Effect of estrogens on skin aging and the potential role of selective estrogen receptor modulators

S. Verdier-Sévrain

Bio-Hybrid, LLC, West Palm Beach, Florida, USA

Key words: SKIN AGING, HORMONE REPLACEMENT THERAPY, TOPICAL ESTROGEN, PHYTOESTROGENS, SELECTIVE ESTROGEN RECEPTOR MODULATORS

ABSTRACT

Estrogens have a profound influence on skin. The relative hypoestrogenism that accompanies menopause exacerbates the deleterious effects of both intrinsic and environmental aging. Estrogens prevent skin aging. They increase skin thickness and improve skin moisture. Beneficial effects of hormone replacement therapy (HRT) on skin aging have been well documented, but HRT cannot obviously be recommended solely to treat skin aging in menopausal women. Topical estrogen application is highly effective and safe if used by a dermatologist with expertise in endocrinology. The question of whether estrogen alternatives such as phytoestrogens and selective estrogen receptor modulators are effective estrogens for the prevention of skin aging in postmenopausal women remains unanswered. However, preliminary data indicate that such treatment may be of benefit for skin aging treatment.

INTRODUCTION

There are approximately 40 million postmenopausal women in the United States, contributing to 17% of the total population. As the population of older women continues to grow at a rapid rate, the challenges of learning more about the health-care concerns and priorities of this group of patients become apparent. The skin is one of the largest organs of the body in which aging-related changes are visible and women are concerned by the deterioration of their skin’s appearance. Skin aging is influenced by genetic, environmental and hormonal factors. Numerous reviews have adequately described the difference between normal cutaneous aging, due to the passage of time, and damage from solar exposure. The prior is referred to as intrinsic aging, and the latter as photoaging.

Intrinsic aging is characterized by smooth, pale, finely wrinkled skin and dryness. Photoaging is characterized by severe wrinkling and pigmentary changes such as solar lentigo and mottled pigmentation. Estrogens affect several skin functions and the estrogen deprivation that accompanies menopause contributes to, and exacerbates, the deleterious effects of age on the skin. Since its first use in the 1940s, systemic estrogen therapy has been known to have an obvious, visible effect on the skin and to be efficient in combating the phenomenon of skin aging.

In this article, we review the effects of estrogen on skin biology and particularly its ability to prevent skin aging. We examine the role of estrogen therapy in skin aging treatment,
discussing successively the indications of hormone replacement therapy (HRT), topical estrogen treatment, and new drugs called selective estrogen receptor modulators (SERMs).

**BIOLOGY OF ESTROGENS IN SKIN**

Estrogens affect several skin functions such as elasticity\(^6\), water-holding capacity\(^7\), pigmentation\(^8\) and vascularity\(^9\). Estrogens prevent skin aging by influencing skin thickness, skin wrinkling and skin moisture\(^10\). Not just the skin but also skin appendages, such as hair follicles, are influenced by estrogens\(^11\).

**Estrogen effects on skin thickness and collagen content**

Collagen is a main constituent of the skin and provides the major support for skin resistance. It was first noticed in 1941 by Albright and colleagues\(^12\) that postmenopausal women with osteoporosis had skin that was noticeably atrophied. Then, Brincat and colleagues\(^13\) demonstrated that there was a decrease in skin thickness and skin collagen content, corresponding to a reduction in bone mineral density, in the years following menopause, particularly in the initial postmenopausal years. More recently, Affinito and colleagues\(^14\) showed that skin collagen decline was closely correlated to years following menopause. They showed that postmenopausal women had decreased amount of types I and III collagen, as well as a decreased type III/I ratio in comparison to premenopausal women. With the correlation noted between skin collagen decline and postmenopausal years, studies have attempted to decipher the effects of estrogens on skin collagen. Several controlled studies have reported that estrogen therapy had a beneficial effect on collagen content and skin thickness\(^15\)–\(^19\) (see Table 1).

**Estrogen effects on skin moisture**

The ability of the skin to hold water is related to the stratum corneum lipids which play a predominant role in maintaining the skin barrier function\(^20\) and also to the dermal glycosaminoglycans, which have a high water-holding capacity\(^21\).

It has been demonstrated that postmenopausal women who were not taking hormone replacement therapy were significantly more likely to experience dry skin compared with those postmenopausal women taking estrogen\(^22\). Pierard-Franchimont and colleagues\(^7\) showed that transdermal estrogen therapy leads to significantly increased water-holding capacity of the stratum corneum, suggesting that estrogen may play a role in the stratum corneum barrier function. Denda and colleagues\(^23\) demonstrated changes in the stratum corneum sphingolipids with aging and suggested a possible hormonal influence. Estrogens also affect dermal water-holding capacity: studies in animal\(^24\) have demonstrated marked increases in glycosaminoglycans within 2 weeks of estrogen therapy and studies in human\(^25\) have shown estrogens to increase dermal hydroscopic qualities.

**Estrogen effects on skin wrinkling**

Wrinkles are modifications of the skin associated with cutaneous aging, appearing preferentially on

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of measurement</th>
<th>Hormones used</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Castelo-Branco et al.(^15)</td>
<td>skin biopsy analysis</td>
<td>conjugated equine estrogens or transdermal 17(\beta)-estradiol</td>
<td>increase in skin collagen of 1.8–5.1% after HRT for 12 months</td>
</tr>
<tr>
<td>Callens et al.(^16)</td>
<td>skin thickness measured by ultrasonography</td>
<td>17(\beta)-estradiol gel or estradiol patches</td>
<td>increase in skin thickness of 7–15%</td>
</tr>
<tr>
<td>Maheux et al.(^17)</td>
<td>skin thickness measured by ultrasonography</td>
<td>conjugated estrogen 0.625 mg</td>
<td>increase in skin thickness by 11.5% after HRT for 12 months</td>
</tr>
<tr>
<td>Sauerbronn et al.(^18)</td>
<td>skin biopsy analysis</td>
<td>valerate estradiol and cyproterone acetate topical 17(\beta)-estradiol</td>
<td>increase in dermis collagen content of 6.49%</td>
</tr>
<tr>
<td>Varila et al.(^19)</td>
<td>skin biopsy analysis</td>
<td></td>
<td>increase in hydroxyproline by 38% after treatment for 3 months</td>
</tr>
</tbody>
</table>

HRT, hormone replacement therapy
sun-exposed areas (actinic aging). Moreover, they can be increased by various intrinsic (heredity, ethnic, hormonal and pathological) or extrinsic factors (irradiation, pollution, temperature, humidity). Histological studies of wrinkles have shown alterations of dermal component with atrophy of dermal collagen, alterations of elastic fibers and marked decrease in glycosaminoglycans\textsuperscript{26}. Creidi and colleagues\textsuperscript{27} showed that a conjugated estrogen cream applied to the facial skin of postmenopausal women resulted in significant improvement in fine wrinkles, as clinically evaluated by dermatologists. Dunn and colleagues\textsuperscript{22} pointed out that postmenopausal women using estrogen were significantly less likely to develop skin wrinkles. As noted earlier, estrogens cause an increase in collagen and glycosaminoglycans in the dermis\textsuperscript{15,24}, which may explain the decrease in skin wrinkling with estrogen treatment. Decreased skin elasticity has been demonstrated in women after menopause\textsuperscript{28}, and changes in the skin elastic fibers have also been reported after application of estriol ointments to the skin of postmenopausal women\textsuperscript{29}.

### Estrogen effects on hair growth

Hair growth encompasses three stages, all known to be influenced by estrogens: growing (anagen), structural regression (catagen) and resting (telogen)\textsuperscript{30}. High systemic estrogen levels during pregnancy prolong the anagen phase of the hair follicle, and the pluming estrogen levels postpartum are thought to cause this excess number of anagen follicles to enter the telogen phase simultaneously, sometimes resulting in clinically significant hair loss, the so-called telogen effluvium \textsuperscript{35}. Androgenetic alopecia also known as female pattern alopecia, is the most common hair loss in women and is most frequently observed after menopause\textsuperscript{32}, suggesting a role of estrogens or the estrogen:androgen ratio. In men, androgenetic alopecia is a dihydrotestosterone-mediated process, characterized by continuous miniaturization of androgen-sensitive hair follicles\textsuperscript{33}. Indeed, it is usually treated with systemic antiandrogens such as cyproterone acetate\textsuperscript{34} in women, or steroidalgenic enzyme inhibitors such as finasteride\textsuperscript{35} in men. Topical estrogen is also used as treatment in women, especially in Europe\textsuperscript{36}. The mechanism involved in estrogen-mediated induction of hair growth in androgenetic alopecia is not well understood. Some studies have shown an increased anagen and decreased telogen rate after estrogen treatment, as compared to placebo\textsuperscript{37}.

Niiyama and colleagues\textsuperscript{38} have demonstrated the ability of estrogen to modify androgen metabolism in dermal papillae of hair follicles.

### MOLECULAR MECHANISMS OF ESTROGEN EFFECTS IN SKIN

Estrogens regulate cell function by binding two nuclear receptors: the estrogen receptor-alpha (ER-\textalpha) and estrogen receptor-beta (ER-\textbeta)\textsuperscript{39}. In addition, the existence of a cell-surface form of estrogen receptor (membrane estrogen receptor) has been recently demonstrated\textsuperscript{40}. The mechanism of estrogen action in skin is not well known and there are still some controversies regarding the expression of ER-\textalpha and ER-\textbeta. Thornton and colleagues\textsuperscript{41} found that ER-\textbeta is the predominant receptor in skin. Others\textsuperscript{42} found that both receptors are expressed and demonstrated the existence of a membrane receptor in the epidermis.

### ESTROGEN THERAPY FOR SKIN AGING

#### Hormone replacement therapy

HRT consists of two components: estrogen and progestogen. The use of estrogen alone (unopposed estrogen) is associated with an increased risk of endometrial hyperplasia and/or carcinoma. In order to avoid this effect, in women with intact uterus and treated with estrogens, progestogens should be used to protect the endometrium. As the estrogen component, natural 17\beta-estradiol is often used in Europe, whereas the conjugated equine estrogen (CEE) derived from pregnant mare’s urine is the preferred product in the US.

HRT carries a small increased risk of serious complications, and the risk increases with duration of the therapy. Recently, recognized experts have provided practical guidelines for postmenopausal HRT and have reviewed the risk of complications\textsuperscript{43–46}. Endometrial cancer occurs up to four times more frequently in women with a uterus who take unopposed estrogen than in non-users. The risk may be reduced by adding a progestogen. Breast cancer risk increases slightly with HRT prescribed longer than 5 years. Venous thromboembolism is rare but increases with estrogen use.

The indication for HRT is the treatment of menopausal symptoms (hot flushes, sweating, insomnia, fatigue, depressed mood and urogenital atrophy). The dose and regimen of HRT need to be individualized, based on choosing the lowest
appropriate dose in relation to the severity of symptoms and on the menopausal age. The standard higher doses used in the past (0.625 mg CEE or 2 mg 17b-estradiol) are not recommended today. Lower-dose HRT (0.3 mg CEE or 1 mg 17b-estradiol) has been shown to be effective and minimizes the side-effects47. Usually, after 3–4 years of hormonal treatment, it is possible to stop HRT with no recurrence of menopausal symptoms. Currently, experts believe that limited, short-term use of HRT (<5 years) administered in the early phase of menopause is relatively safe among healthy women48. Long-term HRT may be appropriate if symptoms persist. In this case, appropriate counseling on the risks and benefits of long-term HRT should be provided. HRT can offer long-term benefits in the central nervous, cardiovascular and skeletal systems. Specifically, it has been demonstrated that HRT is very effective at preventing osteoporosis49. However, there are still controversies about the long-term use of HRT because of the risk of breast cancer with prolonged use of estrogens. In patients at high risk of osteoporosis and fracture, osteoporosis prevention should be continued independently of management of menopausal symptoms, using alternatives to HRT such as selective estrogen receptor modulators (SERMs).

Beneficial effects of HRT on skin aging have been documented by several studies. An analysis of a large cohort of 3875 postmenopausal women aged 40 and more showed that HRT prevents dry skin and wrinkling. Women under long-term substitution had one-third fewer wrinkles than non-substituted patients22. A pilot study of 24 menopausal women examined the effects of different regimens of HRT on skin aging50. Patients were assigned to three groups: transdermal estrogen only (Estraderm TTS® 50), transdermal estrogen and progesterone (Estraderm TTS® 50 and 0.4 mg progesterone vaginal suppository), and oral estrogen and progesterone (2 mg Progynova and 0.4 mg progesterone vaginal suppository). One group served as control. Treatment was continued for 6 months. Epidermal moisture, skin elasticity and skin thickness were significantly improved in all treated groups. A comparison of epidermal hydration and skin elasticity revealed no significant differences between ultraviolet-exposed and non-exposed measurements sites, suggesting that both intrinsic and photoaging may be improved by HRT.

A leading parameter of skin aging is skin thickness, which reflects the status of collagen tissue. As previously reviewed, many studies have demonstrated beneficial effects of HRT on skin collagen content (Table 1). HRT also affects skin elasticity; it has been reported that HRT limits the age-related increase in cutaneous extensibility, thereby exerting a preventive effect on skin slackness6. Despite such beneficial effects of HRT on skin aging, HRT cannot obviously be recommended solely to treat skin aging in menopausal women. Prevention of skin aging with HRT should be regarded as an additional benefit for menopausal women who receive this treatment for other menopausal symptoms.

Topical estrogen treatment

Studies have showed that topical estrogen may prevent skin aging, as seen with HRT. Schmidt and colleagues12 examined the effects of 6-month treatment with topical 0.01% estradiol and 0.3% estriol on skin aging on the face of perimenopausal women. They found improvement similar to that seen in the studies using HRT. Both treatment groups showed increased skin moisture and improvement of elasticity and firmness of the skin with decreased wrinkle depth. No hormonal side-effects were noted, either clinically or by hormone monitoring. Serum hormone levels and the appearance of vaginal smears showed no significant change as compared to before treatment.

Creidi and colleagues27 examined the effect of a topically applied conjugated estrogen cream (Premarin® 0.625 mg/g of cream) in 54 women. After a 24-week treatment period, they found that Premarin cream produced better results than the placebo cream; the difference was statistically significant for skin thickness and fine wrinkles. Premarin cream was well tolerated locally. The general safety of Premarin cream was also excellent; no women had any serious drug-related study events. However, in contrast to the previous study, a modification of the vaginal maturation index was seen in women using the Premarin cream, demonstrating that the CEE has permeated the skin and exerted its effect on the vaginal mucosa. Indeed, it is known that CEE and 17b-estradiol differ in their total estrogenic potency, with CEE possessing greater estrogenic potency48. This suggests that estradiol creams may provide a safer therapy for skin aging compared to CEE creams, since they seem not to induce systemic effects.

It is clear that topical estrogen is an effective treatment for skin aging. Menopausal women
who are not receiving HRT and who do not have any contraindications to HRT would be candidates for topical estrogen therapy.

Since studies have demonstrated a sharp decline in skin thickness and collagen in the years following menopause, particularly in the initial postmenopausal years, it would be critical to begin the treatment within the first postmenopausal years. Additional studies are needed to definitively demonstrate the safety of this treatment. Further investigations should determine the highest effective concentration of estrogens that can be used without the risk of possible systemic side-effects. Based on previous work on the use of topical estrogen for vaginal atrophy in postmenopausal women, it is expected that a short-term use of topical estrogen (<5 years) should prevent skin aging without serious risks. Indeed, recent studies have demonstrated the efficacy and safety of a low dose of 17β-estradiol for postmenopausal vaginal atrophy. Neither systemic estradiol increases nor estrogenic side-effects (endometrial hyperplasia) have been observed with this treatment. The choice of the form of estrogen is also important: as previously discussed, CEE, which possesses a greater estrogenic potency than 17β-estradiol, may induce systemic side-effects. Estriol, a low-potency estrogen that has considerably lower affinity for the estrogen receptor, is commonly prescribed in Europe for topical treatment of menopausal urogenital symptoms. This treatment has been demonstrated to be safe, with no increase risk of endometrial hyperplasia and so may be useful for topical treatment of skin aging.

Such topical estrogen treatment for skin aging will need to be administered by a dermatologist experienced in endocrinology, given that concentration and application areas must be observed in order to avoid systemic side-effects.

Selective estrogen receptor modulators
SERMs act at the level of the estrogen receptor; they bind to ER-α and ER-β. They appear to have either estrogenic or antiestrogenic effects, depending on the tissue. In some tissues such as bone, they mimic the effects of estrogen, while in others they act as antiestrogens and block unwanted estrogenic effects on uterine and breast tissues. Because of this tissue specificity activity, SERMs are potentially a versatile drug class that offers the prospect of developing individualized, targeted treatments for menopause-associated morbidity. SERMs and estrogen agonist molecules that are currently available and currently in development are shown in Table 2.

The question of whether estrogen alternatives such as phytoestrogens and SERMs are effective estrogens for the prevention of skin aging in postmenopausal women remains unanswered. However, preliminary data indicate that such treatment may be of benefit for skin aging treatment.

**Effects of phytoestrogenic SERMs on skin aging**

Phytoestrogens are plant-derived molecules that structurally resemble endogenous estrogens, containing a diphenolic chemical structure that can directly bind to estrogen receptor. They have a relative greater affinity for ER-β than for ER-α. Phytoestrogens exhibit some estrogen agonist-like properties but can also act as partial estrogen receptor antagonists. Because of their mixed agonist/antagonist estrogen receptor profile, phytoestrogens have received considerable attention as potential alternatives to estrogen. Studies have demonstrated that genistein may prevent photoaging in human skin. Other studies have reported that genistein and daidzein stimulate hyaluronic acid production in human keratinocyte culture. A recent European study had examined the effect of a cosmetic cream preparation including isoflavone (Novadiol®) in 234 postmenopausal women and had showed improvement in skin dryness and wrinkles after 12 weeks of treatment.

**Effects of SERMs on skin aging**

An effective SERM for the skin would exert estrogen agonist action in skin and estrogen antagonist action in breast and uterus. The ideal SERM for skin would also exert estrogen action in brain, bone and in the vagina. Among different SERMs currently available or under development, only raloxifene has been studied for its effects in skin. Raloxifene is used in prevention and treatment of postmenopausal osteoporosis. It also decreases the risk of breast cancer and does not stimulate the endometrium. Recent studies have demonstrated that raloxifene exerts stronger stimulative effects on collagen biosynthesis than estradiol in human skin fibroblasts and might reverse some of the postmenopausal changes in skin.
Table 2  Selective estrogen receptor modulators (SERMs) currently available or under development

<table>
<thead>
<tr>
<th>Triphenylethylene derivatives</th>
<th>Benzothiophene derivatives</th>
<th>Dihydronaphthalene derivatives</th>
<th>Tetrahydronaphthalene derivatives</th>
<th>Benzopyran derivatives</th>
<th>Pure steroidal antiestrogens</th>
<th>Phytoestrogens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamoxifen (Nolvadex®, Zeneca Pharmaceuticals)</td>
<td>raloxifene (Evista®, Eli Lilly)</td>
<td>trioxifene</td>
<td>lasofoxifene (Pfizer)</td>
<td>levormeloxifene</td>
<td>ICI 182,780 (fulvestrant Faslodex®)</td>
<td>genistein</td>
</tr>
<tr>
<td>4-Hydroxy-tamoxifen (active metabolite of tamoxifen)</td>
<td>arzoxifene (LY353,380-JCI, Eli Lilly)</td>
<td>nafoxidene</td>
<td></td>
<td></td>
<td>ICI 164,384</td>
<td>genistein</td>
</tr>
<tr>
<td>Toremifene (Fareston®)</td>
<td>zinoxifene</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ospemifene (FC-1271a) (active metabolite of toremifene)</td>
<td>ZK 119010</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Droloxifene</td>
<td>ERA-923</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clomifene (Clomid®, Seraphene®)</td>
<td>bazedoxifene (Wyeth)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miproxifene phosphate (TAT-59)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Idoxifene</td>
<td>GW 5638</td>
<td>GW 7604</td>
<td>MDL-103,323</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ospemifene (active metabolite of EM800)</td>
<td>EM800 (SCH57050)</td>
<td>EM652</td>
<td></td>
<td></td>
<td>RU 39411</td>
<td>daidzein</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
CONCLUSION
The skin is an estrogen-responsive tissue. A better understanding of the hormonal regulation of skin physiology and skin aging may provide the basis for development of new hormonal treatment for skin aging. HRT cannot be recommended solely to treat skin aging in menopausal women but may be considered as an additional benefit in the treatment of menopausal symptoms. Topical estrogen application is highly effective and safe if used by a dermatologist with expertise in endocrinology. Phytoestrogens appear to be effective but their possible side-effects have not been well investigated. SERMs are drugs that offer exciting opportunities for the future treatment of skin aging but, while great strides have been made in developing effective SERMs for menopausal symptoms such as osteoporosis, the challenge of developing an effective estrogen alternative for skin aging treatment remains.

Conflict of interest The author declares having no conflict of interest capable of influencing her judgment.

Source of funding Nil.

References
19. Varila E, Rantalä I, Oikarinen A, et al. The effect of topical oestradiol on skin collagen of...


