Menopause and the effects of Hormone Replacement Therapy on skin aging: A Short Review

Mark P. Brincat[1, 2], Joel Pollacco[1]

[1] Department of Obstetrics and Gynecology, University of Malta Medical School, Msida, Malta.
[2] Department of Medical Education, Queen Mary University of London, Malta Campus (Gozo), Malta

ABSTRACT

Background and purpose: Thinning of the skin, wrinkling and skin dryness are all changes that tend to worsen with age. These changes are all related to dysfunction of the cells making up the dermal layers such as the keratinocytes and fibroblasts. The findings of estrogen receptors on these cells suggest that estrogen deficiency, characteristic of the menopausal state, may be partly responsible for skin aging. In this paper, we aim to provide a narrative review on the associations between menopause, hormone replacement therapy (HRT) and skin aging.

Methods: A search was carried out on databases such as PubMed, Google Scholar for articles published in international peer-reviewed journals using keywords such as, "skin aging and HRT", "skin collagen and HRT", "skin water content and HRT", "skin dryness and HRT", "skin wrinkling and HRT", "wrinkling and HRT".

Results: This search yielded a variety of both observational human and experimental animal studies. The great majority of studies showed interesting associations between improved skin physical parameters and hormone replacement, in particular estrogen use. Some studies were not consistent with such observations and yielded confusing results.

Conclusions: Withdrawal of sex steroid hormones seems to be partly responsible for aging of the skin that occurs in postmenopausal women. Unfortunately, most of the studies were limited by a small number of study participants. Larger, more robust high-quality studies are needed to further assess the relationship between HRT and skin aging changes.

KEYWORDS

Hormone replacement therapy (HRT), skin wrinkles, skin thickness, skin dryness, wound healing.

Introduction

Skin senescent changes are caused by reduced collagen, elasticity and decreased total body water content. The magnitude of these changes is directly proportional to increasing age. However, there is an increasing body of evidence that suggest that skin aging changes are directly correlated to menopausal age rather than chronological age, implying estrogen deficiency as a contributory factor. Indeed, this hypothesis is corroborated by the finding of estrogen receptors on fibroblast cells, endothelial cells, neutrophils and keratinocytes[1], suggesting that estrogen plays a vital role in the health of skin and connective tissues. Menopause is characterized by the cessation of production of the ovarian hormones, estrogen and progesterone [2]. With the increased life expectancy, brought by better medical standards [3], women are spending about one third of their lives in the postmenopausal state [1,4-6]. The skin is the most readily visible organ of the whole body and its health is given paramount importance in Western cultures, with an estimated $664 million spent in the US in 2005 on anti-aging skin care products [7],particularly since the effects of skin aging negatively impact psychosexual function [8-10].

The links between HRT and the Skin

Skin aging changes, in which menopause is at least partly implicated, involve a reduction in skin thickness, elasticity and water content as a result of decreased collagen levels, elastin and glycosaminoglycans [10].

Article history
Received 24 Sep 2023 - Accepted 2 Feb 2024

Contact
Joel Pollacco, MD EFOG-EBCOG; jcpollacco@gmail.com
Mater Dei Hospital
Department of Obstetrics and Gynaecology
Triq id-Donaturi tad-Demm
Msida
MSD 2080
Malta

DOI
10.53260/grem.2450106

HRT, collagen and skin thickness

Collagen is the major structural protein of most connective tissues including the dermis of the skin. The most predominant forms of collagen are types I and III [4,11-13]. Type I collagen imparts most of the skin's structural integrity, accounting for about 80% of the dermis [2],whereas type III collagen, making up about 15% of collagen in the dermis [2], together with elastin is responsible for its elasticity [4]. The estrogen-deficient changes to the collagen component of dermal skin were hinted at as early as 1940 by

Albright [14], who noticed that thin skin was more common in older women with osteoporotic fractures. This was further supported by an observation made by MacConkey [15] who noticed thinner, fragile skin was more common in postmenopausal women.

Indeed, skin thickness, was found to correlate to its collagen content in later studies [16,17]. A study carried out by Brincat *et al*. [18] showed a 48% statistically significant increase in skin mean collagen content in a group of women treated with estradiol and testosterone for 2 to 10 years as opposed to a control group of untreated women. The presence of estrogen receptor on skin tissue components [1] suggests that this might be an estrogenic effect, nevertheless there have been other studies such as the one by Shuster *et al*. [17], which proposes that androgens may have a role in imparting hirsute women with increased skin collagen content and thickness. There is also the possibility that the increased skin collagen content observed by Brincat *et al*. [19] is a synergistic effect of estrogen and testosterone. In the same study, Brincat et al., reported skin collagen content was negatively correlated with menopausal age but not chronological age and positively correlated with skin thickness [19]. This corresponds to the results from other studies such as the open study by Caliens *et al*. [20] in which a statistically significant increase in skin thickness, as measured by an ultrasound technique, was noted in a group of 49 postmenopausal women receiving HRT as opposed to controls. The recruited individuals had similar chronological age, menopausal age, sun exposure and phototype. This strongly supports the hypothesis of hormonal skin aging in postmenopausal women. The same authors suggest that the differences in the skin's physical parameters seen with HRT seem to be related to the dermis [20] Since the dermis is mostly made up of collagen, accounting for up to 75% of the skin's dry weight [2], this is most likely to be related to a decrease in the quantitative or qualitative properties of the produced collagen. The link between HRT and increased skin thickness has been shown as early as 1992, when Castelo-Branco *et al*. [13] demonstrated that postmenopausal women receiving some form of HRT showed increased skin collagen levels, as opposed to a control group, with the greatest increase reported for the HRT group receiving transdermal estrogen. The same authors report a much stronger correlation of skin collagen levels with chronological age, rather than menopausal age. However, this might have been since the majority of postmenopausal women in the study had been in the postmenopausal period for a very short time [13].

A handful of randomized controlled trials have been carried out looking into the effect of HRT on the skin's physical parameters such as thickness and collagen content. Varila *et al*. [21] investigated the effect of topical estradiol application on a group of 12 postmenopausal women, on skin collagen and elastin, from over the sites of patch application as opposed to sites of application of vehicle gel on the contralateral abdominal side. Following treatment with topical HRT, these women were found to have statistically significant increased collagen type I as well as a 38% increase in hydroxyproline levels, that was not affected by chronological or menopausal age. Maheux *et al*. reported a 33% increased dermal thickness in a double-blind placebo randomized controlled trial, investigating the effect of a 6 month course of combined equine estrogens [22]. In addition, the authors also observed in one of their study participants skin morphological changes, such as increased keratinocyte layers and more pronounced rete ridges [22]. The findings from Maheux *et al*., were further corroborated by a double-blind randomized placebo-controlled study carried out by Sauerbronn *et al*. [23], in which there was a 6.49% increase in skin collagen content following the administration for 6 months of oral cyclical HRT.

Skin collagen content was found to be positively correlated with bone density and negatively correlated with menopausal age in a control group of postmenopausal women on no treatment with a 45% decrease in collagen content in women with 15 years of postmenopause. The correlation of collagen content to menopausal age was lost in the treatment group with both values for collagen content and bone density being higher in the treatment group as opposed to the control one [24]. Haapasaari *et al*. [25] reported no statistically significant association between systemic HRT and skin collagen in postmenopausal women. However, this is a finding that is most likely explained by the fact that the study participants they recruited had only been within 6 months to 2 years postmenopause and therefore any significant improvements in skin collagen might not have been significant [5,25].

HRT and skin elasticity

Skin wrinkling especially on the face [26] is another readily visible sign of skin aging, usually as a result of long-term sun exposure, that is contributed to by a decrease in the skin's elasticity. This is a feature for which hormonal skin aging, as a result of postmenopausal estrogen withdrawal, may be partly responsible [27]. The decrease in content of the structural components of the dermis, namely, collagen, elastin and hyaluronic acid causes increased skin rigidity and decreased elasticity leading to skin wrinkling [28].

A cross-sectional study investigating the biophysical properties of the skin, found that these were significantly improved in postmenopausal women who had been taking HRT for at least 5 years, reporting superior parameters related to hydration, sebum production, as well as higher skin relief parameters on the forehead [29]. Pierard-Franchimont *et al*. conducted a prospective longitudinal comparative trial on the effect of oral HRT on a number of non-invasive biophysical tensile properties of facial skin of 140 menopausal women. HRT users significantly improved biological elasticity after five years of HRT treatment as opposed to the control group [26]. In keeping with the study by Pierard-Franchimont *et al*., is another study on a group of 200 healthy Caucasian women, showing statistically significant increased biological elasticity in the HRT treatment group as opposed to controls [6].

A study using non-invasive measurements of facial skin topographic characteristics performed on a group of 11 pre- and postmenopausal women aged 38 to 58 years, receiving HRT showed that there was a statistically significant decrease of 5 to 7% in the skin roughness in the first six months of treatment that increased to a 16% after receiving one year of hormonal treatment [30]. Interestingly enough, when observing for any intragroup differences, skin tensile properties were not found to be correlated to its thickness, suggesting that other skin properties such as sebum production may be more important in preventing skin wrinkles on the face [26]. A single-blinded cross-sectional analysis performed by Wolff *et al*. showed decreased skin rigidity at both the cheek

and forehead in HRT users as well as lower average wrinkle scores in HRT users as opposed to non-users [31].

Contrary to the expected results, in the skin ancillary study of the Kronos Early Estrogen Prevention (KEEPS) trial there was no statistically significant difference found between total wrinkle score at baseline and after four years follow-up, as well as between total facial skin rigidity score for all the three randomized groups of conjugated equine estrogens, estradiol or placebo [28]. Surprisingly, race was found to be the strongest predictor of skin aging in this study. This finding was consistent with a previous study evaluating the baseline characteristics of the skin ancillary study of the KEEPS trial [32], whereby the total skin wrinkle score as well as the wrinkle score from different anatomic sites was significantly lower in black women. Skin wrinkling was found to be positively correlated to chronological age, whilst inversely correlated with body weight. Skin rigidity was more closely associated with time since menopause in the Caucasian population in the same study, suggesting that the latter property is more readily influenced by menopausal age rather than chronological age, as opposed to skin wrinkling which seems to be more importantly influenced by chronological age and race.

HRT and skin water content

Xerosis is one of the commonest features of skin aging. Skin dryness is caused by decreased water content. Skin water content is a product of the amount of water stored in the skin dermis and the rate of transepidermal water loss [5]. Healthy skin dermis is rich in a variety of glycosaminoglycans and proteoglycans. These imbibe water and help keep the skin well hydrated. Mouse studies have shown that estrogen upregulates the production of acid mucopolysaccharides and hyaluronic acid in the skin [33-36]. A large population-based study from the First National Health and Nutrition Examination Survey (NHANES I) showed that postmenopausal women using HRT were less likely to suffer from dry skin than those not on hormonal replacement [4,37].

The proliferation of the epidermal cell layers leads to the formation of the most superior layer, the stratum corneum. The stratum corneum is covered with sebum, an oily secretion produced by the sebaceous glands and these components collectively help reduce trans-epidermal water loss. In a longitudinal randomized study of 24 patients, there was a statistically significant increase in epidermal hydration levels for women on combined oral HRT, combined HRT with transdermal estrogen as well as women on transdermal estrogen [38]. A statistically significant increase in skin surface lipids, suggesting increased sebaceous secretions with HRT was noted in women on combined HRT regimens [38]. The increase in sebaceous gland secretions with estrogen therapy was also confirmed in a study by Caliens *et al*. [20]

Improved hydration of the stratum corneum was also demonstrated in a study by Schmidt *et al*., in which peri-menopausal or postmenopausal women were receiving either 0.3% estriol cream or 0.01% estradiol cream [4,39]. Moreover, Pierard-Franchimont *et al*. [40], in a small study, involving 15 menopausal women receiving cyclic transdermal HRT, showed an increase in the water-holding capacity of the skin. All this shows that HRT may increase skin water content and prevent its dryness by both improving the barrier function of the stratum corneum as well as by increasing dermal hyaluronic acid and acid polysaccharides. The barrier function of the stratum corneum may be improved either directly, by increased epidermal hydration, through the proliferation of the epidermal cell layers or indirectly by increased sebaceous secretions, decreasing the trans-epidermal water loss.

HRT and wound healing

Wound healing involves inflammatory, tissue proliferative and remodeling phases and it comprises a complex interplay between neutrophils, keratinocytes, fibroblasts, and endothelial cells. All these three distinct cell types were found to possess estrogen receptors. Estrogens seem to influence the cutaneous healing process by down-regulating the inflammatory response, modulating cytokine expression, and stimulating re-epithelialization and angiogenesis, while suppressing proteolysis [1]. The role of neo-vascularization in wound healing and its association with estrogen is suggested by an observational study by Margolis *et al*.[41], whereby patients on HRT where less likely to develop venous or pressure ulcers, emphasizing the role of estrogen in securing good blood flow to the skin.

Estrogen seems to prevent the age-related delayed wound healing by dampening the inflammatory response, by downregulating the production of pro-inflammatory cytokines such as macrophage migration inhibitory factor [42] and by the upregulation of other factors such as transforming growth factor – beta 1 levels (TGF-β1) [1,43]. This is in contrast with an animal study carried out by Ashcroft *et al*. [44] in which null mice to secretory leukocyte protease inhibitor showed delayed wound healing as a result of enhanced elastase activity which they attributed to increased TGF-β1 levels. Estrogen seems to have a direct role in the tissue remodelling phase by inhibiting collagenase enzymes, thus decreasing proteolysis. Sato *et al*. demonstrated that in cultured rabbit uterine fibroblasts 17β estradiol effectively inhibited the production of proteolytic enzymes such as collagen [45].

Conclusion

Skin thinning, wrinkling and dryness are all signs of skin aging. All these changes are caused by deficiencies or disordered production of the structural components of the skin, namely collagen, elastin and glycosaminoglycans. Wound healing is a complex process involving inflammation, tissue proliferation, remodeling and its delay is a direct indicator of aged or diseased skin. There is a growing body of evidence to suggest that the withdrawal of estrogen and progesterone in the postmenopausal state can partly contribute to skin aging changes. A number of observational human and experimental animal studies seem to suggest that some of these changes can be reversed by HRT. Unfortunately, these were most often noted to have small sample sizes. Larger, more robust randomized controlled trials are needed in order to further assess the links between HRT and skin aging, in the hope, that one day HRT may be prescribed for the treatment of skin aging conditions in postmenopausal women.

References

1. Ashcroft GS, Ashworth JJ. Potential Role of Estrogens in Wound Healing. Am J Clin Dermatol. 2003;4(11):737-743.
2. Hall GK, Phillips TJ. Skin and hormone therapy. Clin Obstet Gynecol. 2004;47(2):437-449.
3. Wilkinson HN, Hardman MJ. The role of estrogen in cutaneous ageing and repair. Maturitas. 2017;103:60-64.
4. Shah MG, Maibach HI. Estrogen and Skin. Am J Clin Dermatol. 2001;2(3):143-150.
5. Brincat M, Muscat Baron Y, Galea R. Estrogens and the skin. Climacteric. 2005;8(2):110-123.
6. Piérard GE, Hermanns-Lê T, Paquet P, Piérard-Franchimont C. Skin viscoelasticity during hormone replacement therapy for climacteric ageing. Int J Cosmet Sci. 2014;36(1):88-92.
7. Calleja-Agius J, Muscat-Baron Y, Brincat MP. Skin ageing. Menopause Int. 2007;13(2):60-64
8. Archer DF. Postmenopausal skin and estrogen. Gynecol Endocrinol. 2012;28 Suppl 2):2-6.
9. Quatresooz P, Pierard-Franchimont C, Gaspard U, Pierard GE. Skin climacteric aging and hormone replacement therapy. J Cosmet Dermatol. 2006;5(1):3-8.
10. Sator P-G, Schmidt JB, Rabe T, Zouboulis CC. Skin aging and sex hormones in women - clinical perspectives for intervention by hormone replacement therapy. Exp Dermatol. 2004;13 Suppl 4):36-40.
11. Brincat MP. Hormone replacement therapy and the skin. Maturitas. 2000;35(2):107-117
12. Brincat M, O'Dowd T, Magos AL, 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(2):126-129.
13. Castelo-Branco C, Duran M, Gonzalez-Merlo J. Skin collagen changes related to age and hormone replacement therapy. Maturitas. 1992;15(2):113-119.
14. Albright F, Smith PH, Richardson AN. Postmenopausal osteoporosis: its clinical features. JAMA. 1941;116(22):2465-2474.
15. 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(3):219-225.
16. Black M, Bottoms E, Shuster S. Changes in skin collagen and thickness in endocrine disease. Blackwell Science Ltd., Osney Mead Oxford OX2 0EL UK. 1970.
17. Shuster S, Black MM, Bottoms E. Skin collagen and thickness in women with hirsuties. Br Med J. 1970;4(5738):772.
18. Brincat M, Moniz C, Studd J, Darby A, Magos A, Cooper D. Sex hormones and skin collagen content in postmenopausal women. Br Med J (Clin Res Ed). 1983;287(6402):1337-1338.
19. 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(3):256-259.
20. Caliens 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(4):289-294.
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(12):985-989.
22. Maheux R, Naud F, Rioux M, et al. A randomized, double-blind, placebo-controlled study on the effect of conjugated estrogens on skin thickness. Am J Obstet Gynecol. 1994;170(2):642-649.
23. 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(1):35-41.
24. 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(2):126-129.
25. Haapasaari KM, Raudaskoski T, Kallioinen M, et al. Systemic therapy with estrogen or estrogen with progestin has no effect on skin collagen in postmenopausal women. Maturitas. 1997;27(2):153-162.
26. Piérard-Franchimont C, Cornil F, Dehavay J, Deleixhe-Mauhin F, Letot B, Piérard GE. Climacteric skin ageing of the face--a prospective longitudinal comparative trial on the effect of oral hormone replacement therapy. Maturitas. 1999;32(2):87-93.
27. Miller VM, Naftolin F, Asthana S, et al. The Kronos Early Estrogen Prevention Study (KEEPS): what have we learned? Menopause. 2019;26(9):1071-1084,
28. Owen CM, Pal L, Mumford SL, et al. Effects of hormones on skin wrinkles and rigidity vary by race/ethnicity: four-year follow-up from the ancillary skin study of the Kronos Early Estrogen Prevention Study. Fertil Steril. 2016;106(5):1170-1175.e3.
29. Guinot C, Malvy D, Ambroisine L, et al. Effect of hormonal replacement therapy on skin biophysical properties of menopausal women. Skin Res Technol. 2005;11(3):201-204.
30. Kaatz M, Elsner P, Koehler MJ. Changes in skin topography during hormone therapy. Menopause. 2008;15(6):1193-1194.
31. Wolff EF, Narayan D, Taylor HS. Long-term effects of hormone therapy on skin rigidity and wrinkles. Fertil Steril. 2005;84(2):285-288.
32. Wolff E, Pal L, Altun T, et al. Skin wrinkles and rigidity in early postmenopausal women vary by race/ethnicity: baseline characteristics of the skin ancillary study of the KEEPS trial. Fertil Steril. 2011;95(2):658-662.e1-3.
33. Grosman N, Hvidberg E, Schou J. The effect of oestrogenic treatment on the acid mucopolysaccharide pattern in skin of mice. Acta Pharmacol Toxicol (Copenh). 1972;30(5):458-464.
34. 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 Endocrinologica (Copenh). 1977;85(2):429-435.
35. Uzuka M, Nakajima K, Ohta S, Mori Y. The mechanism of estrogen-induced increase in hyaluronic acid biosynthesis, with special reference to estrogen receptor in the mouse skin. Bioch Biophys Acta. 1980;627(2):199-206.
36. Sobel H, Cohen RA. Effect of estradiol on hyaluronic acid in the skin of aging mice. Steroids. 1970;16(1):1-3.
37. Dunn LB, Damesyn M, Moore AA, Reuben DB, Greendale GA. Does estrogen prevent skin aging?: Results from the first National Health and Nutrition Examination Survey (NHANES I). Arch Dermatol. 1997;133(3):339-342.
38. Sator PG, Schmidt J, Sator M, Huber J, Hönigsmann H. The influence of hormone replacement therapy on skin ageing: a pilot study. Maturitas. 2001;39(1):43-55.
39. Schmidt JB, Binder M, Macheiner W, Kainz C, Gitsch G, Bieglmayer C. Treatment of skin ageing symptoms in perimenopausal females with estrogen compounds. A pilot study. Maturitas. 1994;20(1):25-30.
40. Piérard-Franchimont C, Letawe C, Goffin V, Piérard GE. Skin water-holding capacity and transdermal estrogen therapy for menopause: a pilot study. Maturitas. 1995;22(2):151-154.
41. Margolis DJ, Knauss J, Bilker W. Hormone replacement therapy and prevention of pressure ulcers and venous leg ulcers. Lancet. 2002;359(9307):675-677.
42. Ashcroft GS, Mills SJ, Lei K, et al. Estrogen modulates cutaneous wound healing by downregulating macrophage migration inhibitory factor. J Clin Invest. 2003;111(9):1309-1318.
43. Ashcroft GS, Dodsworth J, Boxtel EV, et al. Estrogen accelerates cutaneous wound healing associated with an increase in TGF-β1 levels. Nat Med. 1997;3(11):1209-1215.
44. Ashcroft GS, Lei K, Jin W, et al. Secretory leukocyte protease inhibitor mediates non-redundant functions necessary for normal wound healing. Nat Med. 2000;6(10):1147-1153.
45. Sato T, Ito A, Mori Y, Yamashita K, Hayakawa T, Nagase H. Hormonal regulation of collagenolysis in uterine cervical fibroblasts. Modulation of synthesis of procollagenase, prostromelysin and tissue inhibitor of metalloproteinases (TIMP) by progesterone and oestradiol-17 beta. Biochem J. 1991;275(Pt 3):645-650.

Conflicts of interest

The authors declare having no conflicts of interest.