Chapter 4
Skin Changes in Menopause

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4.1 Introduction

Skin is significantly affected by the aging process, as well as menopause. The changes which occur on the skin during menopause are due to the effects on skin's individual components [1]. Menopause is defined as either permanent cessation of menses or lack of menses for 12 consecutive months. The major change that occurs during menopause is cessation of estrogen production by ovaries, and major source of estrogen from conversion of adrenal androgen to estrogen by the action of aromatase enzyme in peripheral tissues [2].

4.2 Physiological Changes

Effects of Estrogen on Structural Component of Skin.

Estrogen receptors are seen on skin's cellular components [1]. With changes in structure and functions, the skin becomes thinner. The quality of skin decreases its efficacy with aging due to the synergistic action of time, photoaging, hormonal deficiency, decline in metabolic activity, and environmental factors [3].

It is difficult to distinguish between changes which are specific to aging and those due to estrogen deprivation; however estrogen might lead to accelerated aging of skin [3].

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4.2.1 Collagen

Atrophy of collagen fibers is a major factor of aging skin. Thickened, basophilic clumped collagenous material is suggestive of partial degradation of collagen, along with significant decrease in quantity of dermal collagen. The aging of collagen main occurs due to a decrease in the number of immature reducible cross-links between collagen molecules and an increase in nonreducible collagen. There is a reduction in enzymes which helps in post-translational collagen processing, reduction in fibroblasts which synthesize collagen and vessel supply of skin. All these attribute to increase in laxity and wrinkling. There is a strong correlation between loss of collagen and estrogen deficiency, since as much as 30% of collagen loss occurs in the first five years of menopause [3].

4.2.2 Elastin

Elastin fibers are closely interwoven with collagen fibrils, leading to recoil after stretching and prevention of overstretching. Degenerative changes in dermal elastic fibers occur during premature menopause in young women [3].

4.2.3 Elasticity

There is progressive increase in extensibility and reduction in skin elasticity in aging of skin over the face [3].

4.2.4 Water

A good amount of water content is required for a healthy skin, which is dependent on epidermal hydration and cutaneous evaporation. Dermal glycosaminoglycans decrease with age; these glycosaminoglycans are associated with high water-binding capacity and are essential to maintain normal skin hydration [3].

4.2.5 Thickness of Skin

The thinning effect is due to decrease in collagen, water, and glycosaminoglycans, which is seen in the postmenopausal years [3].

4.2.6 Blood Flow

The structural integrity and functioning of capillary blood vessels are very important for healthy skin. The rich capillary network in the dermal papillae is responsible for flush seen following menopause. Peripheral microcirculation also decreases significantly at menopause, especially at the nailfold capillaries [3].

4.3 Sebaceous Glands and Hair

There is a decrease in sebum secretion with aging. Also, there is an increase in facial hair and a decrease in pubic/body hair. Estrogen is also an important regulator of hair follicle growth and cycles. It is known that androgens have a role in the pathophysiology of female pattern hair loss (FPHL), but hair miniaturization in women can also be caused by nonandrogen signals as well. The hormonal changes of menopause lead to decreased growth rate, hair diameter, and percentage anagen. Hair density is affected by chronological age. The compounded effect of these changes may lead to a heightened perception of decreased scalp coverage in middle-aged women. It has been shown that the estrogen-receptor pathway regulates the telogen-anagen follicle transition under the influence of estrogens. The length of the hair follicle's life cycle is increased, owing to the prolongation of the anagen phase of the hair growth cycle. Conversely, with plummeting estrogen levels postpartum, significant loss of hair occurs. Decrease in estrogen levels is known to induce hair fall; hence hormone replacement therapy/topical estrogens are proposed to be used in hair fall [4–6].

4.4 Wound Healing

As aging occurs, the skin becomes more fragile and susceptible to trauma, and there is a decrease in transforming growth factor (TGF)-β. The estrogen induces TGF-β secretion by dermal fibroblasts and enhances the quality and rate of wound healing [3].

The effect of menopause on physical characters of skin is depicted in Fig. 4.1.

Fig. 4.1 Various skin changes seen at perimenopausal age

4.5 Skin Thickness

There is age-related thinning due to a decrease in collagen, water, and glycosaminoglycan content. The skin thickness usually increases up to the age of 35–49 years, followed by thinning [5].

4.6 Elasticity and Distensibility

Aging in skin, mainly over the face, is associated with reduction in skin elasticity and increase in extensibility [5].

4.7 Wrinkles

There is age-related loss of connective tissue in skin, leading to loss of tonicity and increased distensibility, which causes progressive deepening of facial creases. Hormone replacement therapy is suggested to increase in collagen content and elasticity, causing decreased wrinkling [5].

4.8 Blood Flow

The structural and functional integrity of capillary blood vessels along the cutaneous circulation is required to maintain core temperature [5].

Menopause denotes an estrogen-deficient hormonal condition, due to which the skin reflects a conspicuous decline in physical attributes [2]. The decrease in

functional follicles number leads to increase in levels of circulating follicle-stimulating hormone (FSH) and luteinizing hormone (LH) during and after menopause, leading to reduction in levels of estrogen and progesterone [7]. There is abundance in estrogen receptors in epidermis as well as dermis, and to a lesser extent progesterone receptors, leading to significant changes in skin during menopause due to the impact of hormones [7].

The symptoms a woman experiences during menopause is called as climacteric syndrome. Climacteric syndrome can be classified as physical or psychological in nature. Vasomotor symptoms, palpitations, headaches, urogenital symptoms, bone and joint pain, tiredness, disturbed sleep, breast tenderness, and skin aging are the physical symptoms. Depression, loss of memory, poor concentration, irritability, loss of confidence, and tiredness are the psychological symptoms. Alopecia and hirsutism seen during menopause are physical symptoms which cause significant psychological impact [7].

Dermatological problem occurring more commonly during menopause:

Vulvovaginal problems—atrophic vulvovaginitis, vaginitis of uncertain etiology, lichen sclerosus, dysesthetic vulvodynia.

General dermatological problems—hirsutism, recession of the frontal and frontoparietal hairline, postmenopausal frontal fibrosing alopecia, menopausal flushing, oral discomfort, drying of the skin, keratoderma climactericum [8].

4.9 Estrogen-Deficient Skin: Role of Topical Estrogen

Estrogen receptors are found in the skin, with the density of receptors being highest on the genitalia, face, and lower limbs. More estrogen receptors are found in females compared with males. Fewer estrogen receptors are found on the vulva compared with the vagina. The p29 protein found in the cytoplasm of estrogen-sensitive cells is present in the epidermis. A gradient of concentration exists which is highest in the stratum granulosum. Action of estrogen on collagen, elastic fibers, and hyaluronic acid has been demonstrated. Estrogen therefore exerts its effect on both epidermal and dermal components of the skin [8, 9].

Beneficial effects of estrogen on the skin:

Epidermal—decreased atrophy, increased water-holding capacity of the stratum corneum, increased barrier function.

Dermal—increased dermal thickness, increased turnover of hyaluronic acid, increased dermal water content, increase in type III collagen, morphological improvement of elastic fibers—increased number, thickness, and/or vertical orientation of fibers.

General cutaneous effects—increased thickness (7–15%), decreased slackness, decreased extensibility, increased DNA repair capacity (25%), decreased drying and wrinkling of the skin [8].

4.9.1 Topical Estrogen

Estrogens are steroids that are synthesized from cholesterol in the ovary in premenopausal women and in the peripheral tissue postmenopausally.

Two estrogen receptors (ERs), α and β, have predominantly been identified in the skin. Histologically, their relative expression levels start to decline from the perimenopausal years onward as women enter an estrogen-deficient state. Both ERs bind to estradiol with similar affinity; however, the expression profiles of ER-α and ER-β are tissue-specific, with ER-β more widely distributed within the skin than ER-α. Interestingly, ER-α activation is a main driver of reproductive cancers, which makes the selective targeting of ER-β a promising new avenue for targeted intervention [9].

Many studies have shown that upon entering menopause, women detect a swift commencement of skin aging symptoms. One of the first symptoms experienced is increased skin dryness, followed by decreased firmness and elasticity. These symptoms correspond with structural and architectural changes, such as decreased sebum production, collagen content, dermal thickness, and elastin fibers [9–11].

Estrogen helps to retain and restore skin moisture through the promotion of sebum secretion, primarily by regulating the expression of insulin-like growth factor receptors and increasing the production of insulin-like growth factors from fibroblasts, which in turn induces lipogenesis in human sebocytes and leads to moisture retention. Additionally, estrogen therapy elevates the levels of mucopolysaccharides and hyaluronic acids in the dermis to keep the skin hydrated, which improves the barrier function of the stratum corneum and optimizes the surface area of corneocytes [9–11].

Although systemic hormone replacement therapy can reverse signs, such as skin and vaginal dryness and atrophy, the various risks (mainly hyperplasia or cancer of the endometrium, and concern regarding increased risk of breast and ovarian cancer) preclude its use to treat skin disorders [9]

4.10 Cutaneous complication of Hormone Replacement Therapy

Hypersensitivity—sensitivity to adhesives in patches.

Pigmentation—increased incidence of melasma.

Immunological effects—raised levels of anti-DNA antibodies, induction of antiphospholipid antibodies, increased risk of developing SLE, no deterioration in cutaneous disease of SLE among HRT users, dose-dependent estrogen effect on production of IL-1.

Uncommon cutaneous adverse effects—acanthosis nigricans, erythema multiforme, photosensitivity, pompholyx, spider telangiectasia, stomatitis, urticaria [8].

Because maintaining youthful skin is strongly desired by a large portion of today's population, studies that evaluate approaches to reverse skin changes in menopause through alternative medicine and topical therapy have expanded [9].

Fuchs et al. used 0.01% estradiol cream for 6 months over the face (temple hairline)—epidermal thickness significantly increased by 23% compared with controls; markers of skin aging (rete peg pattern, epidermal thickness) significantly improved [12].

Schmidt et al. used 0.3% estriol cream or 0.01% estradiol cream for 6 months over the face—skin aging symptoms (vascularization, firmness, elasticity, moisture, wrinkle depth, and pore size) improved in both groups, but the effects of the topical estriol group were slightly superior to those of the estradiol group with regard to extent and onset [13].

Creidi et al. used 1 g Premarin cream (0.625 mg conjugated estrogen/g of cream) for 24 weeks over the face—skin thickness and fine wrinkles significantly increased in the treatment group compared with placebo; improvement in roughness, laxity, and mottled pigmentation but did not reach statistical significance between the groups [14].

Patriarca et al. used 0.01% micronized 17B-estradiol gel for 16 weeks over the face—epithelial and dermal thickness significantly increased compared with baseline, amount of collagen significantly increased compared with baseline, and keratinocyte proliferation and epidermal thickness increased [15].

Patriarca et al. used 0.01% 17-beta estradiol gel for 24 weeks over the face; hyaluronic acid concentration significantly increased [16].

Masuda et al. used 0.06% estradiol gel (l'estrogel) for 24 weeks over arms leading to fineness of texture (measured by digital microscope) increased in application site (forearm) and cheek (unapplied site) [17].

Silva et al. used 0.01% 17-beta estradiol for 24 weeks over the face leading to Types I and III facial collagen significantly increased at the end of treatment [18].

Although an absence of systemic effects after topical estrogen application has been described by many investigators, few had contrasting results. For instance, Masuda et al. described a decreased incidence of hot flashes in postmenopausal women after application of a gel formulation that contained 0.06% estradiol gel, suggesting that topical applications could indeed exhibit systemic effects via blood circulation in addition to exerting local action on the application site [9, 17].

In general, the systemic absorption of local or topical estrogen therapies is thought to be quite low and does not increase the risk of venous thromboembolic events, as seen with systemic estrogen therapies. Thus, whether the application of topical estrogens may potentially result in unwanted systemic effect is currently unclear, and topical estrogens are not widely used to treat estrogen deficiency [9].

The effects of estrogen deficiency on the skin are an important endogenous cause of aging skin in women. Clinically, topical estrogen products can be used cosmetically to improve skin dryness, texture, and elasticity and reduce wrinkles. However, concerns exist with regard to the safety of topical estradiol. Thus, more research is needed to support the use of topical agents to prevent and treat estrogen deficiency.

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