Skin aging and sex hormones in women – clinical perspectives for intervention by hormone replacement therapy


Abstract: The skin, the largest organ of the body, is the organ in which changes associated with aging are most visible. The skin is a target organ for various hormones, and sex steroids have a profound influence on the aging process. A decrease in sex steroids thus induces a reduction of those skin functions that are under hormonal control. Keratinocytes, Langerhans’ cells, melanocytes, sebaceous glands, collagen content and the synthesis of hyaluronic acid, for example, are under hormonal influence. Topical application of estrogens has a positive effect on skin aging parameters, whilst numerous studies have also shown the positive influence of systemic hormone replacement therapy on skin aging. As an alternative treatment, phytohormones may be administered, with the structural similarity to 17β-estradiol explaining their estrogen-like effects. However, isoflavonoids exhibit an inferior biological potency to synthetic estrogens. Although a large number of publications have documented the effects of sex hormones on the aging process, it is obvious that hormone replacement should not be administered as an independent treatment for skin aging.

Introduction

The skin is one of the largest organs of the body and, like all other tissues, undergoes degenerative processes during aging. The skin represents the major organ in which aging-related changes are visible (1). Skin aging is associated with increased rates of skin diseases, including skin tumors, and with concomitant psychological distress caused by a deterioration in appearance. Although the main focus of public medicine is on age-related chronic diseases of other systems, such as arthritis, heart disease and cancer (2), skin aging and its diseases have become increasingly important. Most women in developed societies can expect to spend one-third or more of their lifetime in the postmenopausal period (2), and the external signs of aging are very important for most of them.

Skin aging is caused by a combination of factors, including genetic disposition and endocrinological background, as well as UV light, life habits (nutrition, nicotine, alcohol, drugs), catabolic factors (infections, tumors) and other environmental influences. Many women notice a sudden onset of the signs and symptoms of skin aging during the menopause, such as an increase in skin dryness, loss of firmness, decrease in elasticity and increase in skin looseness. There is a connection between these clinical signs and phenomena such as a decrease in collagen and elastin, changes in basic substance and the ratio of type I to type III collagen and alterations in vascularization (3). The external signs of skin aging are reflected in the histopathological findings in the skin (4).

The skin is a target organ for various hormones (5). Sex steroids have a profound influence on both skin development and composition; adequate levels are required to facilitate its structural integrity and functional capacity (6). Hormonal action requires the
binding of the hormone to specific receptors (5). Estrogen and other hormone receptors have been detected, inter alia, in keratinocytes, fibroblasts, sebaceous glands, hair follicles, endocrine glands and blood vessels (7). The receptors vary in density according to site, with higher concentrations of estrogen receptors in facial skin than in the skin at the pelvis or breast. Decreased sex hormones thus induce a reduction of those skin functions that are under hormonal control.

In clinical terms, many females experience a sudden onset of skin aging symptoms several months after the menopause. One of the first signs which women experience is increasing skin dryness, followed by a loss of skin firmness and elasticity. The increasing looseness of the skin outweighs other symptoms, such as wrinkles, at this stage. These symptoms correspond to changes in collagenous and elastic fibers that have been reported to be due to estrogen deficiency (8). A significant decrease in skin collagen starting at the menopause has previously been demonstrated (9). This negative effect of the menopausal years on the skin was first described by Albright et al. in 1940, who noted that old women with osteoporotic fractures had a higher incidence of altered skin (10). Among the various types of collagen, types I and III are of major relevance. Type I collagen represents the predominant collagen type in adult human skin, whereas type III collagen, also widely distributed throughout the body, predominates in fetal tissues. Both total collagen content and the ratio of type III to type I collagen decline with age (11). Skin collagen contents in adults decrease by 1% every year (12). This process is more evident in women than in men. Approximately 30% of skin collagen is lost in the first 5 years after the menopause, with an average decline of 2.1% per postmenopausal year over a period of 20 years. Estrogens reverse this trend and increase skin collagen (5). Estrogens also enhance the synthesis of hyaluronic acid, and promote water retention (13). Animal studies have indicated that estrogens induce several changes in the connective tissue of the dermis, including increased mucopolysaccharide incorporation, hydroxyproline turnover and alterations in the extracellular matrix (14).

Epidermal cells – keratinocytes, Langerhans’ cells and melanocytes – are also target cells of steroid hormones (5). The estrogen receptor complex is able to support the expression of growth factors, such as insulin-like growth factor type I (IGF-I), a mitosis-enhancing protein for keratinocytes (15). The Langerhans’ cells are influenced by progesterone, with their number increasing during the luteal phase. Melanocytes are stimulated by 17\(\beta\)-estradiol (16).

Sex steroids are involved in many extragenital organ systems, e.g. the urogenital tract, skin and hair, breast and cardiovascular, nervous and skeletal systems. Considering that most women spend one-third of their lives with estrogen deficiency, the potential field of action for hormone replacement therapy (HRT) is increasing. For some indications, including urogenital or musculoskeletal problems or psychovegetative complaints, HRT has become an established treatment (15). The current discussion on the prevention of cardiovascular and neurodegenerative diseases, however, is controversial. Our aim in this article is to examine the influence of HRT on skin aging.

Endocrinological therapies for skin aging

Topical treatment

In a placebo-controlled study, Creidi et al. examined the effect of a topically applied conjugated estrogen skin care cream (Premarin\textsuperscript® 0.625 mg/g ointment) in 54 women (17). Evaluation criteria were profilometry and measurements of skin thickness by ultrasound. After a 24-week treatment period, there was a significant increase in skin thickness in the Premarin\textsuperscript® group when compared with the placebo group. Even with regard to small wrinkles, a significant decrease was observed in comparison with the placebo group after 12 and 24 weeks. No side-effects were found.

Schmidt et al. published a study on the action of topical 0.3% estriol and 0.01% 17\(\beta\)-estradiol in 59 patients (18). The criteria evaluated by the authors were profilometry, corneometry and clinical signs. Wrinkle depth was significantly reduced and skin hydration was improved. Apart from a rise in prolactin, no other systemic hormonal effects were detected. Histological tests of collagen parameters in 10 patients showed a significant increase in the collagen III fraction at the end of therapy after 24 weeks.

In a recent study, the effects of a 0.01% 17\(\beta\)-estradiol cream were compared with those of a 15% glycolic acid cream and a combination of both (19). The effects examined in 65 patients after 6 months indicated an increase in epidermal thickness, and were most marked in the combination group (38%), followed by the
glycolic acid group (27%) and the 17\(\beta\)-estradiol group (23%).

**Systemic HRT**

HRT consists of two components: estrogens and progestagens. Estrogens administered as monotherapy may result in undesired hyperplasia of the endometrium. In order to avoid this event, synthetic derivatives of progesterone and testosterone, known as progestagens, are combined with an estrogen compound and may be applied in a cyclical or continuous mode. Estrogen monotherapy is, however, feasible in hysterectomized women, with a choice of oral, transdermal and vaginal forms of application available.

Beneficial effects of HRT on the skin have been documented by several studies with respect to skin thickness as a mirror image of collagen content (20–23). A large retrospective multicenter study (first national health and nutrition examination survey, NHANES I), conducted in 3825 women in the USA, showed that women under long-term substitution had one-third fewer wrinkles than non-substituted patients (20). Brincat et al. demonstrated that postmenopausal women with HRT had a significantly higher collagen content than untreated women (21).

One study examined the effects of three types of HRT on skin aging in menopausal women (24): one group was given estrogen only via the transdermal route (Estraderm TTS\textsuperscript{50}), the second received estrogen by transdermal application in combination with vaginally applied progesterone (Estraderm TTS\textsuperscript{50} and 0.4 g progesterone vaginal suppository), and the third group was administered oral estrogen and vaginal progesterone (2 mg Progynova\textsuperscript{50} and 0.4 g progesterone vaginal suppository). One group without treatment served as a control. Treatment was continued for 6 months. Skin surface lipids, epidermal skin hydration, skin elasticity and skin thickness were measured at monthly intervals. Mean levels of epidermal skin hydration, elasticity and skin thickness were improved at the end of treatment based on both subjective and objective evaluation in patients with HRT. Skin surface lipids were increased during combined HRT, which may reflect the stimulatory effects of the progestagen component on sebaceous gland activity, whilst estrogen alone had a sebum-suppressive action (1). A comparison of skin hydration and elasticity in UV-exposed and non-exposed areas revealed no significant difference. This finding suggests that both photoaged and UV-protected skin benefit equally from HRT. These results were confirmed by animal tests using the skin of rats (25).

Although the majority of publications consider the influence of HRT on skin aging to be positive, there are also some authors who doubt or reject any effect of hormone replacement on skin thickness, collagen synthesis or elastin (26).

**Alternatives: phytohormones**

The estrogen-like effects of some plants were first described by Loewe et al. in 1927 (27). Phytoestrogens are classified into three categories: isoflavones, coumestans and lignans. The most thoroughly examined group of substances are isoflavones, which display some similarity to the mammal estrogen molecule and are found, *inter alia*, in soy beans, lentils and red clover. Flavonoids are also contained in wine, especially red wine. The most important isoflavones are genistein and daidecin. The group also includes the precursors formononentein (for daidecin) and biochanin (for genistein). Coumestans only occur in the sprouts of legumes. Lignans have no influence on estrogen receptors. The structural similarity to 17\(\beta\)-estradiol explains the estrogen-like effects, which may be traced back to the interaction of these substances with the estrogen receptor (28). Nutrition in Asian countries, with its large phytoestrogen content, is thought to be the reason why Asian women rarely suffer from climacteric symptoms. The biological potency of isoflavonoids is significantly inferior to that of synthetic estrogens (29). When phytoestrogens are topically applied, they behave like estrogens by causing a proliferation of the epidermis, supporting collagen synthesis and reducing enzymatic collagen degradation.

A controlled open European multicenter study examined the effect of a cosmetic cream preparation including isoflavone (Novadiol\textsuperscript{50}) (234 women; maximum age, 65 years; at least 3 years since the menopause; no HRT or other substances affecting the skin aging process) (30). The length of therapy was 12 weeks. The isoflavone cream was applied twice daily (in the morning at a concentration of 0.0075% isoflavone and in the evening at a concentration of 0.015% isoflavone) on the face, neck and one upper arm. The other arm was untreated and served as a control. Skin dryness and roughness
were significantly improved at the treated areas by 32.9% and 22%, respectively, in comparison with the untreated skin areas. Facial wrinkles were significantly reduced by 22% and skin looseness was significantly reduced by 24%.

**Conclusion**

Numerous publications on the effects of sex hormones on the aging process are available today. Without claiming that HRT can or should ever be regarded as an independent treatment for skin aging, these findings are still interesting, considering that they indicate a beneficial effect of HRT on the skin, despite the fact that the results of the ‘Women’s Health Initiative (WHI) Study’ (31) and the ‘Million Women Study’ (32) have shown negative effects of HRT on other organs. It is clear, however, that HRT must be rejected if considered solely for the prevention of skin aging. As an additional benefit in the treatment of menopausal conditions, provided by a dermatologist with sufficient experience in the discipline of endocrinology, however, it is a very effective instrument to control intrinsic skin aging.

Although the topical application of hormones is certainly a suitable alternative to systemic HRT, it must be ensured that such treatment is also administered by a dermatologist experienced in endocrinology, given that concentrations and application areas need to be observed in order to avoid systemic side-effects.

Phytoestrogens, topical and systemic, appear to be an effective method in the treatment of intrinsic skin aging. However, further data are still required, especially controlled studies on the long-term results of systemic application.

**References**