Chapter 11

Hormone Replacement Therapy and Skin Aging

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Glenda K. Hall, Tania J. Phillips

Contents

11.1 Introduction

Aging is a process associated with a decline in the function of all organ systems. The skin is the largest organ of the human body and is notably affected by aging. Cutaneous aging is characterized by atrophy, wrinkling, dryness, increased laxity, and poor wound healing (Table 11.1). It is influenced by several factors including genetics, cumulative sun exposure, and hormonal status [1]. Declining levels of hormones, especially estrogen, are associated with the aging process. While the effects of estrogen on skin function are not fully understood, effects of estrogen supplementation upon some of these age-related skin conditions in the elderly, specifically postmenopausal women, have been reported. Postmenopausal women who utilize estrogen supplementation tend to have lower wrinkle scores, less xerosis, and relatively thicker skin than women not receiving hormone replacement therapy (HRT). Estrogen supplementation appears to improve wound healing in elderly women.

Table 11.1. Skin functions known to decline with age

Epidermal turnover
Wound healing
Barrier function
Immune function
Sweat production
Sebum production
Vitamin D production

11.2 Estrogens and the Menopause

The estrogens, estradiol, estrone and estriol, are C-18 steroids differentiated by the C-17 side chain [2]. Their individual potencies as estrogens vary, with estradiol being the most potent and estriol being the least potent [2, 3]. Cholesterol is the parent steroid from which all gonadal steroids are derived [4]. Estradiol is predominantly synthesized in the granulosa cells of the ovary where it is converted from androstenedione produced in the theca cells. Estrone is the product of peripheral aromatization and the metabolism of estradiol and estrone results in the formation of estriol [2, 3, 5].

The skin is the largest non-reproductive organ targeted by estrogen. Estrogen interacts with the skin and other tissues through receptors. Two estrogen receptors (ER) have been identified: ERα and ERβ [6, 7]. Both ERs have 60% homology and nearly equal binding affinity for a large number of ligands [8–11]. However, each ER has variable expression among different tissue types as well as within the skin. The vaginal epithelium has the largest concentration of ER within the genital tract [12]. Skin on the face expresses larger concentrations of ER than breast or thigh skin [13]. Despite having structural and functional similarities, the variable concentration of these receptors within the skin suggests that each has a different, cell-specific role [14]. With the menopause, the expression of ER declines [12, 15].

Estrogen production varies with age and is regulated by the hypothalamic-pituitary axis (HPA) (Fig. 11.1). The pituitary gland, under the pulsatile stimulus of hypothalamic gonadotropin-releasing hormone, secretes luteinizing hormone (LH) and follicle-stimulating hormone (FSH). LH stimulates the theca cells to produce androstenedione while FSH stimulates the granulosa cells to convert androstenedione to estradiol. The resulting increase in serum estradiol exerts negative feedback upon the pituitary secretions thereby maintaining serum estradiol levels in the 10–20 mIU/ml range throughout adulthood [16]. At birth, serum estradiol levels drop precipitately and remain low until the onset of puberty at which time a steady rise occurs in women until maturity is reached. Throughout female adulthood, serum estradiol exhibits a diurnal rhythm correlated to LH stimulation [17]. At a genetically predetermined time in a woman's life, menopause occurs and menstruation ends [18]. During the premenopausal years, FSH and LH gradually rise due to a decline in estradiol production resulting in a loss of negative feedback to the pituitary gland [16]. With minimal estradiol production, estrone becomes the predominant circulating estrogen due to continued peripheral aromatization [19, 20].

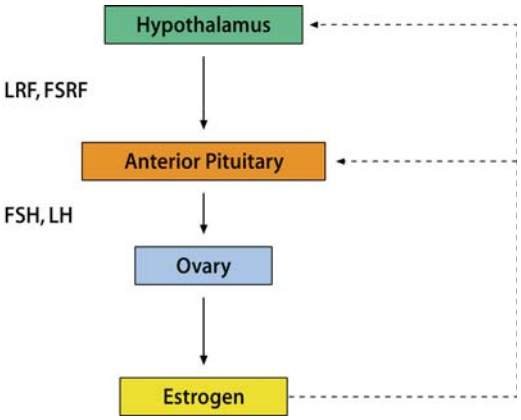

Fig. 11.1. Feedback control of the anterior pituitary and ovary. *LFR* luteotropin, *FSRF* follicle-stimulating releasing factor, *LH* lutenizing hormone, *FSH* follicle-stimulating hormone (reprinted from Phillips TJ, Demircay Z, Sahu M. Hormonal effects on skin aging. Clin Geriatr Med 2001;17:662; with permission from Elsevier)

With the menopause, the decrease in circulating estradiol, along with decreases in the expression of ER, may lead to the various physiological changes observed during this time period.

11.2.1 Synopsis

Estradiol, estrone, and estriol (listed in order of decreasing potency) interact with the skin through α and β ER whose concentration varies within the skin and decreases during the menopause.

The hypothalamic-pituitary axis regulates the production of estrogen which varies with

Table 11.2. Summary of the HERS and WHI trials (*CCE* continuous conjugated estrogens, *MPA* medroxyprogesterone acetate, *WHI* Womens Health Initiative, *HERS* Heart and Estrogen/Progestin Replacement Study)

HERS trial [26]	2,763 postmenopausal women less than 80 years of age with known coronary disease were randomized to either estrogen plus progestin CEE 0.625 mg/day plus MPA 2.5 mg/day (*n*=1,380) or placebo (*n*=1,383)	After 4.1 years of follow-up, no overall cardiovascular benefit and an early increase in coronary events was found with the use of estrogen and progestin
WHI trial [25]	16,608 healthy postmenopausal women aged 50–79 years were randomized to either estrogen plus progestin 0.625 mg CEE plus 2.5 mg MPA (*n*=8,506) or placebo (*n*=8,102)	Stopped early after 5.2 years of follow-up (expected follow-up 8.5 years) when the global index indicated that risks of HRT exceed benefits. Women treated with CEE/MPA had 1.26-fold greater risk of breast cancer than placebo group

age and declines during the perimenopausal years.

11.3 Hormone Replacement Therapy and Aging

HRT was first introduced 70 years ago and, in 2000, was the second most commonly prescribed drug [21]. Relief of menopausal symptoms and either treatment or prevention of osteoporosis are the main reasons documented for prescribing HRT [22]. Previously estrogen was also considered beneficial in the prevention of cardiovascular disease [23]. Recently, however, women have been forced to reconsider the benefits of HRT. While the risks seem low [24], findings from the Women's Health Initiative Trial (WHI) and the HERS (Heart and Estrogen/Progestin Replacement Study) trial have demonstrated a small but apparent increased risk of breast cancer and coronary artery disease in those women utilizing HRT [25, 26] (Table 11.2). However, these studies were performed in older, predominantly obese women, many of whom had preexisting cardiovascular risk factors, such as hypertension and dyslipidemias. In addition, these studies used specific HRT regimens, and the results cannot necessarily be extrapolated to general HRT use [27].

The decline in skin appearance from the perimenopausal years onward suggests that the decrease in sex steroids may play a role in aging. The most common changes include skin atrophy, dryness, laxity, wrinkling, and poor wound healing. While several studies have suggested that many of these signs can be improved or reversed with the use of estrogen, the evidence remains controversial. The decision to use supplemental estrogen for the treatment of cutaneous aging is further clouded by the recent negative associations linked with estrogen use. Thus, physicians should allow women to make informed decisions regarding the safety and efficacy of supplemental estrogen.

The issues surrounding HRT are complicated. Women should carefully consider the risks and benefits of HRT in consultation with their physician (Table 11.3). In general, short-term HRT is indicated for the relief of postmenopausal symptoms, but it would seem prudent to avoid long-term HRT for the prevention of disease [24, 27].

11.3.1 Dermal Collagen Content

Thinning of the skin, clinically appreciated by easy tearing and bruising, is a common sign of aging. Several metabolic activities decrease with aging and thinning of the skin is believed to result from a decrease in dermal collagen synthesis [28, 29]. An average decline of 1–2% per year in dermal collagen content following the menopause has been reported [30]. The association between collagen loss and postmenopausal age, rather than chronological age, may reflect a hormonal etiology [28, 29]. Thus, several stud-

Table 11.3. Risks and benefits of postmenopausal HRT

		Reference
Benefits	Relief of menopausal symptoms	67
	Relief of urogenital atrophy and its symptoms (topical estrogen)	68
	Prevention of fractures in women with osteoporosis	69
Risks	Increased risk of breast cancer in women who used HRT for over 5 years	69
	No role in secondary cardiovascular disease (CVD) prevention	27
	Controversial role in primary CVD prevention	27
	Stroke in older women (17β-estradiol)	70
	Venous thromboembolism	25–27

ies have evaluated the effectiveness of estrogen supplementation on increasing skin thickness and dermal collagen content. The results are quite varied, and comparison among the studies is difficult due to variations in the study designs including the route of estrogen administration, the use of combined progestins, and the length of estrogen exposure. Nevertheless, the majority of evidence demonstrates an increase in skin thickness and/or dermal collagen content with postmenopausal estrogen supplementation [31–37]. Interestingly, the effect of estrogen appears to be dependent on baseline collagen content at the onset of treatment. Estrogen has a preventative role in collagen loss in those women with higher initial collagen levels, and a therapeutic role for collagen synthesis in those women with lower initial collagen levels [38, 39].

Initial studies performed throughout the 1980s by Brincat and various collaborators demonstrated increases in skin thickness and/or collagen content with several different hormone replacement regimens, including varying doses of testosterone [29, 30, 38–40]. An ideal estrogen dose was postulated, based on suboptimal increases, or even decreases, observed in dermal collagen content with varying estrogen doses [38]. More recently, randomized placebo-controlled studies have assessed the effects of estrogen on skin thickness and dermal collagen content. In 1994, a randomized placebo-controlled study of 60 postmenopausal nuns reported increased skin thickness at the level of the greater trochanter after 12 months of therapy with 0.625 mg conjugated estrogens [31]. Skin thickness measurements were performed with ultrasound. Skin biopsies obtained from the same location revealed a 33% increase in dermal thickness. The patient population was selected to decrease confounding variables of aging such as smoking and extrinsic photoaging due to extensive sun exposure. Another randomized, placebo-controlled study evaluated 118 postmenopausal women on one of four possible treatment regimens over a 12-month period [32]. Women were randomized to 0.625 mg conjugated estrogens in a 25-day cycle, 0.625 mg conjugated estrogens every day, 50 μg transdermal estradiol in a 24-day cycle, or no treatment. Each active treatment group received medroxyprogesterone for the last 12 days of each cycle. All active treatment groups had increases in the dermal collagen level while the placebo group experienced a 3.2% decline in dermal collagen content. Transdermal estradiol in combination with a progestin demonstrated the greatest efficacy, with a 5.1% increase in collagen, when compared to oral conjugated estrogens [32]. More recently, a randomized double-blind placebo-controlled study of estrogen in 41 postmenopausal women revealed a 6.5% increase in dermal collagen content for the active treatment group and no change in dermal collagen content for the placebo group [33]. Skin biopsies were obtained from the medial upper arm and were analyzed using computerized image analysis. The active treatment group received 2 mg estradiol in a 21-day cycle with 1 mg cyproterone for the last 12 days of each cycle. Treatment was continued for 6 months.

Several open-label studies have supported the findings from the randomized, controlled trials. A study of 100 postmenopausal women treated with either combination HRT (estradiol and cyproterone) or calcium carbonate for 6 months demonstrated increased skin thickness on ultrasound in the active treatment group and a significant decrease in the calcium treated group [34]. A study of topical estradiol gel confirmed the localized effect of topical estrogen on the skin [35]. The gel was applied to one-half of the lower abdomen for 3 months in 12 postmenopausal women and a vehicle-only gel was applied to the contralateral half of the lower abdomen to serve as a control site. A 38% increase from baseline in skin hydroxyproline content on the estrogen-treated side was demonstrated. In addition, blister fluid analysis revealed increased propeptides of collagen on the estrogen-treated side indicating a stimulatory effect on collagen synthesis. Both local and systemic effects of topical estrogen supplementation were demonstrated in a study of 98 postmenopausal women who were divided into two equally-numbered groups based on hormone replacement utilization [36]. The active treatment group received either estradiol gel (n=36) or transdermal estradiol (n=13). Skin thickness measurements at five locations (inner and outer forearm, forehead, breast, and estrogen application site) were obtained utilizing B-mode ultrasound high-resolution echography. Statistically significant increases in skin thickness as compared to control were found at the inner and outer forearms, and highly significant increases were demonstrated at the breast and the site of estrogen application.

Some studies have disputed the effects of estrogen supplementation on skin thickness and collagen content. Bolognia et al. performed a double-blind placebo-controlled study of 46 postmenopausal women in whom cutaneous symptoms, including the complaint of thinning skin, and cutaneous signs, including bruising, were assessed. No statistically significant difference in the complaints of thinning skin or clinical sign of bruising was found in the group treated with 6 months of 17β-estradiol compared to the placebo group [37]. An open non-randomized trial of 43 postmenopausal women showed no effects of treatment with either 2 mg 17β-estradiol or 2 mg estradiol valerate after 12 months [41, 42]. Utilizing four independent methods to detect changes in the connective tissue (ultrasonographic measurement of skin thickness, assessment of total collagen with a colorimetric method, determination of de novo synthesis of collagen by measuring procollagen propeptides in blister fluid, and immunohistochemistry), the authors concluded that 1 year of systemic estrogen did not affect skin thickness, the amount of collagen, or the rate of collagen synthesis. Interestingly, both of these studies enrolled women with a relatively young postmenopausal age. Bolognia et al. required amenorrhea for 4 months while the latter study required amenorrhea for at least 6 months but less than 2 years. As discussed above, a young postmenopausal age may be associated with a higher baseline collagen content, thus introducing selection bias into the data.

In summary, HRT has been shown to increase skin thickness and dermal collagen content in several studies. However, the extent of the increase varies depending on the dose, route of administration, and duration of treatment. In addition, some studies have not shown positive effects of HRT.

11.3.1.1 Synopsis

Age-related atrophy of the skin has been correlated with decreases in dermal collagen which occurs at a rate of 1–2% per year after the menopause.

The efficacy of supplemental estrogen in treating skin atrophy may be related to the baseline collagen content at the onset of treatment. Thus, it is prophylactic in early menopause and therapeutic later on.

Not all studies have demonstrated beneficial effects of estrogen supplementation on skin atrophy.

11.3.2 Dryness: Water-Holding Capacity and Epidermal Lipid Layer

In a clinical examination of 3875 postmenopausal women, the utilization of HRT decreased the likelihood of dry skin when compared to those who were not receiving HRT [43]. In another study, the use of 0.01% estradiol or 0.3% estriol for 6 months resulted in increased skin moisture via corneometry in 59 postmenopausal women. However, these increases did not reach statistical significance [44]. Skin hydration is highly influenced by the skin's ability to retain water. The status of the stratum corneum and the dermal content of glycosaminoglycans affects the skin's water-holding capacity. A study of 30 postmenopausal women receiving transdermal estrogen supplementation found increases in the water-holding capacity of the stratum corneum through measurements of transepidermal water loss [45]. Glycosaminoglycans are hydrophilic molecules that draw moisture into the dermis. Decreased dermal glycosaminoglycans are associated with aging [46] and are thus felt to contribute to dry skin, wrinkling, and atrophy [47]. Estrogen supplementation in animals has been shown to result in marked increases of glycosaminoglycans within 2 weeks of therapy [48], and one human study has demonstrated increased dermal hydroscopic qualities during states of elevated endogenous estrogen (pregnancy), suggesting a similar mechanism [49].

Changes in the lipid layer of the epidermis are frequently associated with aging and may affect the water-holding capacity of the skin. Significant variation in stratum corneum sphingolipids has been noted among women of varying ages thus suggesting a possible hormonal influence [50]. Increased skin surface lipids have been measured, utilizing a sebumeter, in postmenopausal women receiving transdermal estradiol when compared to non-treated controls (total n=98) [36]. Another study also found increased skin surface lipids and skin moisture in 15 women treated with 6 months of combination HRT (estradiol plus progestin) [51]. These findings suggests that postmenopausal supplementation of estrogen may enhance the skin barrier function, thus preventing dryness.

11.3.2.1 Synopsis

The use of HRT is correlated with a decreased likelihood of dry skin. This finding may be related to increases in hydrophilic dermal glycosaminoglycans.

The composition of stratum corneum sphingolipids is hormonally influenced. Increases in these skin surface lipids, as seen with HRT, may result in improved skin hydration and barrier function.

11.3.3 Wrinkling and Laxity: Elastic Fiber Content

Laxity and wrinkling are cutaneous signs of aging related to the loss of skin elasticity. Estrogen supplementation has been demonstrated to improve non-invasive measurements of laxity and wrinkling. However, studies evaluating the effects of estrogens on the elastic components of dermal tissue have been controversial. In a study of 180 women aged 18–67 years, a progressive increase in skin extensibility and a decrease in skin elasticity was observed with aging [52]. In a sub-cohort of 30 postmenopausal women, the use of HRT (either 0.625 mg/day conjugated estrogens or 2 mg/day estradiol, each with an associated progestin for the last 12 days of each cycle) slowed the progression of these skin changes when compared to age-matched controls not utilizing HRT. Supporting evidence demonstrated steep increases in skin extensibility, measured with computerized suction devices, in menopausal women not utilizing HRT when compared to those utilizing HRT [53].

Studies assessing wrinkling have also been promising. Decreased wrinkle measurements via profilometry were reported in 59 preclimacteric women who applied either estradiol or estriol to the face for 6 months [44]. A randomized, double-blind, placebo controlled study of 54 postmenopausal women reported an improvement in fine wrinkling after applying Premarin cream to the face at bed-time for 24 weeks [54]. However, subject self-assessments did not reveal any changes in perception of facial appearance including fine wrinkling. Data from the largest population-based study to date, the

First National Health and Nutrition Examination which included 28,000 civilians and 3,875 postmenopausal women, indicated that the use of estrogen is associated with less wrinkling in postmenopausal women. Reliability of estrogen use among the 3,875 postmenopausal women, however, has been questioned given that the history of estrogen use was obtained in follow-up surveys conducted 9–15 years after the initial assessments [43].

Invasive studies evaluating the effects of estrogens on elastic fibers have not been uniformly conclusive. Bolognia et al. found degenerative changes in the dermal elastic fibers of women with premature menopause and suggested a possible relationship between estrogen deprivation and changes in dermal elastic fibers [37]. Two small studies have demonstrated increased elastic fibers after therapy with estrogen supplementation, although larger studies have not reached the same conclusion. Localized increases in the concentration and size of elastic fibers were found in 7 of 14 postmenopausal women applying 2 mg of estriol to the abdomen daily for 3 weeks [55]. Morphological improvements in elastic fibers at the site of estradiol application after 3 months of therapy were found in a study of 12 postmenopausal women [35]. On the contrary, an open study of 43 postmenopausal women did not find any change in the proportional area of elastic fibers assessed by computerized image analysis of light microscopy images after 12 months therapy with estradiol [41, 42]. Finally, a recent randomized double-blind placebo-controlled trial of 41 postmenopausal women, despite showing improvements in collagen content, did not show any changes in elastic fiber content after 6 months estradiol therapy [33].

While dermatological examinations have shown clinically significant improvements in laxity and wrinkling after the use of supplemental estrogen, patient self-assessments have not always corroborated these findings.

11.3.3.1 Synopsis

Extensibility of the skin progresses with age. The use of HRT has been shown to slow this progression when compared to cohorts not utilizing HRT.

Fine wrinkling may also be decreased with the use of HRT, especially when applied to the face. However, the improvement does not necessarily correlate with improved patient satisfaction.

11.3.4 Wound Healing

Poor wound healing accompanies aging and is linked to an exuberant inflammatory response resulting in excessive proteolysis of structural elements important in keratinocyte migration [56, 57]. High neutrophil counts in chronic wounds result in elevated levels of proteolytic enzymes such as elastase and other matrix matalloproteinases (MMPs). Studies have demonstrated elevated levels of MMPs in the chronic wounds of elderly patients with reduced levels of fibronectin [58, 59]. Studies have also shown that estrogen plays a crucial role in wound healing [60, 61]. Improved wound healing of acute wounds has been demonstrated in elderly men and women treated with transdermal estradiol in comparison to placebo patch [62]. Other studies have demonstrated a decreased incidence of chronic wounds, such as venous ulcers and pressure ulcers, in women utilizing HRT [63, 64].

Several mechanisms to explain the effects of estrogen on wound healing have been proposed. An antiinflammatory mechanism is supported by a study that demonstrated decreased neutrophil chemotaxis, thereby decreased wound levels of elastase, with the use of estrogen. The decreased levels of elastase allow increased levels of fibronectin and thus improve cellular matrix formation and wound healing [62]. Transforming growth factor-β1 (TGF-β1), a cytokine involved in cell proliferation, differentiation, and matrix production, is also affected by estrogen status. TGF-β1 is decreased in the wounds of elderly females. Estrogen supplementation reverses that decrease and is associated with improved rates of wound healing [57]. Animal models have also demonstrated increased rates of wound repair with the administration of TGF-β1 [59].

Despite the beneficial effects of TGF-β1 on wound healing, this cytokine also adversely affects scarring profile (see below). Finally, studies evaluating macrophage migration inhibitory factor (MIF) have found it to be markedly elevated in the wounds of estrogen-deficient mice. In addition, mice devoid of the MIF gene do not demonstrate exuberant inflammation or delayed wound healing during states of estrogen deficiency [65]. This area of study is still under investigation.

Scarring, the end result of wound healing, is affected by hormonal status. Scars in older subjects are reported to have superior macroscopic (color, texture, and contour) and microscopic appearances when compared to the scars of younger individuals [59]. Favorable appearances include pale, flat scars with regenerated rete ridges, large papillary blood vessels, and a normal basket-weave organization of the collagen bundles. Changes in the quality of scarring may be related to TGF-β1. Neutralization of TGF-β1 in rodent cutaneous wounds led to anti-scarring effects [66]. Utilization of HRT in the elderly population, which is associated with increased levels of TGF-β1, has resulted in less favorable scarring profiles similar to younger subjects. This relationship suggests a hormonal and cytokine interaction on scar formation.

11.3.4.1 Synopsis

Chronic wound healing is characterized by an exuberant inflammatory response with high neutrophil counts and subsequent increases in proteolytic enzymes such as MMPs.

HRT and estrogen supplementation alone have been associated with improved wound healing in animal and human experimental models via an antiinflammatory mechanism and interaction with TGF-β1 and macrophage MIF.

11.4 Summary

Aging is an inevitable process that affects all organ systems including the skin. A decrease in serum estrogen accompanies aging and may contribute to age-related skin changes such as atrophy, wrinkling, dryness, and poor wound healing. Studies investigating the supplemental use of estrogen in the later years have demonstrated some beneficial effects on skin aging parameters. However, the use of HRT is controversial. Thus, the decision to use HRT should be made only after weighing the risks and benefits for each individual.

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