# Oestrogens and the skin

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## Summary

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

*Keywords*: collagen, HRT, menopause, oestrogen, skin

## 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 post-menopausal health care. The hypo-oestrogenism that accompanies menopause is known to induce vasomotor symptoms and vaginal atrophy, as well as exacerbate bone loss; studies have documented that post-menopausal hormone therapy (oestrogen only or oestrogen opposed by a progestin) can reduce the symptoms of menopause and prevent early bone loss. However, other organs that are also intimately dependent on oestrogen have not garnered comparable attention with regard to post-menopausal treatment. For example, oestrogen 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 post-menopausal oestrogen deficiency on skin are not well documented. Further work on the impact of exogenous hormones on women's skin is still in its infancy.

The aim of this paper is to review the clinical literature regarding the physiological effect of oestrogen on structural and physical characteristics of skin. In particular, studies that have examined post-menopausal hormone therapy and the role it may play in maintaining skin integrity and preventing age-related deleterious changes will be discussed. Given the importance of skin for general health and the intriguing information available on a role for oestrogen in skin, further examination of mechanistic and clinical effects of oestrogen on skin parameters is warranted.

## Skin physiology and the role of oestrogen

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 fibres present in dermal connective tissue consist of two main types of fibrous proteins, collagen and elastin.

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*Accepted for publication 09 July 2004*

The collagen fibres (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 fibres are arranged as a thinly distributed subepidermal network and provide the skin with elasticity and resilience.[3] Dermal connective tissue also contains nerve fibres, sensory receptors, and the supportive glycosaminoglycans (GAGs).[4]

Skin quality deteriorates with age due to the synergistic effects of chronological ageing, photoaging, environmental factors, and hormonal deficiency.[4] Hormonal ageing of skin due to oestrogen 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 oestrogen deficiency on skin is thought to contribute to the poor wound healing that accompanies ageing.

An integral role for oestrogen in skin integrity was substantiated with the discovery of oestrogen receptors in dermal fibroblasts and epidermal keratinocytes.[5] Further, a study aimed at identifying specific oestrogen-sensitive structures examined human skin for the ability to bind an antibody against a protein, p29, typically found in oestrogen-responsive cells.[6] Strong and specific binding to the p29 antibody was seen in discrete structures within skin.[6] However, there is a lack of information regarding the effects of oestrogen on these target cells. Expression of both aromatase and 17β-hydroxysteroid dehydrogenase type I – two enzymes involved in the formation of potent oestrogens – has also been demonstrated in skin.[7]

## Effects of oestrogen 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 fibroblasts,[8] oestrogens have no stimulatory effect on procollagen synthesis in cultured human cells.[9] Using a rat model, oestrogen has been shown to inhibit collagen degradation.[10] Given the complex involvement of regulatory factors, receptors, and enzymes in maintaining collagen balance, the exact mechanism for the role of oestrogen 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 *et al.*[11] found a closer correlation between collagen loss and chronological age than between collagen loss and time since menopause, others report a stronger correlation between skin collagen loss and oestrogen deficiency due to menopause.[12–14] The finding of Castelo-Branco *et al.*[11] 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 oestrogen deficient for a long period.[15] It has been suggested that as much as 30% of skin collagen (both type I and III) is lost in the first 5 years after the menopause.[14,16] Brincat *et al.*[12,13] found that total collagen declines by an average of 2.1% per post-menopausal year over a period of 15 years, and this decline can be prevented in women receiving oestrogen therapy.[17] 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.[12,13,18]

Most clinical studies demonstrate a beneficial effect of subcutaneous,[12,13,16–19] topical,[12,13,20,21] or oral[11,22] oestrogen treatment on the collagen content of skin (Table 1). The extent of the reported oestrogen-induced increase has varied, depending upon the dose, route of administration, and duration of hormone treatment. For example, a 3-month study in post-menopausal women found that treatment with topical oestradiol resulted in a 38% increase in total collagen,[21] whereas another study examining both oral and transdermal oestrogen treatment for 12 months found that collagen levels increased significantly, but by only 2–5%, depending on the treatment regimen.[11] 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 oestrogen is proportionate to baseline collagen levels.[12,13] To date, only one clinical study has failed to show a beneficial effect of oestrogen therapy on collagen levels. Haapasaari *et al.*[23] observed no change in collagen levels of post-menopausal women with 1 year of ERT or HRT. However, that study examined the effects of oestrogen 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 level.[24] Based on observations by Brincat *et al.*,[18] 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 oestrogen treatment may be prophylactic for women with high skin collagen levels

  

**Table 1** Oestrogen therapy and collagen content

| Study/Year | Brief description of study | Results |
|---|---|---|
| Brincat, 1983[17] | Skin biopsies taken from untreated post-menopausal women and women who had been treated with oestradiol and testosterone implants for 2–10 y | Mean collagen content was 48% greater in the HRT group than in untreated women |
| Brincat, 1985[16] | Skin biopsies taken from untreated post-menopausal women and women who had been treated with oestradiol and testosterone implants for 2–10 y | Skin collagen content was significantly greater in post-menopausal women on HRT |
| Brincat, 1987[12] | Skin biopsies taken from post-menopausal women who were either given topical oestradiol for 1 y, or were treated with an oestradiol-only implant, an oestradiol 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[13] | Skin biopsies were taken from untreated post-menopausal women and post-menopausal women who had been treated with oestradiol and testosterone implants for 2–10 y | The decrease in collagen seen in untreated women was preventable with HRT use |
| Castelo-Branco, 1992[11] | Skin biopsies were taken from post-menopausal women allocated to 1 of 4 groups (control; CEE [25-day cycle]; CEE [28-day cycle]; transdermal 17β-oestradiol [24-day cycle]) | Oestrogen treatment increased collagen content 2%–5% |
| Savvas, 1993[19] | Skin biopsies were taken from treated or untreated post-menopausal women. Treated women had received subcutaneous oestradiol and testosterone for 3–14 y | Women on HRT had significantly greater levels of collagen III |
| Varila, 1995[21] | Suction blister fluid and skin biopsies taken to analyse collagen content in post-menopausal women administered either topical oestrogen or vehicle for 3 months | Oestradiol treatment resulted in 38% greater hydroxyproline levels |
| Schmidt, 1996[20] | Skin biopsies taken from pre-menopausal women with skin ageing symptoms before and after 6 months of topical oestradiol or topical oestriol treatment | Topical oestrogens increased collagen II levels in the dermis |
| Haasparrasi, 1997[23] | Suction blister fluid used to analyse skin collagen content in 43 early post-menopausal women (mean age, 50–52 y) administered continuous oral 17β-oestradiol and NETA, continuous oral oestradiol valerate or control for 12 months | No effect |
| Sauerbronn, 2000[22] | Skin biopsies taken from post-menopausal women given either HRT (2 mg oestradiol 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 |

and both prophylactic and therapeutic for women with low collagen content.[12,13]

### Elastin fibres

Accelerated degenerative changes in dermal elastic fibres have been observed in young women with premature menopause,[4] and histological studies demonstrate that topical oestrogen can increase the number and thickness of elastic fibres in skin.[25] However, reports from several recent clinical trials that examined the effects of HRT on elastin fibre content in skin demonstrate no observable improvement from baseline with systemic oestrogen therapy.[22,23,26] Importantly, two of these studies treated a small sample ($n \leq 21$) of women for only 6 months,[22,26] and the third involved very early menopausal women.[23]

### Water content

One of the most common dermatological conditions in older women is dry skin.[27] Healthy skin requires substantial water content, which is determined by both cutaneous evaporation rate and epidermal hydration. It has been shown that the transepidermal water flux, or evaporation, varies during the menstrual cycle[28] and decreases with age.[29] 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 oestrogen therapy can lead to a significant increase in the water-holding capacity of the stratum corneum.[30]

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[20,30–32] when compared with a control group, although some differences did not reach statistical significance.[20,32] Other results demonstrated no effect of oestrogen on skin capacitance.[23,33]

In the First National Health and Nutrition Examination Survey (NHANES I),[34] standardized dermatological assessment of 3875 post-menopausal women showed that oestrogen use was associated with a statistically significant decrease in the likelihood of senile dry skin. Given the limits inherent to epidemiological studies, corroboration of a role for oestrogen in skin water content will best be addressed with large double-blind, randomized, controlled studies.[35]

Positive effects of oestrogen on the water content of skin may be related to oestrogen-stimulated increases in mucopolysaccharides and hyaluronic acid levels in skin,[36–39] which correlate to an increased dermal water content,[37] and to increases in skin thickness, which subsequently elevate natural moisturizing factors.[20] An improvement in water-holding capacity of the skin enhances the barrier function of the epidermis and subsequently results in less frequent development of dermatoses.[30]

### Sebaceous secretions

The activity of cutaneous sebaceous glands is regulated by levels of circulating hormones; oestrogen can reduce the size and number of sebaceous glands, as well as the production of sebum, whereas androgens oppose this action, thereby stimulating secretory activity.[4] Indeed, clinical studies have shown that sebaceous secretions decrease with age[40] and oestrogen replacement alone has a sebum-suppressive action,[31] but the addition of a progestin results in significant increases in skin surface lipids.[31,33] In a study by Callens *et al.*[33] 49 post-menopausal women taking oestradiol with progesterone were compared with a control group; a 38% increase in sebum production was observed with hormone treatment.

## Effects of oestrogen 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 post-menopausal years.[12,13] 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 women,[41–44] a strong correlation between skin thickness, collagen content, and bone mineral density has been observed in post-menopausal women.[12,13,45]

Attempts have been made to slow skin thinning with oestrogen therapy for several decades. The majority of clinical trials have demonstrated that post-menopausal women who take HRT have greater skin thickness than non-users.[11,26,31,33,45–49] An HRT-induced increase in thickness is detected in the dermis[26,46,49] through increases in dermal connective tissue, but not the epidermis.[22,26,46,49] An early randomized, double-blind, placebo-controlled study examined the use of conjugated equine oestrogen (CEE) in 60 post-menopausal 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 the placebo.[49] A recent cross-sectional observational study used diagnostic ultrasound to compare skin thickness between HRT users, non-users, and pre-menopausal women.[50] Chen *et al.*[50] found that HRT-treated women had 10% greater skin thickness than non-users and achieved thickness levels comparable to pre-menopausal 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. 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 post-menopausal hormone therapy.

Two studies examining early menopausal women[23,51] found no significant change in skin thickness with oestrogen treatment. Similar to oestrogen's effects on collagen levels, observable benefits of oestrogen on skin thickness is inversely proportional to initial thickness values, and therefore it is not surprising that treatment of early menopausal women did not result in significant changes.

### Elasticity and distensibility

The mechanical properties of skin can be defined and quantified by extensibility and elasticity measurements using computerized devices. Ageing in skin, in particular in the face, is associated with a progressive increase in extensibility and a reduction in skin elasticity. The influence of climacteric ageing on rheological qualities of

skin was quantified using a non-invasive computerized suction device in a recent study by Pierard-Franchimont and colleagues.[51] 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.[52,53] 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.[52,53] Recently, a small ad hoc study involving women aged 45–68 years (mean age, 54.9 years) followed the effect of HRT on rheological measures for 6 months.[31] Significant increases in elasticity were observed for both transdermal and oral oestrogen preparations. 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 ageing.[53]

### 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 quantifying a visual endpoint such as facial wrinkles, few clinical studies have specifically examined HRT and facial wrinkling.

Several observational studies have reported that post-menopausal women treated with oestrogen are less wrinkled than untreated women,[34,54] although in one study, improvement with HRT was only observed in non-smokers.[54] In NHANES I, a cross-sectional analysis of a national probability cohort, the effects of oestrogen use on wrinkling were ascertained in close to 4000 post-menopausal women aged 40 years and older at baseline.[34] 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 oestrogen users (odds ratio, 0.68, 95% CI 0.52–0.89) Results from clinical trials are inconclusive. Optical profilometry and computerized image analysis have been used to demonstrate that topical HRT on the face can improve fine wrinkling[47] and significantly decrease wrinkle depth[20] within 2 months of treatment. However, others have used similar techniques and failed to demonstrate changes in facial wrinkling with HRT.[33,52]

### 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 oestrogen on the cutaneous circulation of women has not been well studied. Consistent with the formation of pre-menstruation oedema in women, cutaneous blood flow has been shown to vary over the course of the menstrual cycle.[28] In addition, peripheral microcirculation at the level of the nail-fold capillaries has been shown to decrease significantly with the menopause.[55]

Oestrogens are known to substantially improve both endothelium-dependent and -independent vascular reactivity in the cutaneous microcirculation of post-menopausal women.[56,57] Studies measuring the effect of HRT on blood flow rates, however, are somewhat inconsistent. Although some have demonstrated that 6–12 months of HRT use increases capillary blood flow in the nail-fold by as much as 20% to 30%,[55] others have reported that long-term oestrogen therapy (> 2 years) does not increase cutaneous vascular flow when compared with untreated women.[58]

## Effect of oestrogen on wound healing

The effects of intrinsic ageing 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 alike.[59] The role of oestrogen 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 oestrogen and wound healing

The initial phases of cutaneous wound healing involve vascularization, granulation, collagen deposition, and re-epithelialization.[60] An early study by Lindhe and colleagues[61] found oestrogen 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 that oestradiol alone has no effect on vascularization;[62,63] by contrast a large study in oophorectomized rats that used similar

microangiographic techniques observed a significant suppression in vascularization in oestrogen-treated animals.[64] Examination of wound vascularization after treatment with oestrogen in combination with a progesterone has also produced inconclusive results. Whereas two studies reported that oestradiol given in conjunction with progesterone decreases vascular exudation during the inflammatory phase of wound healing,[62,63] others have found no effect.[64,65] Recent molecular research on the influence of oestrogen on the cells and vasculature involved in the inflammatory phase of wound repair suggests that oestrogen may reduce the cellular activation of blood platelets and may affect phagocytic activity of neutrophils.[60] A direct association with post-menopausal oestrogen treatment and the inflammatory phase of wound healing remains to be investigated.

The majority of studies on oestrogen's effect on wound collagen deposition and strength have also utilized animal models. Oestrogen treatment has been shown to increase collagen deposition in wounds of oophorectomized rats[66–68] and rabbits;[66] however, others have found that systemic oestrogen exerts either no effect[63,69,70] or decreases collagen deposition,[69,70] depending on dose and time since wounding. Similarly, oestrogen given in conjunction with a progesterone has been shown to either have no effect[70] or to decrease collagen in wound granulomas;[63,70] the effect again can depend on the time since wounding.[70] Consistent with the findings for collagen deposition, measures of wound tensile strength in animals have produced varied results.[66,70,71]

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 oestrogen injected at low doses (0.33–1 μg/kg) improved wound healing time, but higher doses (3.3–10 μg/kg) prolonged healing time.[72] Further, a study in oophorectomized rats showed that prolonged loss of ovarian hormones is associated with slow wound contraction,[73] but these authors did not examine the effect of systemic oestrogen treatment. In general, investigations with animals demonstrate contradictory findings as to the effect of oestrogen levels on the stages of wound healing. These discrepancies are probably due to differences in species, duration of treatment, and methodologies employed.[60]

### Clinical and molecular studies on oestrogen and wound healing

Some of the more recent work on wound healing has examined the molecular role of oestrogen 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-beta 1 (TGF-β1), decreased collagen synthesis, and increased presence of proteases, specifically elastase. The presence of the oestrogen receptor on the major cell type involved in wound repair (i.e. fibroblasts) suggests that oestrogen may directly modulate the function of these cells. Indeed, a study using wound biopsy specimens from healthy females suggested that oestrogen exerts a positive influence on healing, not by increasing fibroblast proliferation within a wound, but rather by inducing TGF-β1 secretion by dermal fibroblasts.[74] In addition, recent clinical studies by Ashcroft and colleagues have demonstrated that oestrogen has a beneficial effect on wound healing by increasing collagen content[59,74] and reducing collagenolysis.[59] In one small study, 10 post-menopausal women taking HRT were compared with age-matched controls.[74] 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 oestrogen reduces activity of the protease elastase in cutaneous wounds when compared with placebo.[59] Decreased elastase would stimulate matrix deposition and allow for faster wound healing. Indeed, that same study observed that topical oestrogen applied to normal elderly skin prior to wounding and 24 h post-wounding significantly accelerated wound healing in both males and females.[59]

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 oestrogens 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 dermatoses,[30] such as ecchymosis.

## Discussion

The technology now exists to further explore the molecular basis of oestrogen's role in maintaining skin integrity. Using gene-chip microarray techniques, oestrogen-responsive genes in skin can be identified, characterized, and monitored under varying hormonal conditions. Determining the oestrogen sensitivity of enzymes responsible for the production and/or degradation

  

of structural components of the skin, such as GAGs or collagen and elastin fibres, will substantially enhance our understanding of the mechanistic role of oestrogen in skin.

When biochemical and histological parameters for oestrogen-sensitive structures in skin have been established at the molecular level, a correlation between these markers, oestrogen status and physical attributes of skin need to be carefully investigated and quantified 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.

Preclinical and clinical data on the effect of oestrogen on skin water content are also promising. Physiological studies on oestrogen 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 physiological 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 oestrogen 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 post-menopausal oestrogen use and its potential application to skin care. Indeed, whereas the less visible benefits of RT have been stressed by health professionals, potential effects of oestrogen on the skin have not been emphasized and may prove meaningful to the target population of post-menopausal women.

## Conclusions

Oestrogen loss profoundly affects the skin. Oestrogen treatment of post-menopausal woman increases collagen content, dermal thickness and elasticity.

## References


1 Barrett-Connor E. Epidemiology and the menopause: a global overview. *Int J Fertil Menopausal Stud* 1993; **38** (Suppl. 1): 6–14.

2 Zichella L. Clinical management of the menopausal woman. *Int J Fertil Menopausal Stud* 1993; **38** (Suppl. 1): 15–22.

3 Uitto J. Connective tissue biochemistry of the aging dermis: age-related alterations in collagen and elastin. *Dermatol Clin* 1986; **4**: 433–46.

4 Bolognia JL, Braverman IM, Rousseau ME, Sarrel PM. Skin changes in menopause. *Maturitas* 1989; **11**: 295–304.

5 MacLean AB, Nicol LA, Hodgkins MB. Immunohistochemical localization of oestrogen receptors in the vulva and vagina. *J Reprod Med* 1990; **35**: 1015–6.

6 Jemec GBE, Wojnarowska F. The distribution of p29 protein in normal human skin. *Br J Dermatol* 1987; **117**: 217–24.

7 Nelson LR, Bulun SE. Oestrogen production and action. *J Am Acad Dermatol* 2001; **45**: S116–S124.

8 Falanga V, Greenberg AS, Zhou L *et al.* Stimulation of collagen synthesis by the anabolic steroid stanozolol. *J Invest Dermatol* 1998; **111**: 1193–7.

9 Mahonen A, Jukkola A, Risteli L, Risteli J, Maenpaa PH. Type I procollagen synthesis is regulated by steroids and related hormones in human osteosarcoma cells. *J Cell Biochem* 1998; **68**: 151–63.

10 Woessner JF Jr. Total, latent and active collagenase during the course of post-partum involution of the rat uterus: effect of oestradiol. *Biochem J* 1979; **180**: 95–102.

11 Castelo-Branco C, Duran M, Gonzalez-Merlo J. Skin collagen changes related to age and hormone replacement therapy. *Maturitas* 1992; **15**: 113–9.

12 Brincat M, Versi E, Moniz CF, Magos A, de Trafford J, Studd JW. Skin collagen changes in postmenopausal women receiving different regimens of oestrogen therapy. *Obstet Gynecol* 1987; **70**: 123–7.

13 Brincat M, Kabalan S, Studd JW, Moniz CF, de Trafford J, Montgomery J. A study of the decrease of skin collagen content, skin thickness, and bone mass in the postmenopausal woman. *Obstet Gynecol* 1987; **70**: 840–5.

14 Affinito P, Palomba S, Sorrentino C *et al.* Effects of postmenopausal hypooestrogenism on skin collagen. *Maturitas* 1999; **33**: 239–47.

15 Shah MG, Maibach HI. Oestrogen and skin. An overview. *Am J Clin Dermatol* 2001; **2**: 143–50.

16 Brincat M, Moniz CJ, Studd JW *et al.* Long-term effects of the menopause and sex hormones on skin thickness. *Br J Obstet Gynaecol* 1985; **92**: 256–9.

17 Brincat M, Moniz CF, Studd JW, Darby AJ, Magos A, Cooper D. Sex hormones and skin collagen content in postmenopausal women. *Br Med J (Clin Res Ed)* 1983; **287**: 1337–8.

18 Brincat M, Moniz CF, Kabalan S *et al.* Decline in skin collagen content and metacarpal index after the menopause and its prevention with sex hormone replacement. *Br J Obstet Gynaecol* 1987; **94**: 126–9.

19 Savvas M, Bishop J, Laurent G, Watson N, Studd J. Type III collagen content in the skin of postmenopausal women receiving oestradiol and testosterone implants. *Br J Obstet Gynaecol* 1993; **100**: 154–6.

20 Schmidt JB, Binder M, Demschik G, Bieglmayer C, Reiner A. Treatment of skin aging with topical oestrogens. *Int J Dermatol* 1996; **35**: 669–74.


 

21 Varila E, Rantala I, Oikarinen A *et al.* The effect of topical oestradiol on skin collagen of postmenopausal women. *Br J Obstet Gynaecol* 1995; **102**: 985–9.
22 Sauerbronn AVD, Fonseca AM, Bagnoli VR, Saldiva PH, Pinotti JA. The effects of systemic hormonal replacement therapy on the skin of postmenopausal women. *Int J Gynaecol Obstet* 2000; **68**: 35–41.
23 Haapasaari K-M, Raudaskoski T, Kallioinen M *et al.* Systemic therapy with oestrogen or oestrogen with progestin has no effect on skin collagen in postmenopausal women. *Maturitas* 1997; **27**: 153–62.
24 Oikarinen A. Systemic oestrogens have no conclusive beneficial effect on human skin connective tissue. *Acta Obstet Gynecol Scand* 2000; **79**: 250–4.
25 Punnonen R, Vaajalahti P, Teisala K. Local oestriol treatment improves the structure of elastic fibers in the skin of postmenopausal women. *Ann Chir Gynaecol* 1987; **76**: 39–41.
26 Kalogirou D, Aroni K, Kalogirou O, Antoniou G, Botsis D, Kontoravdis A. Histological changes induced by tibolone and oestrogen/glucocorticoid on aging skin. *Int J Fertil Womens Med* 2000; **45**: 273–8.
27 Beauregard S, Gilchrest BA. A survey of skin problems and skin care regimens in the elderly. *Arch Dermatol* 1987; **123**: 1638–43.
28 Harvell J, Hussona-Saeed I, Maibach HI. Changes in transepidermal water loss and cutaneous blood flow during the menstrual cycle. *Contact Dermatitis* 1992; **27**: 294–301.
29 Wilhelm KP, Cua AB, Maibach HI. Skin aging: effect on transepidermal water loss, stratum corneum hydration, skin surface pH, and casual sebum content. *Arch Dermatol* 1991; **127**: 1806–9.
30 Pierard-Franchimont C, Letawe C, Goffin V, Pierard GE. Skin water-holding capacity and transdermal oestrogen therapy for menopause: a pilot study. *Maturitas* 1995; **22**: 151–4.
31 Sator PG, Schmidt JB, Sator MO, Huber JC, Honigsmann H. The influence of hormone replacement therapy on skin ageing: a pilot study. *Maturitas* 2001; **39**: 43–55.
32 Schmidt JB, Binder M, Macheiner W, Kainz C, Gitsch G, Bieglmayer C. Treatment of skin ageing symptoms in perimenopausal females with oestrogen compounds. A pilot study. *Maturitas* 1994; **20**: 25–30.
33 Callens A, Vaillant L, Lecomte P, Berson M, Gall Y, Lorette G. Does hormonal skin aging exist? A study of the influence of different hormone therapy regimens on the skin of postmenopausal women using non-invasive measurement techniques. *Dermatology* 1996; **193**: 289–94.
34 Dunn LB, Damesyn M, Moore AA, Reuben DB, Greendale GA. Does oestrogen prevent skin aging? Results from the First National Health and Nutrition Examination Survey (NHANES I). *Arch Dermatol* 1997; **133**: 339–42.
35 Whitmore SE. Oestrogen, skin aging, and study design. *Arch Dermatol* 1997; **133**: 1460–2.
36 Sobel H, Cohen RA. Effect of estradiol on hyaluronic acid in the skin of aging mice. *Steroids* 1970; **16**: 1–3.
37 Grosman N, Hvidberg E, Schou J. The effect of oestrogenic treatment on the acid mucopolysaccharide pattern in skin of mice. *Acta Pharmacol Toxicol* 1971; **30**: 458–64.
38 Kanke Y, Nishina H, Mori Y, Bashey RI. Study of the effect of oestradiol on hexosamine-containing substances and a possible receptor in the skin of male mice. *Acta Endocrinol* 1977; **85**: 429–35.
39 Uzuka M, Nakajima K, Ohta S, Mori Y. The mechanism of oestrogen-induced increase in hyaluronic acid biosynthesis, with special reference to oestrogen receptor in the mouse skin. *Biochim Biophys Acta* 1980; **627**: 199–206.
40 Jacobsen E, Billings JK, Frantz RA, Kinney CK, Stewart ME, Downing DT. Age-related changes in sebaceous wax ester secretion rates in men and women. *J Invest Dermatol* 1985; **85**: 483–5.
41 McConkey B, Fraser GM, Bligh AS, Whitely H. Transparent skin and osteoporosis. *Lancet* 1963; **1**: 693–5.
42 McConkey B, Walton KW, Carney SA, Lawrence JC, Ricketts CR. Significance of the occurrence of transparent skin: a study of histological characteristics and biosynthesis of dermal collagen. *Ann Rheum Dis* 1967; **26**: 219–25.
43 Black MM, Shuster S, Bottoms E. Osteoporosis, skin collagen, and androgen. *BMJ* 1970; **4**: 773–4.
44 Stevenson CJ, Bottoms E, Shuster S. Skin collagen in osteogenesis imperfecta. *Lancet* 1970; **1**: 860–1.
45 Baron YM, Brincat M, Galea R. Increased reduction in bone density and skin thickness in postmenopausal women on long-term corticosteroid therapy. A suggested role for oestrogen add back therapy. *Adv Exp Med Biol* 1999; **455**: 429–36.
46 Cortes-Gallegos V, Villanueva GL, Sojo-Aranda I, Santa Cruz FJ. Inverted skin changes induced by oestrogen and oestrogen/glucocorticoid on aging dermis. *Gynecol Endocrinol* 1996; **10**: 125–8.
47 Creidi P, Faivre B, Agache P, Richard E, Haudiquet V, Sauvanet JP. Effect of a conjugated oestrogen (Premarin®) cream on ageing facial skin. A comparative study with a placebo cream. *Maturitas* 1994; **19**: 211–23.
48 Meschia M, Bruschi F, Amicarelli F, Barbacini P, Monza GC, Crosignani PG. Transdermal hormone replacement therapy and skin in postmenopausal women: a placebo controlled study. *Menopause* 1994; **1**: 79–82.
49 Maheux R, Naud F, Rioux M *et al.* A randomized, double-blind, placebo-controlled study on the effect of conjugated oestrogens on skin thickness. *Am J Obstet Gynecol* 1994; **170**: 642–9.
50 Chen L, Dyson M, Rymer J, Bolton PA, Young SR. The use of high-frequency diagnostic ultrasound to investigate the effect of hormone replacement therapy on skin thickness. *Skin Res Technol* 2001; **7**: 95–7.
51 Pierard-Franchimont C, Cornil F, Dehavay J, Deleixhe-Mauhin F, Letot B, Pierard GE. Climacteric skin ageing of the face – a prospective longitudinal comparative trial on the effect of oral hormone replacement therapy. *Maturitas* 1999; **32**: 87–93.

52 Henry F, Pierard-Franchimont C, Cauwenbergh G, Pierard GE. Age-related changes in facial skin contours and rheology. *J Am Geriatr Soc* 1997; **45**: 220–2.
53 Pierard GE, Letawe C, Dowlati A, Pierard-Franchimont C. Effect of hormone replacement therapy for menopause on the mechanical properties of skin. *J Am Geriatr Soc* 1995; **43**: 662–5.
54 Castelo-Branco C, Figueras F, Martinez de Osaba MJ, Vanrell JA. Facial wrinkling in postmenopausal women. Effects of smoking status and hormone replacement therapy. *Maturitas* 1998; **29**: 75–86.
55 Haenggi W, Linder HR, Birkhaeuser MH, Schneider H. Microscopic findings of the nail-fold capillaries – dependence on menopausal status and hormone replacement therapy. *Maturitas* 1995; **22**: 37–46.
56 Arora S, Veves A, Caballero AE, Smakowski P, LoGerfo FW. Oestrogen improves endothelial function. *J Vasc Surg* 1998; **27**: 1141–6.
57 Lim SC, Caballero AE, Arora S *et al.* The effect of hormonal replacement therapy on the vascular reactivity and endothelial function of healthy individuals and individuals with type 2 diabetes. *J Clin Endocrinol Metab* 1999; **84**: 4159–64.
58 Brooks EM, Morgan AL, Pierzga JM *et al.* Chronic hormone replacement therapy alters thermoregulatory and vasomotor function in postmenopausal women. *J Appl Physiol* 1997; **83**: 477–84.
59 Ashcroft GS, Greenwell-Wild T, Horan MA, Wahl SM, Ferguson MW. Topical oestrogen accelerates cutaneous wound healing in aged humans associated with an altered inflammatory response. *Am J Pathol* 1999; **155**: 1137–46.
60 Calvin M. Oestrogens and wound healing. *Maturitas* 2000; **34**: 195–210.
61 Lindhe J, Birch J, Branemark PI. Wound healing in oestrogen treated female rabbits. *J Periodontal Res* 1968; **3**: 21–3.
62 Nyman S, Lindhe J, Zederfeldt B. The vascularity of wounded areas in estradiol and progesterone treated female rabbits: a microangiographic study. *Acta Chir Scand* 1971; **137**: 631–7.
63 Pallin B, Ahonen J, Rank F, Zederfeldt B. Granulation tissue formation in oophorectomized rats treated with female sex hormones: I. A histological study. *Acta Chir Scand* 1975; **141**: 702–9.
64 Lundgren D. Influence of oestrogen and progesterone on vascularization of granulation tissue in preformed cavities: a microangiographic study. *Scand J Plast Reconstr Surg* 1973; **7**: 85–90.
65 Nyman S, Lindhe J, Zederfeldt B, Solvell L. Vascular permeability in wounded areas of estradiol and progesterone treated female rabbits. *Acta Chir Scand* 1971; **137**: 709–14.
66 Cretti A. O wplywie estradiolu i progesteronu na gojenie sie ran. *Roczniki Akademii Medycznej im Juliana Marchlewskiego w Bialymstoku Supplement* 1966; **14**: 1–60.
67 Ramamurthy NS, McClain SA, Pirila E *et al.* Wound healing in aged normal and ovariectomized rats: effects of chemically modified doxycycline (CMT-8) on MMP expression and collagen synthesis. *Ann N Y Acad Sci* 1999; **878**: 720–3.
68 Pirila E, Ramamurthy NS, Maisi P *et al.* Wound healing in ovariectomized rats: effects of chemically modified tetracycline (CMT-8) and oestrogen on matrix metalloproteinases-8-13 and type I collagen expression. *Curr Med Chem* 2001; **8**: 281–94.
69 Murthy CP, Prakash A, Pandit PN, Sharma LK. Effects of oestrogen on wound healing – an experimental study. *Indian J Surg* 1974; **36**: 1–7.
70 Pallin B, Ahonen J, Zederfeldt B. Granulation tissue formation in oophorectomized rats treated with female sex hormones. II. Studies on the amount of collagen and on tensile strength. *Acta Chir Scand* 1975; **141**: 710–4.
71 Nyman S, Lindhe J, Zederfeldt B. Influence of oestrogen and progesterone on tissue regeneration in oophorectomized rabbits. *Acta Chir Scand* 1971; **137**: 131–9.
72 Roth GS, Harman SM, Lamberg SI. Altered ovarian regulation of wound healing during aging. *Proc Soc Exp Biol Med* 1981; **166**: 17–23.
73 Calvin M, Dyson M, Rymer J, Young SR. The effects of ovarian hormone deficiency on wound contraction in a rat model. *Br J Obstet Gynaecol* 1998; **105**: 223–7.
74 Ashcroft GS, Dodsworth J, van Boxtel E *et al.* Oestrogen accelerates cutaneous wound healing associated with an increase in TGF-b1 levels. *Nat Med* 1997; **3**: 1209–15.