

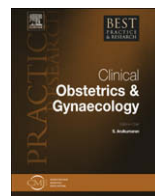


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Contents lists available at ScienceDirect

Best Practice & Research Clinical Obstetrics and Gynaecology

journal homepage: www.elsevier.com/locate/bpobgyn



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Effects of hormone replacement therapy on connective tissue: why is this important?

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Keywords:

menopause
collagen
oestrogen
hormone replacement therapy
skin
carotid artery media
intervertebral discs
connective tissue

Oestrogen deprivation has a negative effect on connective tissue and its turnover, although it can be difficult to distinguish these changes from those related to age. Such an effect can be prevented to some extent, and in some cases reversed, with oestrogen therapy. This has been shown to happen in the skin dermis, bone matrix, carotid artery media and intervertebral discs. This effect is also likely to extend to the extracellular non-collagenous matrix in all these systems, as oestrogen has profound effects on connective tissue turnover, regardless of the site. This has implications not only in maintaining the structure and aesthetic appearance of tissue, but also its strength and stiffness, and the functioning of neighbouring and surrounding organs. Large-scale clinical trials are necessary to help make informed recommendations regarding postmenopausal oestrogen use and its role in connective tissue turnover.

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'Although we have effective treatment for osteoporosis, each year millions of our grandmothers are crippled and disfigured, because they don't have easy and sufficient access to diagnosis and medication ... the women who have cared for us, now need us to care enough to urge policy makers to give them access to proven therapies before they break a bone' (Queen Rania of Jordan)

It has been shown repeatedly that, in addition to a negative effect on the bone matrix, the menopause also has a negative effect on connective tissue in the skin dermis, carotid artery media and intervertebral discs. The connective tissue of the adult body is mainly composed of Type I collagen.

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Many studies have shown the positive effects of oestrogen on connective tissue, regardless of site or type.¹

Skin

The skin is the largest organ in the body and is stratified into three layers: epidermis, dermis and subcutaneous.² Eighty percent of the dry weight of adult skin consists of collagen. The predominant form of collagen found in adult human skin is Type I, followed by Type III.³

The effects of the menopause on the skin are thought to include atrophy, decreased collagen and water content, decreased sebaceous secretions, loss of elasticity, and manifestations of hyperandrogenism.⁴ As much as 30% of skin collagen (Type I and III) is lost in the first 5 years after the menopause.^{5,6} Total collagen declines, on average, by 2.1% per postmenopausal year over a period of 15 years.^{7,8} Most clinical trials have shown that postmenopausal women who take hormone replacement therapy (HRT) have thicker skin compared with non-users.^{9–14}

However, the exact role of oestrogen on the integrity of collagen is still unclear.¹⁵ A number of studies have shown a strong correlation between loss of skin collagen and oestrogen deficiency due to the menopause.^{5,7} The cumulative effect of oestrogen deficiency on the skin is thought to contribute to poor wound healing in older patients.¹⁵

In mice, oophorectomy alone was sufficient to accelerate skin ageing and increase sensitivity to ultraviolet (UV) radiation. In one study, hairless mice were used to assess the effects of oophorectomy with or without chronic UVA or UVB radiation on sagging and wrinkling of skin, elasticity of skin, and matrix metalloproteinase activities in the skin. Even without UV irradiation, skin elasticity decreased significantly during the 3–13 weeks after oophorectomy, accompanied by a significant increase in elastase activity in the skin. After UVA or UVB irradiation, skin elasticity decreased significantly to a greater extent in the oophorectomy group than in the sham operation group, and this was accompanied by a reciprocal increase in elastase activity but not in the activities of collagenases I or IV in the skin.¹⁶

Anabolic steroids have been shown to increase collagen synthesis in human dermal fibroblasts.¹⁷ In rats, oestrogen has been shown to inhibit collagen degradation.¹⁸ On the other hand, oestrogens have no stimulatory effect on procollagen synthesis in cultured human cells.¹⁹

One study showed a closer correlation between collagen loss and chronological age than between skin collagen loss and time since the menopause.⁹ This finding may be explained by the fact that the study participants were between 40 and 55 years of age and had recently undergone surgical menopause; consequently, they had not been oestrogen deficient for a long time.²⁰ However, when more than 1 year had elapsed since the menopause, a more pronounced reduction in skin collagen content was noted.⁹

There is evidence to show that the decline in skin collagen content can be prevented in women receiving oestrogen therapy.²¹ A beneficial effect of subcutaneous^{6–8,21–23}, topical^{7,8,24,25} and oral^{9,26} oestrogen treatment has been demonstrated on the collagen content of skin. The extent of the oestrogen-induced increase in collagen content was dependent upon the route of administration, dose and duration of hormone treatment. Moreover, there are differences in the methods employed to assess collagen levels, so results between studies are often not comparable.¹⁵

The increase in collagen with oestrogen is proportionate to baseline collagen levels.^{7,8} One study observed no change in collagen levels of postmenopausal women following 1 year of HRT.²⁷ This can be explained by the fact that, given the short time since the menopause, the amount and synthetic rate of collagen may have been optimal.²⁸ A delay in the collagen decrease after the onset of the menopause has been reported.²² Oestrogen treatment may be prophylactic for women with high skin collagen levels and even therapeutic for women with low collagen content.^{7,8} More research is necessary to confirm whether this also applies to low-dose oestrogen.

Like collagen, elastin is a fibre-forming functional protein. Elastin fibres are closely linked and interwoven with the collagen fibrils so that they can recoil after transient stretching and are prevented from overstretching. Young women who underwent premature menopause were observed to have accelerated degenerative changes in dermal elastic fibres.²⁹ Histological studies have demonstrated that topical oestrogen can increase the number and thickness of skin elastic fibres.³⁰ Recent clinical

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