SKIN

IN-DEPTH REVIEWS

Revisiting the Beneficial Effects of Estrogen on the Skin: A Comprehensive Review of the Literature and a Look to the Future

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ABSTRACT

The process of aging is associated with anticipated cutaneous changes such as epidermal thinning, dehydration, loss of barrier function, and decreased extracellular matrix components. These physiologic changes translate to clinical findings such as atrophy, pigmentary changes, and wrinkling. Over the past century, the role of decreased circulating estrogens in the process of cutaneous aging has been elucidated. Estrogen replacement, both systemic and topical, has been shown to have positive effects on aging skin by promoting fibroblast proliferation and increasing collagen density. However, despite these positive effects on skin health and appearance, estrogens also display a wide-range of actions on various other systems. Even topical estrogen application can result in unwanted systemic effects. Research into alternative substances such as soft estrogens—synthetic, non-hormonal molecules that produce local, cutaneous estrogenic effects and are then metabolized to inactive compounds prior to being absorbed into the systemic circulation— suggests that estrogenic-like benefits on aging skin could be harnessed safely, while avoiding the potential pitfalls associated with estrogen use.

INTRODUCTION

Medical advances and public health initiatives have led to a 62% increase in mean life expectancy over the course of the last century.[1] This significant improvement in lifespan has led to new challenges in addressing physiologic aging processes and treating diseases that are rarely encountered in younger individuals. Although all organ systems undergo change with increasing age, the integumentary system—given both its size and its exposure to the external environmental forces—is highly susceptible.

As the skin ages, its structure begins to change in predictable ways. Processes such as thinning of the epidermis[2] and decreased density of collagen and elastin fibers[3] lead to perceptible changes in appearance such as atrophy and wrinkling. It is increasingly apparent that hormonal changes play a significant role in this process. Observation of increased susceptibility to age-associated changes in the skin of post-menopausal women has led to understanding of the importance of estrogens in the maintenance of integumentary health and appearance.[4]

In this article, we review the historical observations that have led to the current understanding of estrogenic interaction with the skin, we summarize research detailing the positive effects of estrogen on aging skin, and we discuss the controversies related to the use of estrogen-containing compounds for skin rejuvenation. Finally, we discuss areas of active investigation aimed at devising novel, non-hormonal synthetic products that locally recapitulate the positive effects of estrogen while avoiding unwanted extracutaneous side effects.

HISTORICAL PERSPECTIVE

Anecdotal observations suggesting the importance of estrogens to skin health date back to at least the first decades of the 20th century, when it was commonplace for estrogen-containing products to be marketed as over-the-counter cosmetic facial creams.[5] Major changes were introduced when the Federal Food, Drug, and Cosmetic Act of 1938—brought about by concern over instances of injury and death related to use of consumer products—formally defined cosmetic products as those that do not alter structure or function of tissues.[6] Under this doctrine, creams and ointments containing hormones—formerly mainstay ingredients of over-the-counter products—were reclassified as drugs and placed under the jurisdiction of the FDA.

With increased regulation, widespread use of estrogen-containing topical products for skin rejuvenation predictably decreased. However, this created an impetus for formal and systematic investigation into the cutaneous effects of estrogens. As early as the 1940s, evidence linking application of topical estrogens to the reversal of age-related skin changes began to appear in the scientific literature. In an early experiment, Goldzieher extrapolated that the beneficial effects of estrogens on genital atrophy in post-menopausal women might apply to the skin more broadly.[7] He tested his hypothesis by treating the skin of five post-menopausal women with topical estrogen ointments, containing either estradiol or diethylstilbestrol (a synthetic nonsteroidal estrogen no longer in use due to its effects on the children of women exposed during pregnancy). After six weeks of treatment, biopsies of the treated individuals revealed thickening of the atrophic epidermis and increased hypodermal connective tissue—changes not noted from biopsies of three control individuals treated with a vehicle alone. These results led Goldzieher to conclude that application of topical estrogens might be useful for the reversal of age-related pathologic changes. These early findings demonstrating the effects of estrogens on integumentary structure were replicated by Eller and Eller three years later in a larger group of patients.[8]

Despite these promising early observations in human subjects, work in castrated mice provided contradictory data, with low-dose, short-duration estrogen therapy increasing epidermal thickness and high-dose, long-duration therapy paradoxically leading to acceleration of epidermal thinning.[9] In 1950, Dunaif and Finnerty showed that in ovariectomized mice, injections of low doses of estrogen slowed epidermal thinning whereas high-dose injections were associated with an exacerbation of the process, corroborating the earlier findings.[10]

These same researchers noted that topical application of estrogen resulted in increased epidermal proliferation, although lower topical concentrations produced a more profound positive effect than higher doses. These findings led Dunaif and Finnerty to hypothesize that estrogens act locally at the

skin to promote epidermal thickening, but that this effect is antagonized when higher systemic concentrations are achieved, possibly due to a secondary mechanism of action at a remote site.[10]

These early experiments laid the scientific foundation for the treatment of aging skin with estrogens. Subsequent work over the past several decades has continued to elucidate the mechanisms by which estrogenic compounds delay and reverse age-associated atrophy. Although not well understood at the time, many of the estrogenic effects on skin noted by these pioneer researchers are now thought to be related to the integumentary system's function as a peripheral endocrine organ—producing, altering, and responding to hormonal signals.

ESTROGEN, THE SKIN, & THE ENDOCRINE THEORY OF AGING

Although the primary functions of the skin have traditionally been barrier function, sensation, and temperature regulation, more recent research has begun to delineate the role of hormones (including estrogen) in influencing the structure and function of the skin. Additionally, the ability of the skin to manufacture and metabolize hormones has become increasingly apparent.[11] These observations have made clear the integument's role in the endocrine system.

The neuroendocrine theory of aging proposes that senescent processes are a result of naturally-occurring changes in the complex signaling network of the hypothalamic-pituitary-adrenal axis.[12] Resultant deficiencies in the communication between different organs involved in this system lead to structural changes, and in many cases, decreased functionality. Decreases in estrogen in particular have been implicated in age-related pathology in a variety of organ systems and appear to have an important impact on multiple components of the skin, as outlined previously.[13] The endocrine theory of aging, when considered in the context of the skin, offers an explanation as to why many of the skin-related changes often associated with aging (reduced elasticity, increased wrinkle formation, atrophy)[14] are accelerated after the onset of menopause.

Estrogen signaling represents a complex, incompletely understood pathway.[15] Multiple hormone receptors (ER-α and ER-β), which are differentially expressed in varying tissue types, respond to endocrine signals relayed by circulating estrogens.[15] Even within the environment of the skin alone, estrogen receptors are expressed in varying proportions by multiple skin cell types, including keratinocytes, fibroblasts, melanocytes, and cells of the epidermal appendages.[16]

Although a detailed explanation is beyond the scope of this review, it is important to understand that the underlying positive effects of exogenous estrogen administration on aged skin are likely related to replacing the endogenous signal that becomes diminished with increasing age (and is accelerated in women with the onset of menopause). The action of estrogenic molecules on their hormone receptors have varied and complex consequences on DNA transcription. [16]. It is this alteration in gene expression that presumably leads to the observed beneficial effects of estrogen on the skin: increased collagen and elastin concentrations, improved skin thickness, enhanced keratinocyte proliferation, and decreased inflammation (Table 1).

Table 1. Observed beneficial effects of estrogens on the skin.

Increased extracellular matrix components	Collagen[18-20,22] Elastin[2] Fibrillin[2]
Increased retention of moisture	Increased hyaluronic acid and mucopolysaccharides[3]
Increased thickness of cutaneous layers	Epidermis[23] Dermis[24]

EFFECT ON EXTRACELLULAR MATRIX

As the human body ages, the concentration of connective tissue components in the dermis, collagen and elastin, both diminish—a process greatly accelerated by menopause in females.[17] Decreased collagen leads to loss of firmness and also has potential implications for wound healing, while loss of elastin leads to decreased skin turgor.

Multiple studies have measured the effects of exogenous estrogen on skin collagen levels. Work by Brincat et al. in the 1980s demonstrated significantly increased collagen content in the skin of post-menopausal women treated with systemic estrogen/testosterone implants (48% greater than the untreated group, $p<0.01$)[18] and topical estradiol gel (increase in abdominal skin collagen content over 1 year treatment period, <0.001)[19]. These and other studies also provided evidence that local, topical therapy may be more efficacious in increasing skin collagen levels than systemic therapy.[20] This finding mirrors the earlier observations of Dunaif and Finnerty and provides support for the endocrine theory in the process of cutaneous aging.[10]

A study by Varila et al. measured the effects of topical estradiol treatment once daily for three months on the skin of the lower abdomen in 12 post-menopausal women, with contralateral skin being subjected only to vehicle application. Upon follow-up, blisters were induced and hydroxyproline (the principal component of collagen) and procollagen levels from the blister fluid were measured. The treated skin showed a 38% increase in hydroxyproline over the control skin ($p=0.012$) and also an increase in procollagen ($p=0.024$). Electron microscopy revealed increased density of collagen and elastin fibers.[21] Similar increases in expression of procollagen, tropoelastin, and fibrillin-1 mRNA have been seen in aged skin treated with topical 17β-estradiol.[2]

More recent investigations have also shown similar results with topical estradiol therapy. In 2017, Silva et al. performed a randomized trial comparing the effects of topical estradiol and genistein (a phytoestrogen) on the facial skin of 30 women. Biopsy revealed increased levels of Type I and Type III collagen compared to pre-treatment in both groups, although the increase in collagen concentration was significantly greater in the group treated with topical estradiol ($p<0.001$).[22] In addition to having a positive effect on extracellular collagen and elastin fibers, estrogenic action leads to increased concentrations of hyaluronic acid and mucopolysaccharides, which promotes skin moisture.[3]

EFFECT ON SKIN THICKNESS

Thin, atrophied skin is a common physiologic change associated with increasing age. The impact of estrogens on delaying and reversing this process is well-documented.[3] In 1994, Maheux et al. performed the first randomized, double-blind, controlled trial assessing the effects of systemic estrogen

replacement on skin thickness. After 12 months of treatment, epidermal thickness as measured by ultrasonography—increased significantly compared to baseline in the treatment group ($p<0.001$) and with no significant change in the control group. Likewise, the thickness of the dermis, as measured by skin biopsy, also increased significantly in the treatment group.[23] Patriarca et al. demonstrated similarly enhanced epidermal and dermal thickness in facial skin treated with topical estradiol in a group of patients on chronic systemic estrogen replacement therapy.[24]

POTENTIAL CONCERNS

Despite the skin benefits, potential concerns have been raised as well. There has been some conflicting reports regarding a potential association between estrogens and malignant melanoma in women.[5] A large case-control study conducted by Smith et al. did not provide conclusive evidence of a link between oral contraceptive use or oral estrogen replacement therapy and melanoma incidence.[25] Another potential concern with the use of estrogenic compounds for the treatment of aging skin relates to topical utilization, which is associated with the development of undesirable facial telangiectasias.[5] Furthermore, pigmentary changes including melasma are a concern with oral estrogen replacement and have been described with topical use as well.[26]

Perhaps the most publicized concern related to estrogens, however, comes from the Women's Health Initiative (WHI) study. The WHI was a large, double-armed randomized trial (estrogen-only and combined estrogen-progestin hormone replacement therapy versus placebo) comprised of 27,000 post-menopausal women, aimed at recapitulating and clarifying earlier epidemiologic findings suggesting a potential benefit of hormone replacement therapy (HRT) in protecting against cardiovascular disease and osteoporosis. [27] The trial was discontinued early due to an unexpected increase in thromboembolic adverse events in both treatment groups, including coronary events, stroke, and venous thromboembolism.[28] Additionally, an increased incidence of invasive breast cancer was seen in the treatment groups.[28]

Publication of data from the WHI and resultant pickup by the press led to a decline in the use of HRT, with the proportion of post-menopausal women maintained on this therapy dropping by a factor of four over a ten-year period.[29] However, extrapolation of the findings of the WHI to topical application on aging skin is problematic. The WHI focused solely on oral HRT (and specifically a formulation containing approximately 10 additional active metabolites beyond 17β estradiol) and did not consider topical use. Furthermore, the positive cutaneous effects of estrogen were overlooked altogether in this study.[5] More recent examinations of the WHI data has revealed several issues with the conclusions.[27]

ESTROGEN ALTERNATIVES

In an effort to selectively harness the positive effects of estrogen stimulation while avoiding the negative effects, selective estrogen receptor modulators (SERMs) were developed (Table 2). SERMs are a therapeutic class of compounds which can act as estrogen receptor agonists in specific tissue types while having anti-estrogenic effects in others.[16] This medication class holds the potential to incite an estrogenic effect where needed without unintended increased risk of adverse effects, such as carcinogenesis and coronary vascular

disease. Although the major goals of SERM development have been breast cancer treatment and the prevention of osteoporosis, one study by Sumino et al. demonstrated similar increases in skin elasticity in a group of 17 postmenopausal women treated with the SERM raloxifene compared to 19 women treated with HRT.[30] Certainly there is potential for a novel SERM with efficacy in prevention and treatment of age-related skin pathology to be developed.[30]

Phytoestrogens—estrogen-like compounds derived from plants—also hold promise in recapitulating the positive effects of estrogens on the skin (Table 2). Recent research has shown promise in the use of phytoestrogens (both dietary and as contained in cosmeceutical products) to improve age-related skin changes[17,31], although the effects may be subpar compared to traditional estrogens.[22] Additionally, phytoestrogens are considered to be endocrine disruptors and thus may have potential deleterious effects of their own.[32] Significantly more research into the therapeutic effects and safety profile of phytoestrogens is needed prior to widespread use in the treatment of aging skin.

SOFT DRUG DESIGN & SOFT ESTROGENS

The optimism associated with the use of SERMs and phytoestrogens for treatment of aging skin lies in the promise of harnessing the powerful skin-protective effects while minimizing the far-reaching endocrine actions of these molecules on other organ systems. However, the ideal situation would be one in which these extracutaneous effects could be predictably avoided all together. The realm of soft drug design is an area of interest that holds potential for creating such a situation.

Table 2. Potential alternatives to estrogen therapy for treatment of aging skin.

Class	Pros	Cons
Selective estrogen receptor modulators (SERMS)	Agonist or antagonist effect on estrogen receptor depending on type of tissue	Act at multiple sites Cutaneous effects under-studied
Phytoestrogens	Shown to have positive effects on age-related skin changes	Efficacy may be subpar compared to traditional estrogens Considered endocrine disruptors May have far-reaching systemic effects
Soft estrogens	Predictable metabolism to inactive compounds in the hypodermis No significant systemic absorption Activity limited to the skin Decreased potential for drug-drug interactions	Not commercially available

The overarching principle behind soft drug design is to optimize therapeutic index by specifically targeting metabolism considerations when synthesizing a new therapeutic agent.[33] The goal is to develop a close structural analogue of a known compound that exerts a desired therapeutic action locally near the site of delivery and is

promptly and predictably metabolized to inactive metabolites prior to becoming systemically distributed. Apart from this advantage in toxicity, these soft drugs are outside the purview of the cytochrome P450 system and thus drug-drug interactions are unlikely.

By altering the chemical structure of known therapeutic agents in a way that predictably alters metabolism, soft drugs have been developed for a wide variety of applications. For example, the addition of an ester group to active compounds leads to local metabolism by ubiquitously-distributed plasma esterases. This allows for medications to be rendered inactive by esterases after acting locally, prior to significant systemic absorption. .[34] Currently, several United States patents exist for topical estradiol-16α-carboxylic acid esters and 15α-carboxylic acid esters that act locally as "soft estrogens."[35,36]

These compounds are irreversibly metabolized to inactive compounds by esterases in the hypodermis (and plasma), thus allowing for local cutaneous estrogenic effects while avoiding unwanted systemic actions. This has been corroborated in rat models.[43] Unlike classic estrogens, the activity of the compounds is limited to the skin. As opposed to SERMs, the selective action of soft estrogens is not related to variable activation of different estrogen receptor subsets, but rather altered metabolism, ensuring only local effects and preventing systemic distribution. Although not yet commercially available, these synthetic, non-hormonal products hold great promise in harnessing the "holy grail" of estrogenic benefits on aging skin while sidestepping some of the concerns raised by the use of traditional estrogenic compounds.

CONCLUSION & FUTURE DIRECTIONS

Aging of the skin is a complex, multi-faceted process that has not only cosmetic but also medical and quality of life implications. The process appears to be triggered in part by decreasing levels of circulating estrogens with increasing age. Although there is significant evidence supporting the positive effects of topical estrogen replacement to combat age-related skin pathology, risk of systemic absorption and resultant untoward adverse effects limit the utility and practicality of such a strategy. The key to combatting the ill effects of aged skin will lie in developing a product that harnesses the protective local effects of estrogens while avoiding the remote, endocrine-related effects on other organ systems. While SERMs and phytoestrogens hold some promise in this regard, the concept of applying "soft drug design" to the development of locally-acting compounds with estrogenic activity limited to the cutaneous microenvironment holds perhaps the most promise in safely harnessing the positive cutaneous effects of estrogens while avoiding unwanted systemic activity. To prevent significant morbidity in an aging population, continued research leading to the availability of such products will be paramount.

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References:

1. Ten great public health achievements--United States, 2001-2010. *MMWR Morbidity and mortality weekly report.* 2011;60(19):619-623.
2. Son ED, Lee JY, Lee S, et al. Topical application of 17beta-estradiol increases extracellular matrix protein synthesis by stimulating tgf-Beta signaling in aged human skin in vivo. *The Journal of investigative dermatology.* 2005;124(6):1149-1161.
3. Shah MG, Maibach HI. Estrogen and skin. An overview. *American journal of clinical dermatology.* 2001;2(3):143-150.
4. Wilkinson HN, Hardman MJ. The role of estrogen in cutaneous ageing and repair. *Maturitas.* 2017;103:60-64.
5. Draelos ZD. Topical and oral estrogens revisited for antiaging purposes. *Fertility and sterility.* 2005;84(2):291-292; discussion 295.
6. Administration UFaD. How did the Federal Food, Drug, and Cosmetic Act come about? 2018; https://www.fda.gov/AboutFDA/Transparency/Basics/ucm214416.htm. Accessed February 9, 2018, 2018.
7. Goldzieher MA. The effects of estrogens on the senile skin. *Journal of gerontology.* 1946;1:196-201.
8. Eller JJ, Eller WD. Estrogenic ointments; cutaneous effects of topical applications of natural estrogens, with report of 321 biopsies. *Archives of dermatology and syphilology.* 1949;59(4):449-464.
9. Bullough HF. Epidermal thickness following oestrone injections in the mouse. *Nature.* 1947;159(4029):101.
10. Dunaif CB, Finerty JC. The effects of estrogen administration upon epidermal proliferation. *The Journal of investigative dermatology.* 1950;15(5):363-371.
11. Zouboulis CC. The human skin as a hormone target and an endocrine gland. *Hormones (Athens, Greece).* 2004;3(1):9-26.
12. Toescu EC. Neuroendocrine Theory of Aging. In: Gellman MD, Turner JR, eds. *Encyclopedia of Behavioral Medicine.* New York, NY: Springer New York; 2013:1311-1315.
13. Saville CR, Hardman MJ. The Role of Estrogen Deficiency in Skin Aging and Wound Healing. In: Farage MA, Miller KW, Fugate Woods N, Maibach HI, eds. *Skin, Mucosa and Menopause: Management of Clinical Issues.* Berlin, Heidelberg: Springer Berlin Heidelberg; 2015:71-88.
14. Monteleone P, Mascagni G, Giannini A, Genazzani AR, Simoncini T. Symptoms of menopause - global prevalence, physiology and implications. *Nature reviews Endocrinology.* 2018.
15. Stevenson S, Thornton J. Effect of estrogens on skin aging and the potential role of SERMs. *Clinical interventions in aging.* 2007;2(3):283-297.
16. Thornton MJ. Estrogens and aging skin. *Dermato-endocrinology.* 2013;5(2):264-270.
17. Irrera N, Pizzino G, D'Anna R, et al. Dietary Management of Skin Health: The Role of Genistein. *Nutrients.* 2017;9(6).
18. Brincat M, Moniz CF, Studd JW, Darby AJ, Magos A, Cooper D. Sex hormones and skin collagen content in postmenopausal women. *British medical journal (Clinical research ed).* 1983;287(6402):1337-1338.
19. Brincat M, Versi E, O'Dowd T, et al. Skin collagen changes in post-menopausal women receiving oestradiol gel. *Maturitas.* 1987;9(1):1-5.
20. Oikarinen A. Systemic estrogens have no conclusive beneficial effect on human skin connective tissue. *Acta obstetricia et gynecologica Scandinavica.* 2000;79(4):250-254.
21. Varila E, Rantala I, Oikarinen A, et al. The effect of topical oestradiol on skin collagen of postmenopausal women. *British journal of obstetrics and gynaecology.* 1995;102(12):985-989.

22. Silva LA, Ferraz Carbonel AA, de Moraes ARB, et al. Collagen concentration on the facial skin of postmenopausal women after topical treatment with estradiol and genistein: a randomized double-blind controlled trial. *Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology.* 2017;33(11):845-848.
23. Maheux R, Naud F, Rioux M, et al. A randomized, double-blind, placebo-controlled study on the effect of conjugated estrogens on skin thickness. *American journal of obstetrics and gynecology.* 1994;170(2):642-649.
24. Patriarca MT, Goldman KZ, Dos Santos JM, et al. Effects of topical estradiol on the facial skin collagen of postmenopausal women under oral hormone therapy: a pilot study. *European journal of obstetrics, gynecology, and reproductive biology.* 2007;130(2):202-205.
25. Smith MA, Fine JA, Barnhill RL, Berwick M. Hormonal and reproductive influences and risk of melanoma in women. *International journal of epidemiology.* 1998;27(5):751-757.
26. Snyder A, Schiechert RA, Zaiac MN. Melasma Associated with Topical Estrogen Cream. *The Journal of clinical and aesthetic dermatology.* 2017;10(2):57-58.
27. Langer RD, Manson JE, Allison MA. Have we come full circle - or moved forward? The Women's Health Initiative 10 years on. *Climacteric : the journal of the International Menopause Society.* 2012;15(3):206-212.
28. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *Jama.* 2002;288(3):321-333.
29. Sprague BL, Trentham-Dietz A, Cronin KA. A sustained decline in postmenopausal hormone use: results from the National Health and Nutrition Examination Survey, 1999-2010. *Obstetrics and gynecology.* 2012;120(3):595-603.
30. Verdier-Sévrain S. Effect of estrogens on skin aging and the potential role of selective estrogen receptor modulators. *Climacteric : the journal of the International Menopause Society.* 2007;10(4):289-297.
31. Amori P, Lotti J, Lotti T, Vitiello G. Spontaneous retrospective clinical evaluation of a new phytoestrogen-based cosmetic gel cream on postmenopausal women's skin. *Journal of biological regulators and homeostatic agents.* 2017;31(2 Suppl. 2):147-151.
32. Bennetau-Pelissero C. Risks and benefits of phytoestrogens: where are we now? *Current opinion in clinical nutrition and metabolic care.* 2016;19(6):477-483.
33. Bodor N, Buchwald P. Soft drug design: general principles and recent applications. *Medicinal research reviews.* 2000;20(1):58-101.
34. Graffner-Nordberg M, Sjodin K, Tunek A, Hallberg A. Synthesis and enzymatic hydrolysis of esters, constituting simple models of soft drugs. *Chemical & pharmaceutical bulletin.* 1998;46(4):591-601.
35. Hochberg RB. Estradiol-16α-carboxylic acid esters as locally active estrogens. In: Google Patents; 2002.
36. Hochberg R. 15α-substituted estradiol carboxylic acid esters as locally active estrogens. In: Google Patents; 2006.