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Review

Skin ageing

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Abstract

Cutaneous ageing manifests itself as a progressive reduction in maximum function and reserve capacity of skin tissue. It is not a unique and uniform biological event. Skin comprises three layers: epidermis, dermis and subcutaneous tissue. Collagen atrophy is a major factor in skin ageing. There is a strong correlation between skin collagen loss and estrogen deficiency due to the menopause. Skin ageing, especially in the face, is associated with a progressive increase in extensibility and a reduction in elasticity. With increasing age, the skin also becomes more fragile and susceptible to trauma, leading to more lacerations and bruising. Furthermore, wound healing is impaired in older women. Estrogen use after the menopause increases collagen content, dermal thickness and elasticity, and it decreases the likelihood of senile dry skin. Large-scale clinical trials are necessary to help make informed recommendations regarding post-menopausal estrogen use and its role in the prevention of skin ageing.

Keywords: Collagen, estrogen, hormone replacement therapy, menopause, skin ageing

Introduction

> Consumers refuse to age. Most women want to look as young as possible, and are constantly searching for any solution that promises that miracle.

This is what is claimed by beauty industry experts. In this quest for eternally youthful skin, it was estimated that, in 2005, $664 million was spent in the US on anti-ageing skin care products. Indeed, this market experienced a 33% growth between 2001 and 2005.[1]

Cutaneous ageing manifests itself as a progressive reduction in maximum function and reserve capacity of skin tissues. It is not a unique and uniform biological event. Factors aggravating the clinical aspects of ageing include the effects of past or present diseases, as well as diverse environmental influences and physiological variations.[2] Brincat suggested that there are seven types of skin ageing, as set out in Table 1.[3] This article reviews the connections between skin ageing, postmenopausal estrogen deficiency and hormone replacement therapy (HRT).

Table 1 The seven types of cutaneous ageing[3]

Ageing types	Determining factor
Chronological	Passage of time
Genetic	Inherited diseases (e.g. premature ageing syndromes)
Photo-ageing	Ultraviolet and infra-red irradiation
Behavioural	Diet, tobacco, alcohol abuse, drug addiction
Catabolic	Chronic debilitating diseases (e.g. infections, cancers)
Endocrine	Dysfunction or ageing of hormone systems (e.g. ovaries, testes, thyroid)
Gravitational	Gravitational force

Skin physiology

The skin is the largest organ in the body, and is the primary barrier against pathogen invasion and dehydration. It comprises a complex mosaic of cells of diverse embryonic origin that, under normal conditions, coexist side by side.

Skin consists of three layers: epidermis, dermis and subcutaneous tissue. It also contains hair follicles, sebaceous glands and sweat glands. The epidermis consists primarily of keratinocytes and melanocytes, and forms the thin outer layer. The dermis is the deeper layer, forming the main bulk of the skin. Its function is to provide a tough matrix to support the blood vessels, nerves and appendages that are embedded in it.

The fibres present in the dermal connective tissue are predominantly collagen and elastin.[4] Some 80% of the dry weight of adult skin consists of collagen. Collagen fibres, produced by fibroblasts, are arranged parallel to the skin surface. This gives the skin a high tensile strength and prevents it from being torn by overstretching. In contrast, elastin constitutes about 5% of the dermis, and provides the skin with elasticity and resilience.[5] Elastin fibres are arranged as a thinly distributed subepidermal network, and are also produced by fibroblasts. The dermal connective tissue additionally contains sensory receptors and the supportive glycosaminogylcans (GAGs).[6]

Skin quality deteriorates with age due to the synergistic effects of chronological ageing, photo-ageing, hormonal deficiency and environmental factors (see Table 1).[6] Skin ageing results from a decline in several

Box 1 Functions of the skin that decline with age[7]

- Epidermal turnover
- Immune function
- Wound healing
- Vascular reactivity
- Injury response
- Sweat production
- Barrier function
- Sebum production
- Sensory perception
- Vitamin D production

metabolic activities. The dermis undergoes morphological, physical and chemical changes during ageing.[4] Overall, many of the skin's functions are known to decline with age (see Box 1).[7]

The effects of postmenopausal estrogen deficiency are thought to include: atrophy; decreased collagen and water content; decreased sebaceous secretions; loss of elasticity; and manifestations of hyperandrogenism. The cumulative effects of estrogen deficiency on the skin are thought to contribute to poor wound healing in older patients.[8] In mice, oophorectomy alone is sufficient to accelerate skin ageing and increase sensitivity to ultraviolet radiation.[9] This results in further deterioration of skin quality and increased wrinkling. Thus, estrogen deficiency may account for the accelerated skin ageing seen in postmenopausal women.

Effects of ageing and estrogen on structural components of the skin

Collagen

The predominant form of collagen found in adult human skin is type I, followed by type III.[10] The genes for human collagen type I are located on chromosomes 7 and 17. Collagen is synthesized by fibroblasts from procollagen molecules by the action of neutral endoproteases. The fibrils of collagen undergo a series of post-translational modifications in order to enhance their stability and tensile strength. In young people, microscopic examination of collagen from the dermis of skin areas not exposed to the sun shows thin, wavy, uniform fibrillar units.

The skin becomes thinner and changes structure and function with age.[11,12] In the elderly, the skin contains thickened, clumped basophilic collagenous material, indicating partial degradation of collagen. Collagen atrophy is a major factor in skin ageing. Studies show a significant decline in the quantity of dermal collagen with ageing.

During ageing, there is a decrease in the enzymes concerned with post-translational processing of collagen. The amounts of hydroxyproline and glycosylated hydroxylysine in type I collagen decrease with age. Collagen ageing results from progressive cross-linking between the collagen molecules. A larger proportion of the cross-links between collagen molecules become non-reducible, that is, the number of immature and reducible cross-links decrease with age. The molar ratio of glycosylated hydroxylysine residues to unsubstituted hydroxylysine residues has been found to increase with age. There is a reduction in the number of fibroblasts that synthesize collagen and vessels that supply the skin. This leads to an increase in laxity and hence wrinkles.[4]

The exact effect of estrogen on collagen integrity is still unclear.[8] Anabolic steroids have been shown to increase collagen synthesis by human dermal fibroblasts. In rats, estrogen has been shown to inhibit collagen degradation. However, estrogens have no stimulatory effect on procollagen synthesis in cultured human cells.[13]

There is a strong correlation between skin collagen loss and estrogen deficiency due to menopause.[8,14–18] As much as 30% of skin collagen (both type I and type III) is lost in the first five years after the menopause. Total collagen content declines by an average of 2.1% per postmenopausal year over 15 years. This decrease in skin collagen correlates with age-related decreases in bone mineral density. This is consistent with the presence of type I collagen in bone.[19] Although one study found a closer correlation between collagen loss and chronological age than between skin collagen loss and time since menopause,[15] the study participants were between 40 and 55 years of age and had recently undergone surgical menopause. Consequently, the participants may not have been estrogen deficient sufficiently long for the correlation to become apparent.[18] Moreover, one year after the menopause there was a more pronounced reduction in skin collagen content.[18]

The decline in skin collagen content can be prevented by administering estrogen.[8,18] A beneficial effect of subcutaneous, topical or oral estrogens has been demonstrated on skin collagen content.[20–23] The extent of the estrogen-induced increase in collagen content varies with the route of administration, dose and duration of hormone treatment. As there are differences in the methods employed to assess collagen levels, results between studies are often not comparable.[8] The increase in collagen with estrogen is proportional to baseline collagen levels. However, one study observed no change in collagen levels of postmenopausal women following one year of HRT.[24] This can be explained by the fact that, given the short time since menopause, the amount and synthesis of collagen may not yet have fallen.[25] Collagen levels and metabolism do not change immediately after the menopause.[14]

Elastin

Like collagen, elastin is a fibre-forming functional protein. Elastin fibres are closely linked and interwoven with the collagen fibrils so that they can recoil after transient stretching and are prevented from overstretching. Women with a premature menopause have accelerated degenerative changes in dermal elastic fibres.[6] Histological studies demonstrate that topical estrogen can increase the number and thickness of skin elastic fibres.[26] Clinical trials, however, demonstrated no observable improvement in elastin fibre content from baseline with systemic estrogen therapy,[23,24,27] although these studies were small, short (6 months) or treated women shortly after the onset of menopause.

Water

Healthy skin has a substantial water content, which is determined by cutaneous evaporation and epidermal

hydration.[8] Transepidermal water flux decreases with age.[11] There are minor quantities of various glycosaminoglycans (including versican and heparan sulfate) in the dermis, which are closely associated with skin collagen. These glycosaminoglycans have a high water-binding capability, and are essential for normal skin hydration. Total dermal glycosaminoglycan content decreases significantly with age.[4] It has been postulated that collagen and glycosaminoglycans may interact to produce the age-related changes in the properties of collagen. It is possible that hydration of the dermis, influenced by glycosaminoglycans, may be more important than the extent of collagen cross-linking.

Dry skin is one of the commonest dermatological conditions in older women.[28] An epidemiological survey of 3875 postmenopausal women aged 40 years and over found that 36.2% had dry skin. Estrogen use was associated with a statistically significant decrease in the likelihood of senile dry skin (odds ratio 0.76, 95% CI 0.60–0.97).[29] These positive effects may be related to estrogen-stimulated increases in mucopolysaccharides and hyaluronic acid levels in skin, which correlate with an increased dermal water content.[11] These increases may also lead to an increase in skin thickness.

Sebaceous glands and hair

Sebum secretion decreases with age. Overall, there is a 38% increase in sebum production in postmenopausal women taking HRT, when compared with controls. Combined HRT increases skin surface lipids.[30,31]

Possible changes in postmenopausal women include an increase in facial hair, and a decrease in body and/or pubic hair. The onset of menopause can lead to a diffuse or an androgenic alopecia.[32–34] Another type of hair loss seen with ageing is frontal fibrosing alopecia, which is a variant of lichen planopilaris. The latter has been associated with menopause; however, hair loss persists despite hormone treatment.[35]

Effects of ageing and estrogen on physical characteristics of the skin

Skin thickness

There is an increase in skin thickness up to the age of 35–49 years, followed by an age-related thinning.[8] For the initial 15–18 postmenopausal years, the decrease in skin thickness accelerates, with as much as a 1.13% annual decline.[14,16] The thinning effect is due to decreases in collagen, water and glycosaminoglycans.[8] There is a high incidence of thin skin in osteoporotic women and there is a strong correlation between skin thickness, collagen content and bone density in postmenopausal women.[19] Most clinical trials have shown that postmenopausal women who take HRT have greater skin thickness than non-users.[36–38]

Elasticity

Skin ageing, especially in the face, is associated with a progressive increase in extensibility and a reduction in skin elasticity.[8] Skin elasticity declines 0.55% per year after the menopause. Twelve months of HRT has been found to increase elasticity by 5.2%.[39] HRT delays the deterioration in the extensibility of the skin, slowing the progress of cutaneous slackening secondary to menopause.[31,40]

Wrinkles

The loss of connective tissue in cutaneous ageing results in increased distensibility and loss of skin tone, leading to a progressive deepening of facial creases and wrinkling.[8] In untreated perimenopausal women, there is a rapid increase in skin extensibility, as detected by computerized measurements of skin deformability. The mechanical properties of the skin improve with estrogen.[41] Facial wrinkling improves with estrogens but worsens with smoking.[40,42] However, few clinical studies have specifically examined HRT and facial wrinkling, probably owing to technical challenges in quantification.[8]

Blood flow

The dermis and epidermis are nourished by arterioles and capillaries that pass upwards from the subcutaneous layer. The integrity of the structure and function of capillary blood vessels is important for healthy skin. There is a rich capillary network in the dermal papillae, which is responsible for the menopausal flush.[43] Core temperature haemostasis is maintained by the cutaneous circulation. Peripheral microcirculation at the level of the nail-fold capillaries decreases significantly during the menopause.[44] After 6–12 months of HRT, capillary blood flow increases in the nail-fold by as much as 20–30%.[44] The endothelium-dependent and endothelium-independent vascular reactivity in the cutaneous microcirculation improves substantially in postmenopausal women who receive estrogen.[45]

Wound healing

With increasing age, the skin becomes more fragile and susceptible to trauma, leading to more lacerations and bruising. Older women have been shown to heal less well, possibly because they have low levels of transforming growth factor (TGF)-β.[8] Venous ulcers and pressure sores are among the chronic wounds commonly suffered by the elderly. These cause significant suffering and cost, thus imposing a burden for patients and physicians alike.[46]

Cutaneous wound healing involves vascularization, granulation, collagen deposition and re-epithelialization.[47] The effect of estrogen levels on the stages of wound healing is still unclear, because of contradictory findings in animal studies.[8] In humans, estrogen has been shown to induce TGF-β secretion by dermal fibroblasts, and this can enhance the rate and quality of wound healing.[48]

Effects on sexuality

Skin changes can affect psychosexual function.[49,50] The appearance of wrinkles and skin sagging can lower

self-esteem. Altered peripheral nerve function, especially in the genital area, can lead to reduced libido and dyspareunia.[50]

Conclusions

Chronological age, environmental factors and the menopause have a profound impact on skin. Estrogen treatment in postmenopausal women increases dermal thickness, collagen content and elasticity. However, large-scale clinical trials are necessary to help provide the basis on which to make informed recommendations regarding postmenopausal estrogen use and its role in the prevention of skin ageing.

Competing interests: None declared.

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