

Estrogens and the skin

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ABSTRACT

Objective A review of the medical literature concerning the effect of the menopause and its hormonal treatment on the skin.

Methods An extensive Medline and Pubmed internet search utilizing the key words: collagen, elastin, estrogen, hormone replacement therapy, skin and aging.

Results The literature review demonstrated a wide array of research ranging from basic science work to clinical implications of the effects of the menopause and its treatment on the skin.

Conclusion Estrogen loss at menopause has a profound influence on skin. Estrogen treatment in postmenopausal women has been repeatedly shown to increase collagen content, dermal thickness and elasticity, and data on the effect of estrogen on skin water content are also promising. Further, physiologic studies on estrogen and wound healing suggest that hormone replacement therapy (HRT) may play a beneficial role in cutaneous injury repair. Results on the effect of HRT on other physiologic characteristics of skin, such as elastin content, sebaceous secretions, wrinkling and blood flow, are discordant. Given the responsiveness of skin to estrogen, the effects of HRT on aging skin require further examination, and careful molecular studies will likely clarify estrogen's effects at the cellular level.

INTRODUCTION

Due to an increased life expectancy, women in the West can now expect to spend more than one-third of their lifetime after menopause^{1,2}, leading to increased concern regarding postmenopausal health care. The hypoestrogenism that accompanies menopause is known to induce vasomotor symptoms and vaginal atrophy, as well as exacerbate bone loss; studies have documented that postmenopausal hormone therapy (estrogen only (ERT) or estrogen opposed by a progestin (HRT)) can reduce the symptoms of menopause and prevent early bone loss. However, other organs that are also intimately dependent on estrogen have not garnered comparable attention with regard to postmenopausal treatment. For exam-

ple, estrogen has a profound influence on skin. Despite skin being the largest organ of the body, and the primary barrier against pathogen invasion, dehydration, and elemental damage, the effects of postmenopausal estrogen deficiency on skin are not well documented. Further, work on the impact of exogenous hormones on women's skin is still in its infancy.

This aim of this paper is to review the clinical literature regarding the physiological effect of estrogen on structural and physical characteristics of skin. In particular, studies that have examined postmenopausal hormone therapy and the role it may play in maintaining skin integrity and preventing age-related deleterious changes will

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be discussed. Given the importance of skin for general health and the intriguing information available on a role for estrogen in skin, further examination of mechanistic and clinical effects of estrogen on skin parameters is warranted.

SKIN PHYSIOLOGY AND THE ROLE OF ESTROGEN

The skin is the largest organ of the body. Anatomically, skin is comprised of two main layers: the epidermis forms the thin outer layer and is made primarily of keratinocytes and melanocytes; the dermis is the deeper layer that comprises the main bulk of skin. The dermis is predominantly made up of connective tissue and blood vessels. The fibers present in dermal connective tissue consist of two main types of fibrous proteins, collagen and elastin. The collagen fibers (mainly types I and III) are produced by fibroblasts, are arranged parallel to the skin surface, and are responsible for the main mass and tensile strength of skin. In contrast, elastin fibers are arranged as a thinly distributed subepidermal network and provide the skin with elasticity and resilience³. Dermal connective tissue also contains nerve fibers, sensory receptors and the supportive glycosaminoglycans (GAGs)⁴.

Skin quality deteriorates with age due to the synergistic effects of chronologic aging, photoaging, environmental factors and hormonal deficiency⁴. Hormonal aging of skin due to estrogen loss at menopause is thought to include atrophy, decreased collagen content, water content, and sebaceous secretions, loss of elasticity, and manifestations of hyperandrogenism. Further, the cumulative effect of estrogen deficiency on skin is thought to contribute to the poor wound healing that accompanies aging.

An integral role for estrogen in skin integrity was substantiated with the discovery of estrogen receptors in dermal fibroblasts and epidermal keratinocytes⁵. Further, a study aimed at identifying specific estrogen-sensitive structures examined human skin for the ability to bind an antibody against a protein, p29, typically found in estrogen-responsive cells⁶. Strong and specific binding to the p29 antibody was seen in discrete structures within skin⁶. However, there is a lack of information regarding the effects of estrogen on these target cells. Expression of both aromatase and 17 β -hydroxysteroid dehydrogenase type I – two enzymes involved in the formation of potent estrogens – has also been demonstrated in skin⁷.

EFFECTS OF ESTROGEN ON STRUCTURAL COMPONENTS OF SKIN

Collagen content

In normal human dermis, collagen is a relatively stable molecule, synthesized from procollagen molecules by the action of specific enzymes and degraded by collagenases. Although anabolic steroids have been shown to increase collagen synthesis in human dermal fibroblasts⁸, estrogens have no stimulatory effect on procollagen synthesis in cultured human cells⁹. Using a rat model, estrogen has been shown to inhibit collagen degradation¹⁰. Given the complex involvement of regulatory factors, receptors and enzymes in maintaining collagen balance, the exact mechanism for the role of estrogen on collagen integrity is not known.

A reduction in collagen is traditionally considered the principal factor in the pathogenesis of skin atrophy. Although Castelo-Branco and colleagues¹¹ found a closer correlation between collagen loss and chronologic age than between collagen loss and time since menopause, others report a stronger correlation between skin collagen loss and estrogen deficiency due to menopause¹²⁻¹⁶. The finding of Castelo-Branco and colleagues¹¹ may be explained by the fact that the individuals in that study were between 40 and 55 years of age, had recently undergone surgical menopause, and had therefore not been estrogen-deficient for a long period¹⁶. Castelo-Branco and colleagues have gone on to show a parallel decline between bone mass and skin collagen, possibly due to the connective tissue component which is common to both organs¹². It has been suggested that as much as 30% of skin collagen (both types I and III) is lost in the first 5 years after the menopause^{15,17}. Brincat and colleagues^{13,14} found that total collagen declines an average of 2.1% per postmenopausal year over a period of 15 years, and this decline can be prevented in women receiving estrogen therapy¹⁸. Consistent with the presence of type I collagen in bone, the decrease in skin collagen content has been shown to correlate with age-related decreases in bone mineral density^{13,14,19}.

Most clinical studies demonstrate a beneficial effect of subcutaneous^{13,14,17-20}, topical^{13,14,21,22} or oral^{11,23} estrogen treatment on the collagen content of skin (Table 1). The extent of the reported estrogen-induced increase has varied, depending upon the dose, route of administration and duration of hormone treatment. For example,

Table 1 Estrogen therapy and collagen content

<i>Study/year</i>	<i>Brief description of study</i>	<i>Results</i>
Brincat, 1983 ¹⁸	Skin biopsies taken from untreated postmenopausal women and women who had been treated with estradiol and testosterone implants for 2–10 years	Mean collagen content was 48% greater in the HRT group than in untreated women
Brincat, 1985 ¹⁷	Skin biopsies taken from untreated postmenopausal women and women who had been treated with estradiol and testosterone implants for 2–10 years	Skin collagen content was significantly greater in postmenopausal women on HRT
Brincat, 1987 ¹³	Skin biopsies taken from postmenopausal women who were either given topical estradiol for 1 year, or were treated with an estradiol-only implant, an estradiol and testosterone implant, or a testosterone-only implant for 6 months	All treatment regimens increased collagen to levels proportionate to the levels at the start of treatment
Brincat, 1987 ¹⁴	Skin biopsies were taken from untreated postmenopausal women and postmenopausal women who had been treated with estradiol and testosterone implants for 2–10 years	The decrease in collagen seen in untreated women was preventable with HRT use
Castelo-Branco, 1992 ¹¹	Skin biopsies were taken from postmenopausal women allocated to 1 of 4 groups (control; CEE (25-day cycle); CEE (28-day cycle); transdermal 17 β -estradiol (24-day cycle))	Estrogen treatment increased collagen content 2–5%
Savvas, 1993 ²⁰	Skin biopsies were taken from treated or untreated postmenopausal women. Treated women had received subcutaneous estradiol and testosterone for 3–14 years	Women on HRT had significantly greater levels of collagen III
Varila, 1995 ²²	Suction blister fluid and skin biopsies taken to analyze collagen content in postmenopausal women administered either topical estrogen or vehicle for 3 months	Estradiol treatment resulted in 38% greater hydroxyproline levels
Schmidt, 1996 ²¹	Skin biopsies taken from premenopausal women with skin aging symptoms before and after 6 months of topical estradiol or topical estriol treatment	Topical estrogens increased collagen II levels in the dermis
Haapasaari, 1997 ²⁴	Suction blister fluid used to analyze skin collagen content in 43 early postmenopausal women (mean age, 50–52 years) administered continuous oral 17 β -estradiol and NETA, continuous oral estradiol valerate or control for 12 months	No effect
Sauerbronn, 2000 ²³	Skin biopsies taken from postmenopausal women given either HRT (2 mg estradiol valerate, cycled with 1 mg cyproterone acetate) or placebo for 6 months	HRT-treated group experienced a 6.5% increase in collagen after 6 months. No difference was seen in control group

a 3-month study in postmenopausal women found that treatment with topical estradiol resulted in a 38% increase in total collagen²², whereas another study examining both oral and transdermal estrogen treatment for 12 months found collagen levels increased significantly, but by only 2–5% depending on the treatment regimen¹¹. In addition, results between studies are often not comparable due to differences in the methods employed to assess collagen levels.

The increase in collagen with estrogen is proportionate to baseline collagen levels^{13,14}. To date, only one clinical study has failed to show a

beneficial effect of estrogen therapy on collagen levels. Haapasaari and colleagues²⁴ observed no change in collagen levels of postmenopausal women with 1 year of ERT or HRT. However, that study examined the effects of estrogen on very early menopausal women, on average within the first year of menopause, and the authors recognize that, given the short time since menopause, the amount and synthetic rate of collagen may have been at an optimum level²⁵. Based on observations by Brincat and colleagues¹⁹ that demonstrate a delay in the collagen decrease after the onset of menopause, HRT would not be

expected to have an effect on collagen levels in such early menopausal women. Cumulatively, these studies suggest that estrogen treatment may be prophylactic for women with high skin collagen levels and both prophylactic and therapeutic for women with low collagen content^{13,14}.

Elastin fibers

Accelerated degenerative changes in dermal elastic fibers have been observed in young women with premature menopause⁴, and histologic studies demonstrate that topical estrogen can increase the number and thickness of elastic fibers in skin²⁶. However, reports from several recent clinical trials that examined the effects of HRT on elastin fiber content in skin demonstrate no observable improvement from baseline with systemic estrogen therapy^{23,24,27}. Importantly, two of these studies treated a small sample ($n \leq 21$) of women for only 6 months^{23,27}, and the third involved very early menopausal women²⁴.

Water content

One of the most common dermatologic conditions in older women is dry skin²⁸. Healthy skin requires substantial water content which is determined by both the cutaneous evaporation rate and epidermal hydration. It has been shown that the transepidermal water flux, or evaporation, varies during the menstrual cycle²⁹ and decreases with age³⁰. A sensitive measure of functional changes in water-holding capacity of the skin is the plastic occlusion stress test (POST). One small clinical study on 15 healthy menopausal women used the POST method to show that transdermal estrogen therapy can lead to a significant increase in the water-holding capacity of the stratum corneum³¹.

Notable alterations in epidermal hydration result in changes in the capacitance of the stratum corneum. Several small trials that have measured skin capacitance have demonstrated that HRT can improve the water content of skin^{21,31-33} when compared with a control group, although some differences did not reach statistical significance^{21,33}. Other results demonstrate no effect of estrogen on skin capacitance^{24,34}.

In the First National Health and Nutrition Examination Survey (NHANES I)³⁵, standardized dermatologic assessment of 3875 postmenopausal women showed that estrogen use was associated with a statistically significant decrease in the likelihood of senile dry skin. Given limits inherent to epidemiologic studies, corroboration of a role

for estrogen in skin water content will best be addressed with large double-blind, randomized, controlled studies³⁶.

Positive effects of estrogen on the water content of skin may be related to estrogen-stimulated increases in mucopolysaccharides and hyaluronic acid levels in skin³⁷⁻⁴⁰, which correlate to an increased dermal water content³⁸, and to increases in skin thickness, which subsequently elevate natural moisturizing factors²¹. An improvement in water-holding capacity of the skin enhances the barrier function of the epidermis and subsequently results in less frequent development of dermatoses³¹.

Sebaceous secretions

The activity of cutaneous sebaceous glands is regulated by levels of circulating hormones; estrogen can reduce the size and number of sebaceous glands, as well as the production of sebum, while androgens oppose this action, thereby stimulating secretory activity⁴. Indeed, clinical studies have shown that sebaceous secretions decrease with age⁴¹ and estrogen replacement alone has a sebum-suppressive action³², but the addition of a progestin results in significant increases in skin surface lipids^{32,34}. In a study by Callens and colleagues³⁴, 49 postmenopausal women taking estradiol with progesterone were compared with a control group; a 38% increase in sebum production was observed with hormone treatment.

EFFECTS OF ESTROGEN ON PHYSICAL CHARACTERISTICS OF SKIN

Skin thickness

Skin thickness increases up to the age of 35-49 years, followed by an age-related thinning. During the menopausal years, the decrease in skin thickness accelerates with as much as a 1.13% annual decline for the initial 15-18 postmenopausal years^{13,14}. Decreases in collagen, water and GAG content all contribute to the thinning effect. Consistent with early studies that note a high incidence of thin skin in osteoporotic women⁴¹⁻⁴⁵, a strong correlation between skin thickness, collagen content and bone mineral density has been observed in postmenopausal women^{13,14,46}.

Attempts have been made to slow skin thinning with estrogen therapy for several decades. The majority of clinical trials have demonstrated that

postmenopausal women who take HRT have greater skin thickness when compared with non-users^{11,27,31,34,46–50}. An HRT-induced increase in thickness is detected in the dermis^{27,47,50} through increases in dermal connective tissue, but not the epidermis^{23,27,47,50}. An early randomized, double-blind, placebo-controlled study examined the use of conjugated equine estrogen (CEE) in 60 postmenopausal nuns for 1 year and found that CEE use for 1 year was associated with a 30% increase in dermal thickness on skin biopsies when compared with placebo⁵⁰. A recent cross-sectional observational study used diagnostic ultrasound to compare skin thickness between HRT users, non-users and premenopausal women⁵¹. Chen and colleagues⁵¹ found that HRT-treated women had 10% greater skin thickness than non-users and achieved thickness levels comparable to premenopausal individuals. Interestingly, the benefit with HRT was similar for women taking therapy from 6 months to 6 years, suggesting a therapeutic role for HRT during the initial period of treatment and a prophylactic role thereafter. Estradiol cream applied to the face showed a significant increase on epidermal skin thickness of 23%. Markers of skin aging such as rete peg pattern and epidermal thickness appeared to be reversed with estradiol cream applied to the face⁵². The absolute changes in thickness measured in these studies are notably small (in the sub-mm range) and may not necessarily be clinically relevant. However, these studies suggest that hormonal status influences skin thickness and that skin atrophy, specifically dermal atrophy, can be ameliorated with postmenopausal hormone therapy.

Two studies examining early menopausal women^{24,52} found no significant change in skin thickness with estrogen treatment. A recent study utilizing skin calipers to measure the skin thickness over the middle metacarpophalangeal joint showed that estrogen users had thinner skin than never-users. Similar to estrogen's effects on collagen levels, observable benefits of estrogen on skin thickness are inversely proportional to initial thickness values, and therefore it is not surprising that treatment of early menopausal women did not result in significant changes⁵³.

Elasticity and distensibility

The mechanical properties of skin can be defined and quantitated by extensibility and elasticity measurements using computerized devices. Aging in skin, in particular the face, is associated with a progressive increase in extensibility and a reduc-

tion in skin elasticity. The influence of climacteric aging on rheologic qualities of skin was quantitated using a non-invasive computerized suction device in a recent study by Pierard-Franchimont and colleagues⁵⁴. These authors monitored changes in the tensile properties of skin on the upper part of the cheeks of 140 early-menopausal women over 5 years. They found that, in the absence of HRT, distensibility in the facial skin increased by 1.1% per year and elasticity decreased by 1.5% per year, in agreement with other reports^{55,56}. The women enrolled in the study who were given HRT for 5 years experienced little change in skin extensibility and elasticity, in support of earlier findings that HRT can mitigate age-related changes in tensile properties^{55,56}. Recently, a small ad hoc study involving women aged 45–68 years (mean age, 54.9 years) followed the effect of HRT on rheologic measures for 6 months³². Significant increases in elasticity were observed for both transdermal and oral estrogen preparations. A recent study by Sumino and colleagues indicated that HRT increased forearm skin elasticity in postmenopausal women. Postmenopausal subjects receiving conjugated equine estrogen increased their forearm skin elasticity by 5.2%, while controls lost 0.55% skin elasticity over 12 months⁵⁷. Conjugated equine estrogen cream has also been shown to be beneficial for increasing skin thickness and reducing fine wrinkles, possibly due to the increased water content retained in the skin⁴⁸. Through its ability to limit age-related increases in cutaneous extensibility and to improve elasticity, HRT has been shown to exert a preventative effect on skin slackness commonly associated with aging⁵⁴.

Wrinkles

The normal age-associated loss of connective tissue in skin results in increased distensibility, and loss of tonicity is accompanied by a progressive deepening of facial creases and wrinkling. The documented association between HRT and increases in collagen content and elasticity suggest HRT would be expected to decrease wrinkling. However, due to technical challenges in quantitating a visual endpoint such as facial wrinkles, few clinical studies have specifically examined HRT and facial wrinkling.

Several observational studies have reported that postmenopausal women treated with estrogen are less wrinkled than untreated women^{35,58}, although, in one study, improvement with HRT was only observed in non-smokers⁵⁸. In NHANES

I, a cross-sectional analysis of a national probability cohort, the effects of estrogen use on wrinkling were ascertained in close to 4000 postmenopausal women aged 40 years and older at baseline³⁴. Among all women in the NHANES I cohort, after adjustment for age, body mass index and sunlight exposure, the odds of wrinkling were substantially lower in estrogen users (odds ratio, 0.68, 95% confidence interval 0.52–0.89). Results from clinical trials are inconclusive. As opposed to number of pregnancies and menopausal age, HRT use has been shown to lower the risk of facial wrinkling as assessed by an eight-point photographic scale⁵⁹. Optical profilometry and computerized image analysis have been used to demonstrate that topical HRT on the face can improve fine wrinkling⁵² and significantly decrease wrinkle depth²¹ within 2 months of treatment. A more recent study assessed the tensile functions of facial skin over 5 years of HRT compared to a group of controls. A computerized suction device measuring facial skin distensibility, viscosity and elasticity showed that HRT helped to mitigate the effects of climacteric ageing⁶⁰. However, others have used similar techniques and failed to demonstrate changes in facial wrinkling with HRT³⁴.

Blood flow

Healthy skin requires integrity in both the structure and function of capillary blood vessels, and cutaneous circulation is important in humans in maintaining core temperature homeostasis. The effect of estrogen on the cutaneous circulation of women has not been well studied. Consistent with the formation of premenstruation edema in women, cutaneous blood flow has been shown to vary over the course of the menstrual cycle²⁹. In addition, peripheral microcirculation at the level of the nail-fold capillaries has been shown to decrease significantly with menopause⁶¹.

Estrogens are known to substantially improve both endothelium-dependent and -independent vascular reactivity in the cutaneous microcirculation of postmenopausal women^{62,63}. Studies measuring the effect of HRT on blood flow rates, however, are somewhat inconsistent. A 6-month study utilizing laser Doppler velocimetry on the foot dorsum indicated that HRT users had a lower venoarteriolar reflex, indicating that HRT did not impair supine cutaneous microcirculation or post-ischemic hyperemia⁶⁴; while some have demonstrated that 6–12 months of HRT use increases capillary blood flow in the nail-fold by as much as

20–30%⁶¹, others have reported that long-term estrogen therapy (> 2 years) does not increase cutaneous vascular flow when compared with untreated women⁶⁵.

EFFECT OF ESTROGEN ON WOUND HEALING

The effects of intrinsic aging on cutaneous wound healing are profound. Age-related skin changes include increased susceptibility to trauma, resulting in fragile skin that tears and bruises easily. In addition, chronic wounds commonly suffered by the elderly – venous ulcers and pressure sores – inflict significant suffering and cost, and they impose a burden for physicians and patients alike⁶⁶. The role of estrogen and/or progesterone in age-related decreases in wound healing is poorly understood. Historically, the vast majority of research in wound healing has used animal models and has produced inconclusive results. More recently, limited data from molecular and human studies appear promising.

Preclinical studies on estrogen and wound healing

The initial phases of cutaneous wound healing involve vascularization, granulation, collagen deposition, and re-epithelialization⁶⁷. An early study by Lindhe and colleagues⁶⁸ found estrogen injections did not affect the vascularization of wound areas in oophorectomized rabbits. These data are in agreement with studies in various other animal models that show estradiol alone has no effect on vascularization^{69,70}, but contrast a large study in oophorectomized rats that used similar microangiographic techniques to observe a significant suppression in vascularization in estrogen-treated animals⁷¹. Examination of wound vascularization after treatment with estrogen in combination with a progesterone has also produced inconclusive results. While two studies report that estradiol given in conjunction with progesterone decreases vascular exudation during the inflammatory phase of wound healing⁷², others have found no effect^{73,74}. Recent molecular research on the influence of estrogen on the cells and vasculature involved in the inflammatory phase of wound repair suggests that estrogen may reduce the cellular activation of blood platelets and may affect phagocytic activity of neutrophils⁶⁶. Reduced estrogen levels have adverse effects on the inflammatory reaction. Hypoestrogenemia has been associated with impaired cytokine signal

transduction, unchecked in inflammation and altered probic balance, which may have a major impact on wound healing⁶⁹. A direct association with postmenopausal estrogen treatment and the inflammatory phase of wound healing remains to be investigated.

The majority of studies on estrogen's effect on wound collagen deposition and strength have also utilized animal models. Estrogen treatment has been shown to increase collagen deposition in wounds of oophorectomized rats^{73–75} and rabbits⁷³; however, others have found that systemic estrogen exerts either no effect^{70,76,77} or decreases collagen deposition^{78,79}, depending on dose and time since wounding. Similarly, estrogen given in conjunction with a progesterone has been shown to either have no effect⁷⁹ or to decrease collagen in wound granulomas^{71,79}; the effect again can depend on the time since wounding⁷⁹. Consistent with the findings for collagen deposition, measures of wound tensile strength in animals have produced varied results^{74,79,80}.

There is very limited information from animal studies on how any effects of hormone treatment translate into wound healing rates. One early study in young and senescent rats found that estrogen injected at low doses (0.33–1 µg/kg) improved wound healing time, but higher doses (3.3–10 µg/kg) prolonged healing time⁸⁰. Further, a study in oophorectomized rats showed that prolonged loss of ovarian hormones is associated with slow wound contraction⁸¹, but these authors did not examine the effect of systemic estrogen treatment. In general, investigations with animals demonstrate contradictory findings as to the effect of estrogen levels on the stages of wound healing. These discrepancies are likely due to differences in species, duration of treatment and methodologies employed⁶⁷.

Clinical and molecular studies on estrogen and wound healing

Some of the more recent work on wound healing has examined the molecular role of estrogen on the cells and metabolic processes involved in wound repair. For example, age-related delays in wound healing have been partially attributed to low levels of transforming growth factor-β1 (TGF-β1), decreased collagen synthesis and increased presence of proteases, specifically elastase. The presence of the estrogen receptor on the major cell type involved in wound repair (i.e. fibroblasts) suggests that estrogen may directly modulate the function of

these cells. Indeed, a study using wound biopsy specimens from healthy females suggests that estrogen exerts a positive influence on healing, not by increasing fibroblast proliferation within a wound, but rather by inducing TGF-β1 secretion by dermal fibroblasts⁸². In addition, clinical studies by Ashcroft and colleagues have demonstrated that estrogen has a beneficial effect on wound healing by increasing collagen content⁶⁶ and reducing collagenolysis⁶⁶. In one small study, ten postmenopausal women taking HRT were compared with age-matched controls⁸². The women underwent two 4-mm biopsies from the upper inner arm; healing was monitored. Hormone replacement therapy use was associated with significantly accelerated wound healing. In addition, a randomized, double-blind study of elderly males and females demonstrated that topical estrogen reduces activity of the protease elastase in cutaneous wounds when compared with placebo⁶⁶. Decreased elastase would stimulate matrix deposition and allow for faster wound healing. Indeed, that same study observed that topical estrogen applied to normal elderly skin prior to wounding and 24-h post-wounding significantly accelerated wound healing in both males and females⁶⁶. Data on wound healing in humans are very limited but promising, and further work is necessary before valid conclusions can be drawn regarding the use of HRT and wound-healing properties of skin. Data have demonstrated that estrogens may prevent the age-related decline in skin collagen, may increase the water-holding capacity, enhance the epidermal barrier function and decrease alterations in elasticity of the skin. Cumulatively, these results suggest that older women who use HRT may have healthier skin than non-users and may be at lower risk for the development of dermatoses³¹ such as ecchymosis.

ESTROGENS AND HAIR

Hair growth is influenced by the hormonal milieu. High levels of estrogen during pregnancy encourage hair growth. It has been shown that the estrogen-receptor pathway regulates the telogenanagen follicle transition under the influence of estrogens⁸³. 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.

Hair loss has been associated with the onset of the menopause. A particular form of hair loss, frontal fibrosing alopecia, is a variant of lichen planopilaris and has been associated with the postmenopausal phase. Hormonal therapy for this condition has been tried; however, the hair loss appears to persist despite hormonal treatment⁸⁴.

Hormonally related alopecia is characteristically seen in women with androgen-producing tumors. Androgenic alopecia may also occur in genetically susceptible individuals. The predominance of androgens associated with hair loss is emphasized by the indirect mode of action on the hair follicle by the sex steroids. Immunohistochemical staining techniques reveal a paucity or reduction of estrogen and progesterone receptors in the hair follicle, contrasting with a high concentration of androgen receptors⁸⁵.

SKIN COLLAGEN, AGING AND ESTHETICS

Older skin is affected by three main factors: chronologic aging, estrogen deficiency and photoaging. Hormone replacement therapy is known to reverse the effects of estrogen deficiency, but it has no effect on the changes due to photoaging such as solar lentigines (liver spots) or telangiectasias, which are due to repeated exposures to ultraviolet light.

During the aging process, both the collagen content and the production of GAGs in connective tissue decrease. With increasing age, the enzyme responsible for collagen breakdown, procollagen lysylhydroxyproline transferase, is found in higher intracellular concentrations⁸⁶. Collagen type I imparts toughness and moderate elasticity, which are important functions of the skin dermis. GAGs are hydrophilic and responsible for the dermal water content. The dermis obtains a certain level of turgor this way, protecting it against excessive tissue compression whilst maintaining the suppleness of the skin.

The loss of the connective tissue component and the GAGs of the dermis leads to increased rigidity and diminished elasticity. The resultant skin aging of the face in particular is characterized by a progressive increase in extensibility associated with a loss of elasticity. The resultant effect is wrinkling, dryness and atrophy. The loss of turgor is accompanied by a progressive deepening of facial creases⁵⁴. Computerized measurements of skin deformability and visco elasticity have revealed a steep increase in skin extensibility in untreated perimenopausal women⁵⁵. The Na-

tional Health and Nutrition Examination Survey indicated that these skin characteristics may be partially reversed in women by estrogen³⁵. Estrogen replacement therapy appears to limit the age-related increase in cutaneous extensibility, therapy exerting a preventive effect on skin slackness. Hormone replacement therapy has been shown to limit the number and depth of wrinkles as assessed by optical profilometry and computerized image analysis⁵⁶.

The maximum prevention of skin aging appears to occur if estrogens are started early. Smokers are known to develop a high wrinkle score, which has not been shown to respond to estrogen replacement therapy⁸⁷.

ACNE AND WOUND HEALING

Sex steroids have also been used for the treatment of atrophic acne scars. Estriol iontophoresis indicated photographic and clinical improvement of acne scars. This method may replace the current more invasive treatments such as dermabrasion, chemopeeling and bovine collagen implantation⁸⁸.

Wound healing may also be influenced by the hormonal status of a woman. Older women have been shown to heal less well. This has been attributed to the low levels of transforming growth factor (TGF)- β . Preclinical studies indicated that TGF- β increased with the administration of hormone replacement therapy. There appears to be an estrogen-induced increase in latent TGF- β secretion by dermal fibroblasts affecting the rate and quality of wound healing⁸⁹.

SKIN CANCERS AND SEX STEROIDS

The presence of estrogen receptors in some skin tumors has led to several studies assessing the association between sex hormone status and cutaneous malignancies. Estrogen-receptor positivity has been demonstrated in most skin tumors by both histochemical and biochemical assays⁹⁰. Cutaneous melanoma cytosol appears to contain a high-affinity low-capacity receptor for estrogen⁹¹. Estrogens have been shown to influence melanocyte pigment formation⁹². Several aspects of melanocyte function respond directly to estrogenic stimulation. Melanin synthesis and extrusion were increased by estrogens. This response may be via a non-classical mechanism similar to that in other tissues of neural crest origin, since it has been shown that both an estrogen and a 'pure' anti-estrogen had equivalent results. Several lines of

biological evidence have suggested a relationship between malignant melanoma and estrogens⁹³. However, the low frequency of estrogen receptivity of malignant melanomas appears to preclude the use of estrogen-receptor status for hormonal manipulation in the treatment of these tumors. Although estrogen-receptor status may not be of clinical use in the management of malignant melanomas, epidemiological data clearly show a survival benefit for female patients with this type of skin cancer⁹⁴.

Nevertheless, the evidence linking female sex hormones with malignant melanoma has been contradictory. In one study⁹⁵, the assessment of exogenous and endogenous hormonal variables has shown that women with melanoma compared to controls were twice as likely to have been pregnant, while the menopause and body mass index acted as interactive factors. Women with melanoma were three times more likely to be obese and report a natural menopause. It thus appears that melanoma cannot be regarded as a contraindication for hormone replacement therapy, with the very rare exception of melanotic adenocarcinoma of the uterus⁹⁶.

Other rare tumors of the skin may also be influenced by sex steroids. Sex steroids may affect epidermal growth factor metabolism, changing the biological behavior of seborrheic keratosis and acrochondrons in patients with dysplastic nevus syndrome⁹⁷. Mammary tissue is histogenetically related to sweat glands. In fact, cutaneous mucinous carcinoma shows strong similarities to its mammary counterpart, including the expression of the estrogen receptor. It has been suggested that some skin mucinous carcinomas may respond to anti-estrogenic therapies⁹⁸.

Some cutaneous vascular tumors, by virtue of the presence of estrogen receptors, may also be affected by sex steroids⁹⁹. Hemangiomas, the rare angiofibroma and other myxoid neoplasias of the skin may be influenced by the hormonal status of the patient. The increased concentration of estrogen receptors in the female genital region is suggested, as angiofibroma is more common in this site, and overall is more common in women¹⁰⁰.

FUTURE DIRECTIONS

The technology now exists to further explore the molecular basis of estrogen's role in maintaining skin integrity. Using gene-chip microarray techniques, estrogen-responsive genes in skin can be identified, characterized, and monitored under

varying hormonal conditions. Determining the estrogen sensitivity of enzymes responsible for the production and/or degradation of structural components of the skin, such as GAGs or collagen and elastin fibers, will substantially enhance our understanding of the mechanistic role of estrogen in skin.

When biochemical and histologic parameters for estrogen-sensitive structures in skin have been established at the molecular level, a correlation between these markers, estrogen status and physical attributes of skin needs to be carefully investigated and quantitated in large, randomized, placebo-controlled trials. In addition, larger, controlled clinical trials of HRT use and visible measures of skin, such as the assessment of wrinkles, are necessary. Large trials involving HRT and skin should take into consideration patients' evaluation of changes related to their skin appearance, and they should factor patient satisfaction into any perceived benefit of treatment.

CONCLUSIONS

In addition to chronologic age and environmental factors, menopause and the accompanying estrogen loss are known to have a profound impact on skin. However, the effects of ERT on the skin of older women have garnered relatively little clinical attention.

Estrogen treatment in postmenopausal women has been repeatedly shown to increase collagen content, dermal thickness, and elasticity. Preclinical and clinical data on the effect of estrogen on skin water content are also promising. Physiologic studies on estrogen and wound healing suggest that HRT may play a beneficial role in cutaneous injury repair; however, molecular studies have yet to articulate the mechanisms. Differences on other structural and physiologic characteristics of skin with HRT are limited, and results are somewhat discordant due to differences in protocol, hormone regimen and assessment measures.

Careful examination of the molecular effects of estrogen on skin parameters is necessary. In addition, research is needed to identify any correlation between quantitative measures of skin characteristics and observed manifestations in skin appearance. Further large-scale, clinical trials are also required in order for physicians to make informed recommendations regarding postmenopausal estrogen use and its potential application to skin care. The large, randomized, controlled Women's Health Initiative (WHI)¹⁰¹, which re-

cently reported preliminary results indicating that benefits of HRT for prevention of chronic diseases did not outweigh potential risks (mean follow-up, 5.2 years), did not address the effects of estrogen on skin or sexual health, both of which are highly important to women entering menopause. Because the average age of WHI participants at baseline was 63 years, it is possible that early initiation of HRT after menopause may be associated with a different risk/benefit profile, including potential benefits on skin. While health professionals will

likely continue to emphasize the use of estrogen to relieve menopausal symptoms, the potential effects of estrogen on the skin deserve more attention and may prove meaningful to the target population of postmenopausal women.

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