epidermal dysfunction to aging-associated disorders.[25]

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We briefly review here the link between the skin and aging-associated disorders and highlight the potential of improvements in cutaneous conditions in the management of some aging-associated disorders.

Association of the Skin with Aging-Associated Conditions

Although the pathogenesis of aging-associated disorders is not fully elucidated yet, the crucial role of chronic, low-grade inflammation, often termed "inflammaging", in the development of these chronic disorders is hypothesized. Indeed, aged humans display higher circulating levels of proinflammatory cytokines and C-reactive protein.[26,27] Inflammation has been linked to the pathogenesis of aging-associated diseases, such as type 2 diabetes, obesity, and Alzheimer's disease.[28–30] Correspondingly, inflammatory dermatoses are the risk factors of aging-associated health conditions. Here, we brief the link of the skin conditions to aging-associated disorders in the elderly.

Psoriasis

The common aging-associated disorders include cardiovascular diseases, type 2 diabetes and cognitive impairment.[31,32] Prevalence of all of these disorders is higher in individuals with psoriasis than in those without psoriasis. For example, the prevalence of type 2 diabetes is 4% higher in individuals with psoriasis than in those without psoriasis (10.3% vs 6.2%).[33] The odds ratio of psoriasis for diabetes mellitus is 1.61 (95% CI 1.53–1.70, $p < 0.001$).[34] The hazard ratio for type 2 diabetes correlates positively with the involvement of surface area in individuals with psoriasis.[35] Similarly, the prevalence of metabolic syndrome is higher in individuals with psoriasis than in the controls (30.3% vs 21.7%), with an odds ratio of 2.077 (95% CI 1.84–2.34).[36] Likewise, the adjusted hazard ratio of psoriasis for cancers is 1.66 (95% CI 1.38–2.00).[37] Individuals with psoriasis also exhibit higher incidence of cardiovascular events than the controls.[38] Interestingly, risk for ischemic heart disease in males with moderate-to-severe psoriasis is higher than that in females (adjusted hazard ratio = 1.67, 95% CI 1.30–2.15 for males; adjusted hazard ratio = 0.99, 95% CI 0.53–1.83 for females).[39] The risk for myocardial infarction is 2.24-time greater in patients with moderate-to-severe psoriasis than in the controls.[39] However, one study showed no association of psoriasis and cardiovascular events.[32] Moreover, psoriasis increases the risk of Alzheimer's disease, particularly in those without systemic treatment, with an adjusted hazard ratio of 1.09 (95% CI 1.07–112, $p < 0.0001$).[40] Psoriasis also increases the risk of both vascular (hazard ratio = 1.41, 95% CI = 1.09–1.82, $p < 0.01$) and non-vascular dementia (hazard ratio = 1.13, 95% CI = 1.11–1.15, $p < 0.01$).[41] Furthermore, the link between obesity and psoriasis has also been demonstrated by several studies. Either obesity or metabolic syndrome increases risk of psoriasis,[42–44] while psoriasis increases risk of obesity, with an odds ratio of 1.66.[45] Thus, obesity and psoriasis negatively affect each other. Collectively, this bulk of evidence demonstrates a link between psoriasis and some aging-associated disorders.

Atopic Dermatitis

Atopic dermatitis is another common inflammatory dermatosis linked to aging-associated disorders such as obesity and mild cognitive impairment.[31,46] The association of atopic dermatitis with central obesity is stronger in females than in males.[47] Atopic dermatitis is also a risk factor for other aging-associated disorders. Studies showed that atopic dermatitis increases risk for multiple cardiovascular events, including myocardial infarction, stroke, heart failure, ischemic stroke and angina.[48,49] The prevalence of cardiovascular diseases is more than 1% higher in individuals with atopic dermatitis than in the controls (5.5% vs 4.1%), with hazard ratio of 1.42 (95% CI 1.33–1.52).[50] Atopic dermatitis also increases the risk for hyperlipidemia and hypertension with hazard ratio of 33.02 (95% CI 32.37–33.69, $p < 0.0001$) and 4.86 (95% CI 4.65–5.09, $p < 0.0001$), respectively.[51] Atopic dermatitis is associated with coronary heart diseases with an adjusted odds ratio of 1.96 (95% CI 1.02–3.77, $p = 0.04$).[52] In contrast, one study showed the atopic dermatitis decreases the risk for myocardial infarction and hypertension.[53] No association between atopic dermatitis and cardiovascular events has also been reported.[54,55] The link between atopic dermatitis and diabetes mellitus is inconclusive. One study demonstrated that genetically predicted atopic dermatitis is a risk factor for type 2 diabetes, with an odds ratio of 1.07 (95% CI 1.02–1.11, $p = 0.003$),[56] while another study showed that the prevalence of atopic dermatitis is lower in individuals with type 2 diabetes than in those without type 2 diabetes.[53] However, a study in a large cohort showed that individuals with type 2 diabetes are more likely to have atopic dermatitis, with an adjusted odds ratio of 5.62 (95% CI 2.15–14.6, $p < 0.001$).[57] Thus, whether atopic dermatitis predisposes to type 2 diabetes or vice versa remains to be determined. Recent studies

demonstrated that atopic dermatitis also increases the risk of dementia and Alzheimer's diseases, with hazard ratio of as high as 3.74.[58–60] The link between atopic dermatitis and aging-associated disorders is also evidenced by a positive correlation of the prevalence of these disorders with the severity of atopic dermatitis.[61] Hence, atopic dermatitis is associated with some aging-associated disorders.

Other Inflammatory Dermatoses

Numerous studies have demonstrated that other inflammatory dermatoses are also linked to aging-associated disorders. For example, the prevalence of hypertension is higher in individuals with hidradenitis suppurativa than in the controls (34.3% vs 3.0%, $p < 0.0001$), while the prevalence of diabetes mellitus in patients with hidradenitis suppurativa is over 10 times higher than that of controls (20.4% vs 1.5%, $p < 0.0001$).[62] Hidradenitis suppurativa is also strongly associated with metabolic syndrome (odds ratio = 2.08, 95% CI: 1.61–2.69) and obesity (odds ratio = 2.58, 95% CI: 2.00–3.23).[63] Moreover, fasting insulin levels are negatively correlated with the severity of hidradenitis suppurativa ($p = 0.04$).[64] One study showed that weight loss can mitigate hidradenitis suppurativa.[65] Thus, whether hidradenitis suppurativa predisposes to obesity or vice versa is not clear. Rosacea is another common inflammatory skin disorder. Individuals with rosacea have a higher risk for cardiovascular diseases and hyperlipidemia.[66–68] The prevalence of hyperlipidemia, hypertension and metabolic diseases is positively correlated with the disease severity in individuals with rosacea,[69] while the age of the patients with rosacea is positively correlated with the prevalence of cardiovascular ($p = 0.11$) and metabolic disorders ($p < 0.001$).[70] An over 14-year follow-up study showed that body mass index positively correlates with the risk for rosacea at least in females ($p < 0.0001$).[71] Because of the pathogenic role of inflammation in both obesity and rosacea,[29,72,73] management of one condition can benefit the other one. The links of seborrheic dermatitis and bullous pemphigoid to neurological, metabolic and cardiovascular diseases have also been well documented.[74–77] Taken together, the bulk of evidence indicates a link between dermatoses and aging-associated disorders. Since the association of cutaneous inflammation with obesity and cognitive impairment has been fairly well summarized in previous publications,[31,46] here we only summarize the evidence of the link between dermatoses and other aging-associated disorders (Supplementary Table 1).

Epidermal Dysfunction

In addition to dermatoses, several studies have demonstrated alterations in epidermal function in some aging-associated disorders. Coronary artery disease is common in the elderly. Transepidermal water loss rates, an indicator of epidermal permeability, are 23% higher in individuals with coronary artery disease than in those without coronary artery disease.[78] Elevated transepidermal water loss rates and reduced stratum corneum hydration levels have been observed in individuals with type 2 diabetes.[79] Individuals with obesity also exhibit higher transepidermal water loss rates than normal controls (14.27 ± 4.4 vs 11.3 ± 2.7, $p < 0.05$).[80] Interestingly, the severity of obesity is positively correlated with epidermal permeability. For example, basal transepidermal water loss rates on the forearm are highest in individuals with obesity, followed by those with overweight and normal/underweight (11.5, 8.8 and 6.9 g/h/m^2, respectively).[81] Our recent study showed a positive correlation between body mass index and transepidermal water loss rates on the shin of females (Pearson $r = 0.07197$, $p < 0.05$).[82] Body mass index also correlates positively with skin surface pH while negatively correlating with stratum corneum hydration levels. This line of evidence also indicates a link between some aging-associated health conditions and epidermal dysfunction.

Perspectives

Cutaneous Inflammation Contribution to Aging-Associated Disorders

As aforementioned above, some chronic inflammatory dermatoses are linked to aging-associated disorders, which are likely mediated by inflammation. This assumption is supported by several clinical observations. Individuals with either psoriasis or atopic dermatitis exhibit higher circulating levels of proinflammatory cytokines.[83–86] The adjusted odds ratios for obesity and overweight are 1.47 (95% CI 1.31–1.63) and 1.19 (95% CI 1.09–1.30), respectively, in individuals with severe psoriasis.[87] In individuals with psoriasis, the risk for either type 2 diabetes or cardiovascular disorders correlates positively with the severity of psoriasis.[35,88,89] Accordingly, treatments of psoriasis with either TNF-α inhibitor or IL-17a inhibitor or

methotrexate improve psoriasis, accompanied by decrease in cardiovascular events.[90,91] Treatments of psoriasis with TNF-α inhibitor for each 6 months can significantly reduce the risk for cardiovascular events (adjusted hazard ratio = 0.73, $p < 0.01$).[92] Another study showed that treatments of psoriasis with etanercept for 24 weeks significantly decrease Psoriasis Area and Severity Index (PASI) (50%), circulating levels of insulin (25%) and IL-6 (55%).[93] Similarly, treatments of psoriasis with adalimumab for 6 months significantly improve both PASI and insulin sensitivity.[94] This evidence indicates the contribution of inflammation in psoriasis to the pathogenesis of some aging-associated disorders.

Regarding atopic dermatitis, topical treatments of atopic dermatitis with either glucocorticoids or tacrolimus improve atopic dermatitis, insulin sensitivity (12.6%) and inflammation markers in the circulation (30% reduction in C-reactive protein, 27% reduction in IL-6),[95] strongly suggesting the influence of cutaneous inflammation on systemic inflammation and its sequelae such as insulin resistance. Obesity and atopic dermatitis can negatively impact each other. For example, weight loss alone can improve atopic dermatitis.[96,97] Notably, association of obesity with atopic dermatitis is only observed in individuals with previously diagnosed atopic dermatitis (>1-year history of atopic dermatitis) but not newly diagnosed atopic dermatitis,[98] suggesting the pathogenic role of atopic dermatitis-associated chronic inflammation in obesity.

Taken together, this bulk of evidence suggests that chronic cutaneous inflammation can predispose to the development of some aging-associated disorders. Treatments of these inflammatory dermatoses can alleviate and/or prevent the development of some of these disorders, including obesity, diabetes mellitus, cardiovascular disorders and dementia, which all are aging-associated and most likely inflammation-driven disorders.

Chronologically aged humans will eventually suffer from one or more aging-associated disorders, which are linked to inflammaging. However, the worldwide prevalence of psoriasis is less than 2% in individuals aged over 55 years,[99,100] while the prevalence of eczematous dermatitis (including atopic dermatitis) is 30–37.7% in individuals aged ≥65 years.[101,102] Thus, large portion of chronologically aged humans do not have inflammatory cutaneous diseases. Then, the question is what is/are the sources of inflammaging. One theory is the gut microbiota dysbiosis, in part, attributing to aging-associated inflammaging, in addition to the changes in lifestyle, diet and oxidative stress.[103,104] Aged humans exhibit gut microbiota dysbiosis.[103] Prolonged gut microbiota dysbiosis can cause sustained increase in intestinal permeability, inducing chronic inflammation, and consequently leading to the development of inflammaging-related diseases.[105,106] However, the contribution of the skin to inflammaging and its associated disorders cannot be underestimated, although the surface area of the skin is much smaller (≈2 m^2 for males and 1.9 m^2 for females) than that of gut (≈32 m^2).[107,108] The skin is sitting at the interface between the body and the harsh environment, making the skin more vulnerable to a variety of biological, chemical and physical insults, including UV irradiation, air pollution, allergens, irritants, temperature, microorganisms, humidity, etc. in comparison to the gut. Clinically, chronologically aged human skin presents signs and symptoms of inflammation. Up to 78% of aged humans experience pruritus, a sign of cutaneous inflammation.[109] The prevalence of dry skin (xerosis) can be as high as 58% in the elderly.[110] Dry skin can increase expression levels of proinflammatory cytokines and mast cells in the skin, in addition to increases in sensitivity of the skin to hapten challenge.[111–114] Expression levels of proinflammatory cytokines are higher in both the skin and the circulation of aged mice than that of young mice.[115] In aged humans, stratum corneum hydration levels correlate negatively with circulating levels of proinflammatory cytokines.[116] Both proinflammatory cytokines and histamine are the key mediators in pruritus.[117–119] Correspondingly, over 20% of aged individuals with dry skin complain of pruritus,[120] while 69% of aged humans with pruritus have dry skin.[1] Moreover, pruritus can provoke scratches, causing the disruption of epidermal permeability barrier. Disruption of epidermal permeability barrier alone can increase production and release of proinflammatory cytokines in the epidermis, and the density of mast cells in the dermis, leading exacerbation of pruritus.[121,122] Thus, aged skin undergoes a vicious cycle of pruritus and inflammation. Furthermore, another remarkable alteration in the aged epidermis is the elevation in skin surface pH.[82,123,124] Elevation in skin surface pH not only delays the recovery of epidermal permeability barrier[125] but also induces cutaneous inflammation via protease-activated receptor signaling.[126,127] Sustained cutaneous inflammation can induce inflammation in extracutaneous tissues. In support of this assumption, disruption of epidermal permeability barrier increases levels of proinflammatory cytokines in both the skin and circulation of either normal or athymic mice, suggesting the contribution of the skin to inflammation in both the skin and the circulation.[115] Hence, epidermal dysfunction can contribute, in part, to inflammaging and its associated disorders.

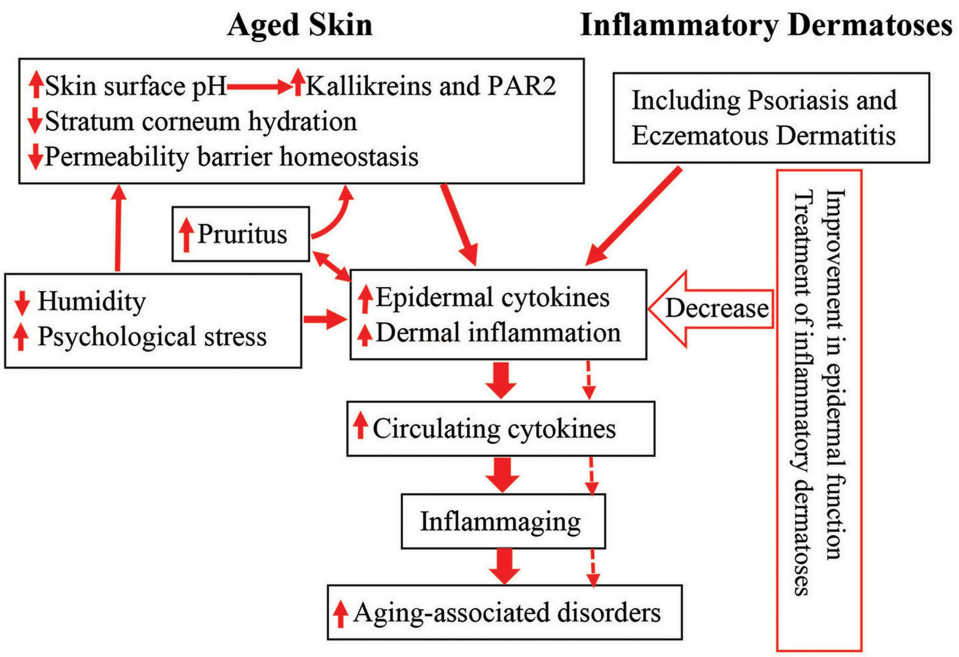

Figure 1 Schematic diagram: link between cutaneous conditions and aging-associated disorders in the elderly. Aged humans exhibit epidermal dysfunction. Both epidermal dysfunction and inflammatory dermatoses can provoke cutaneous inflammation. Prolonged cutaneous inflammation can result in inflammaging, leading to the development of inflammaging-associated disorders in the elderly (indicated in solid arrows). Conversely, either appropriate treatment of inflammatory dermatoses or improvement in epidermal function can decrease cutaneous inflammation, preventing the development and progression of inflammaging, consequently alleviating inflammaging-associated disorders in the elderly (indicated in dotted arrows).
Abbreviation: PAR2, protease-activated receptor 2.

Improvement in Cutaneous Conditions Can Mitigate Some Aging-Associated Health Conditions

Individuals with chronic cutaneous inflammatory dermatoses, such as psoriasis and atopic dermatitis, have high prevalence of aging-associated disorders, including atherosclerotic cardiovascular disease, obesity and type 2 diabetes.[128] Conversely, treatment of psoriasis or atopic dermatitis improves insulin sensitivity and reduces the risk for cardiovascular events.[92,94,95] Recent studies also demonstrate the benefits of topical emollients in alleviation of aging-associated disorders. For example, topical applications of emollient for 10 days lower expression levels of proinflammatory cytokines, including IL-1α, IL-1β, IL-6 and TNF-α, in both the skin and the circulation of aged mice.[115] Likewise, circulating levels of IL-1β, IL-6 and TNF-α are also markedly decreased in aged humans following topical applications of an emollient for one month.[129] Importantly, improvement in epidermal function with topical emollient mitigates the progression of mild cognitive impairment in the elderly.[25] In addition, constipation is common in the elderly, with a prevalence of 26% for women and 16% for men aged ≥65 years.[130] The prevalence of constipation is associated with dementia (odds ratio = 1.18, p = 0.0032) and non-amnestic mild cognitive impairment (odds ratio = 1.30, p = 0.003).[131] Our recent 3-year clinical trial showed that topical applications of emollient to the skin decrease the prevalence of constipation from 27% to 2% in the elderly, while in the untreated control group, the prevalence increases from 33% to 49% (unpublished data). Taken together, this evidence indicates that improvement in cutaneous conditions, including epidermal function, can mitigate at least some aging-associated disorders in the elderly.

Conclusions

The pathogenesis of aging-associated disorders is attributable, at least in part, to inflammaging. In addition to gut microbiota dysbiosis, cutaneous inflammation can be one of the origins of inflammaging, contributing to the development of aging-associated disorders. In addition to inflammatory dermatoses, epidermal dysfunction can also contribute to inflammaging. Aged humans display multiple functional abnormalities in the epidermis. Either increased epidermal

permeability or elevated skin surface pH or reduced stratum corneum hydration can induce cutaneous inflammation. Excessive exogenous insults such as in low humidity environment can exacerbate cutaneous inflammation, provoking pruritus. Pruritus-induced scratching can disrupt the epidermal permeability barrier, in turn, inducing and/or worsening downstream inflammation. Hence, either chronic inflammatory dermatoses or epidermal dysfunction can cause inflammaging. Accordingly, treatment of inflammatory dermatoses and correction of epidermal functional abnormalities can decrease inflammation (Figure 1). Therefore, improvement in cutaneous conditions can benefit at least some of aging-associated health conditions in the elderly.

Disclosure

The authors report no conflicts of interest in this work.

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