Treatment of Estrogen-Depleted Skin

Timothy J. Falla, PhD; Lijuan Zhang, PhD

Due to depleted estrogen levels in the skin, peri- and postmenopausal women commonly experience a very specific set of skin conditions. These include increased dryness, decreased elasticity, and increased wrinkling. Few products and technologies have been specifically developed for this demographic and as our population ages, a higher proportion of a woman's life is spent postmenopause. The underlying deficiencies, elicited by reduced estrogen levels, are a lack of collagen synthesis and of cell proliferation and migration, and a reduced blood supply. This article reviews current and potential strategies for addressing these factors.

Intrinsic aging of the skin is determined by genetics and hormonal status. With aging, hormonal status, particularly in women, is governed by decreases in the activity of pituitary, adrenal, and gonadal secretions and, as a result, skin aging is inextricably linked to declines in hormones, including estrogen, testosterone, dehydroepiandrosterone, and growth hormones.[1] With continued increases in life expectancy, women and their skin are spending at least one-third of their lives (more than 20 years) in this reduced hormonal state.[2]

Reduction in estrogen during menopause affects a wide range of skin functions including hair growth,[3-5] pigmentation,[6-8] elasticity,[9] and water-holding capacity.[10] This hormonal reduction leads to increased dryness,[11] decreased elasticity,[12,13] and increased wrinkling.[14] Hypoestrogenia leads to changes in collagen content and alterations in glycosaminoglycan concentrations and water content. As a result, there is a direct correlation between reduced estrogen levels and the phenomenon of skin aging. Thirty percent of collagen is lost in the first 5 years postmenopause with a 2.1% reduction per year over 20 years.[15] Associated with the loss of collagen is a 1.1% decrease in skin thickness per postmenopausal year.[16,17] The effect of estrogen depletion on skin aging has been investigated through the comparison of postmenopausal women taking systemic estrogen versus those who have not. In such cases estrogen treatment has increased dermal thickness, keratinocyte proliferation,[18] and collagen content.[19] In addition, women taking estrogen have been found to have increased dermal hydration,[11] decreased wrinkling,[20] and increased skin elasticity.[11] Since its first use in the 1940s, systemic estrogen therapy has been known to have obvious, visible effects on the skin.[14,21]

Systemic estrogen is primarily prescribed for the severe symptoms experienced by peri- and postmenopausal women, such as the prevention of osteoporosis, vasomotor symptoms, and heart disease. However, the mechanisms of estrogen signaling are complex and encompass multiple signaling pathways with estrogen receptors being widespread throughout the skin and other organs.[22] As a result, health risks have been associated with the use of systemic estrogen and such products are marketed with strong warnings of adverse effects including the risk for breast and uterine cancer.[23]

Drs. Falla and Zhang are from Helix BioMedix, Inc, Bothell, Washington.

Drs. Falla and Zhang are employees of Helix BioMedix, Inc.

Correspondence: Timothy J. Falla, PhD, Helix BioMedix, Inc, 22118 20th Ave SE, Ste 204, Bothell, WA 98021 (tfalla@helixbiomedix.com).

SELECTIVE ESTROGEN RECEPTOR MODULATORS

Selective estrogen receptor modulators (SERMs) have been specifically designed to exhibit agonistic or antagonistic effects upon tissue-specific estrogen receptors. For example, tamoxifen citrate blocks estrogen action in breast cancer cells but stimulates proliferation of uterine cells. As with estrogen, tamoxifen citrate has been shown to stimulate wound healing and improve scarring through the stimulation of fibroblast proliferation and migration.[24,25] With the development of new generations of SERMs such as lasofoxifene (Pfizer), arzoxifene (Eli Lilly), and bazedoxifene (Pfizer), there remains the promise of safer and more specific ways of modulating estrogen receptors. However, even though there have been European regulatory approvals for a number of SERMs for osteoporosis, safety concerns still are a major hurdle for this class of compounds and it will be some time before their efficacy and application to other postmenopausal symptoms such as wound healing and skin integrity can even be tested.

TOPICAL ESTROGENS

The use of topical estrogens provides for an application of the hormone to aging skin while potentially avoiding some of the risks of systemic use. Clear benefits have been demonstrated with the use of topical estrogen on photoaged and sun-protected skin.[14,26] These include increases in epidermal thickness and decreases in fine wrinkles.[27,28] It should be noted that differences in collagen induction by topical estrogen in sun-exposed versus sun-protected skin indicate that different mechanisms may be at play in these 2 distinct skin types.[29] Evidence from this work indicates that topical estrogen is not capable of increasing procollagen in sun-exposed skin despite producing beneficial effects.[29] However, until there is definitive data demonstrating the safety of topical estrogen use, including systemic exposure risk, there remains concern over its use for skin treatment.[30]

In women, the decline in the effectiveness of skin repair mechanisms follows menopause. Observations have been made regarding the ability of estrogen to improve wound healing in postmenopausal women.[31,32] In addition, the application of topical estrogen also has been demonstrated to accelerate wound healing in the elderly.[33] Of note is that the activities supplied to the skin by estrogen have a great deal in common with those associated with wound healing, and reduced estrogen levels have been shown to have a notable negative impact on cutaneous healing.[31] The age-related delay in cutaneous healing is mitigated by the use of topically applied estrogen through increases in collagen levels, decreases in elastase levels, and a reduction in neutrophil numbers.[34,35] The cellular responses at the heart of this stimulation include the induction of cell proliferation, cell migration, and angiogenesis.[35,36] Such effects are likely elicited through the presence of both intracellular estrogen receptors (ERs), estrogen receptor 1 α (ESR1) and estrogen receptor 2 β (ESR2), and extracellular ERs, ESR1, on a range of cells, including dermal fibroblasts and epidermal keratinocytes, that are up-regulated at physiological concentrations of estrogen.[35,36] The induction of angiogenesis by estrogen is of particular interest as it specifically correlates with the changes in cutaneous vascularity seen in postmenopausal skin resulting in decreased capillary blood flow.

PHYTOESTROGENS

An alternative to the direct use of estrogen is the use of the structurally related phytoestrogens and in particular the soy isoflavone, genistein.[37] A number of studies have demonstrated that isoflavones, genistein in particular, stimulate wound healing.[38] In a wound-healing model in ovariectomized mice, genistein (1 mg/kg subcutaneously) substantially accelerated healing.[38] And genistein aglycone (10 mg/kg subcutaneously) substantially improved skin healing and wound tensile strength in ovariectomized rats.[39] In a similar study examining skin condition endpoints in ovariectomized rats, 14 weeks of 20 and 40 mg daily intake of red clover isoflavones substantially improved epidermal thickness, and increased collagen content versus control animals.[40]

Genistein preferentially is an agonist for ESR1 and therefore, due to the distribution of ESR1 versus ESR2, exhibits a different tissue interaction profile compared with estrogen.[37] For example, estrogenic effects upon hepatocytes, and therefore serum lipid levels, and the uterus, hence uterotropic activity, are primarily mediated through ESR1 as opposed to ESR2.[41] It should be noted that genistein also inhibits tyrosine kinase and topoisomerase II, is an antioxidant, and scavenges free radicals. As a result, not all of its beneficial activities may be ESR2-related.

In a 6-month study of 30 postmenopausal women, daily treatment with 100 mg isoflavone-rich soy concentrate demonstrated a remarkable improvement in skin wrinkling, dermal collagen, and the number of elastic and collagen fibers.[42]

Natural sources of genistein include soy beans, fava beans, kudzu, and lupin. However, to provide a more consistent and reproducible source, synthetic genistein

has been produced and is marketed under the name Bonistein (DSM) as a neutraceutical for bone loss in postmenopausal women and as an ingredient in skin protection products. Other commonly used and structurally related phytoestrogens include formononetin, bichanin, and repensol. Efforts have continued in the search for novel phytoestrogens that can be used to treat menopausal symptoms, such as 8-prenylnaringenin from hops.[44]

RETINOIDS

The retinoids encompass vitamin A (retinol), natural derivatives such as retinoic acid (tretinoin), retinaldehyde, and retinyl esters, and synthetic derivatives such as isotretinoin. Their mechanism of action is through the retinoic acid receptor (RAR) family and the retinoid X receptors.[44] Binding of these receptors leads to increases in epidermal proliferation leading to epidermal thickening, biosynthesis and deposition of glycosaminoglycans, and compaction of the stratum corneum. The majority of studies and characterization has been focused on retinoic acid and retinol primarily in relation to photoaging. However, in a 9-month study conducted by Kligman et al[45] on 6 women with an average age of 74 years, once-daily tretinoin cream 0.0255% produced a marked increase in epidermal thickness, the induction of keratinocyte uniformity, and increases in angiogenesis and elastic material. A 1% retinol (95% ethanol propylene glycol; 7:3 by volume) study on 53 individuals (aged 80 years and older) produced decreases in the levels of matrix metalloproteinases, collagenase, and gelatinase in 7 days.[46] In addition, an increase in fibroblast growth and collagen synthesis was observed. The retinoid of choice for peri- and postmenopausal skin is a balance between irritancy and efficacy. Retinol is 20 times less potent than tretinoin but has been reported to have notably less irritation.[47,48] However, the activities that this class of molecules produces have made the application of retinoids to estrogen-depleted skin a widely used approach.

INNATE IMMUNITY MODULATION

The induction of collagen in fibroblasts by estrogen is likely as a result of increased levels of transforming growth factor β1.[49] However, the primary regulator or mediator of estrogen's effect upon the skin and wound healing is the proinflammatory cytokine macrophage migration inhibitory factor (MIF).[50] Using a microarray-based analysis, profiled changes in gene expression within the wounds of mice that were wild type or null for MIF in the presence or absence of estrogen have been recorded.[51] This study identified more than 600 differentially expressed genes and established MIF as a key player in the wound-healing process, regulating many novel repair/inflammation-associated gene targets. Moreover, MIF affected virtually all of the effects of reduced estrogen on wound repair. In humans, serum and wound levels of MIF increased with age and were strongly down-regulated by estrogen in vivo. The inhibition of MIF in the skin provides an attractive target for restoring dermal repair mechanisms to estrogen-reduced skin for improved skin integrity, health, and healing. The area of small molecule inhibition of MIF has been the focus of a lot of attention, particularly in relation to autoimmune diseases such as rheumatoid arthritis and, as a result, raises the potential for the development of a natural or synthetic approach to MIF inhibition in the skin.

Based on the central role that MIF plays in the interaction between estrogen, skin, and wounds, modulation of the innate immune system holds promise in the treatment of peri- and postmenopausal skin and wounds.[52] The cathelicidin peptide (LL-37) provides a front-line component in innate immunity, stimulating and modulating the cutaneous immune system. These functions include chemoattraction and activation of immune and/or inflammatory cells, the production and release of cytokines and chemokines, acceleration of angiogenesis, promotion of wound healing, neutralization of harmful microbial products, and bridging of both innate and adaptive immunity.[53,54] This has led to a number of therapeutic approaches targeting these pathways to treat conditions such as rosacea, psoriasis, infectious disease, and inflammation.

Heptapeptide-7 is a fragment of the well-characterized, innate immunity, wound-healing peptide, HB-107,[55] which has been demonstrated to stimulate keratinocyte proliferation and migration and induce collagen synthesis.[56] Microarray analysis of heptapeptide-7–treated dermal keratinocytes revealed an up-regulation of cell division, growth factor, and extracellular matrix genes in a clinical study of 32 women (with a mean age of 54 years) in which forehead wrinkles and skin texture were greatly improved with the use of the peptide.

Heptapeptide-7 appears to elicit its effect upon the skin in a similar fashion to the body's own protect-and-repair mechanism performed by LL-37. This is not unexpected as both sequences are associated with innate immunity and wound healing in vivo. The cathelicidin peptide, induced in human skin upon injury, accelerates wound healing, increases keratinocyte proliferation and migration, is immunomodulatory,

and appears to operate through the activation of growth factors.[57,58] Heptapeptide-7 induces the proliferation and migration of keratinocytes either directly or through growth factors such as platelet-derived growth factor. It also, likely through the same innate pathway, induces the production of collagen. However, as opposed to LL-37, which increases cytokine (eg, IL-6 and IL-8) levels, heptapeptide-7 appears to calm the inflammatory response by down-regulating IL-33 and toll-like receptor 2 which are constitutively expressed in keratinocytes.[56]

Heptapeptide-7 provides evidence that the parameters associated with wound healing can be applied to menopausal skin because the pathological requirements of estrogen-deficient skin are similar to those provided by the innate immune system to wounds. As a result, skin barrier function, moisturization, elasticity, thickness, and texture can all be improved with application of specific wound bioactivities to estrogen-deficient skin. However, it should be noted that the selection of innate immune modulators for specific skin conditions should be performed on a case-by-case basis. For example, heptapeptide-7, like estrogen, stimulates collagen, but LL-37 actively suppresses the synthesis of collagen in dermal fibroblasts.[59]

CONCLUSION

Nonsteroidal alternatives to estrogen do exist and can provide a number of the essential bioactivities lost during peri- and postmenopause. It should be noted that surgical or mechanical intervention, such as laser resurfacing, volume fillers, and botulinum toxin type A injections, provides a separate and distinct approach not discussed here. However, the physical process of chemical peeling is well-documented to lead to the stimulation of key elements of dermal rejuvenation including collagen deposition and thickening of the dermis and epidermis.[60] In addition, the combination of such peels with mechanical techniques provides for enhanced results.[61,62] In a reduced-estrogen state, skin can become less smooth in addition to the more fundamental changes that occur. α-Hydroxy acids such as glycolic, mandelic, malic, and citric acids have been shown to improve skin texture in particular in combination with other actives such as retinoids.

Recent studies have sought to identify downstream mediators of estrogenic effects to avoid the broader and unwanted effects of estrogen treatment. One such approach is the stimulation of extracellular matrix components, cell proliferation, dermal repair, or growth factors using short peptide sequences. Peptides such as palmitoyl pentapeptide-3 (Sederma, Le Perray en Yvelines), palmitoyl hexapeptide-14 (Grant Industries), tetrapeptide-21 (Evonik), palmitoyl tripeptide-5 (Pentapharm), and hexapeptide-10 (Lipotec) have all been demonstrated to stimulate certain of these factors.[63] The origin of these sequences includes procollagen, innate immunity peptides, collagen, and thrombospondin type 1. In the majority of cases, they mimic the effects of natural sequences in repair and regeneration functions, which are naturally triggered upon injury or damage.

Estrogen-depleted skin is specifically lacking in collagen stimulation, cell proliferation and migration, and blood supply. This can be positively affected by treatment with estrogens, phytoestrogens, and retinoids, or by modulating downstream pathways such as wound healing and cutaneous innate immunity. In the future, SERMs may provide a safer alternative to estrogen therapy. Stimulating the individual factors of postmenopausal skin using a combination of bioactive molecules is also a strategy that has been adopted. Naturally occurring peptides in the body, such as carnosine (β-alanyl-L-histidine), recently have been included in postmenopausal-targeted products. In the case of carnosine, antioxidant and antiglycation activities provide the benefit. Examples of a wide range of botanicals include caffeine (skin tightening and firming), coumarin (increased blood flow), and jasmine (moisturization).

Skin containing reduced levels of estrogen presents a very specific set of issues that are not readily addressed by standard skin care products. As women spend a higher and higher proportion of their lives in postmenopause, more products will need to be developed that specifically target their skin type.

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