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Review

The role of bioidentical hormone replacement therapy in anti-aging medicine: a review of the literature

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Abstract

The changes in skin and overall appearance that occur with increasing age can be partly attributed to declining hormone levels. While hormonal deficiencies are most commonly associated with postmenopausal females, males are also subject to age-related testosterone decline and may benefit from replacement of deficient hormones. However, great disparities exist between the recommendations of scientific societies and actual use of hormone supplements in aging patients. The purpose of this literature review is to discuss the role of hormones in the aging process of the skin, explain the safety profile of hormone replacement therapy, specifically discussing the superiority of bioidentical hormones, and highlight the benefits of hormone replacement in anti-aging of the skin. In summary, this literature review suggests that hormone replacement with bioidentical hormones is a safe and effective way to prevent skin aging.

Introduction

As our population ages, both men and women will live a longer portion of their life in a hormone deficient state. Hormone level decline is a common cause of many patient complaints, including patient-perceived aging. Based on this principle, hormonal replacement therapy (HRT) is believed to prevent age-related diseases and is used as such. Despite evidence supporting the efficacy of HRT as an anti-aging medicine, great disparities exist between the published recommendations of scientific societies and actual clinical application of hormone supplements in aging patients. The purpose of this literature review is to discuss the role of hormones in the aging process of the skin, explain the safety profile of hormone replacement therapy, specifically by discussing the superiority of bioidentical hormones over their synthetic counterparts, and highlight the benefits of hormone replacement in anti-aging of the skin.

Changes in skin with age

Many changes to the epidermis and dermis occur with increasing age. Examples of these changes include epidermal and dermal thinning, as well as simultaneous loss of collagen, elastin, and hyaluronic acid, which results in a flattened epidermal-dermal junction.[1,2] Studies have demonstrated that collagen bundles decrease in both quantity and quality, due to an increased activity of matrix metalloproteases that chemically alter and degrade existing collagen bundles. Ultimately, this leads to an increase in distensibility and loss of tonicity, creating deeper facial creases.[3,4] As a patient ages, keratinocyte shape changes as well. This results in an increase in the number and size of pores as well as an increase in the development of age spots.[5] Lastly, the overall volume of the hypodermis decreases due to a loss of subcutaneous fat.[6] The combined effect of all these age-related changes result in thin, wrinkled, and sagging skin.

Role of hormones in aging skin

Estrogens serve many roles in maintaining a youthful appearance. Specifically, estrogens are known to increase collagen and skin thickness by inhibiting matrix metalloproteases[7–9] and stimulating the proliferation of keratinocytes.[10,11] Estrogens also act as natural antioxidants, as they protect against oxidative stress and inflammation.[11] They can also enhance wound healing by increasing blood flow.[7–9]

As estrogen levels decline in the years following menopause, skin aging accelerates. Collagen can decrease as much as 30% in the first 5 years following menopause, suggesting a strong association with estrogen deficiency.[7] Moreover several reports have suggested positive associations between the levels of circulating estrogens and perceived age, attractiveness, and enhanced skin health.[7–9] In 1999, Wildt and Petermann were the first to demonstrate that blood 17β-estradiol levels accurately predict age estimation in women. Blinded observers were asked to predict the age of 100 perimenopausal women. The study demonstrated that age was overestimated when serum 17β-estradiol levels were low and underestimated when levels 17β-estradiol were high (Fig. 1),[12] suggesting that higher levels of 17β-estradiol result in a more youthful appearance.

While there is less literature on declining levels of progesterone, testosterone, dehydroepiandrosterone (DHEA), and human growth hormone (HGH) in relation to their effects on skin aging, studies have demonstrated that replacing these hormones leads to thickened skin and restored elasticity.[13–18]

Safety of hormone replacement

Estrogens

In the discussion of estrogen replacement therapy, it is imperative to discuss the Women's Health Initiative (WHI), a large scale study initiated by the United States (US) National Institutes of Health in 1991 to address major health issues affecting post-menopausal women sparked fear in the medical community that HRT increased the risk for heart disease and breast cancer. In 2013, the WHI Hormone Therapy Trials summary was published, consisting of data from 117 different publications and including 27,347 women ages 50–79 enrolled at 40 US centers. The women were grouped into three categories and received different treatment: Group 1 received conjugated equine estrogens (0.625 mg/day) in conjunction with medroxyprogesterone acetate (2.5 mg/day) with a median intervention time of 5.6 years; group 2, with a prior history of hysterectomy, received conjugated equine estrogens (0.625 mg/day) without medroxyprogesterone with a median intervention time of 7.2 years; and group 3 received a placebo. These patients were followed for a total of 13 years. The results of the study were grim. Post-menopausal women taking estrogen with progesterone increased their risk for cardiovascular disease and invasive breast cancer.[19] Despite these harsh conclusions bleeding into the spotlight and influencing public perception, follow-up studies were conducted to assess the validity of the WHI. These new results were compelling and changed the trajectory on how we view the safety of HRT.

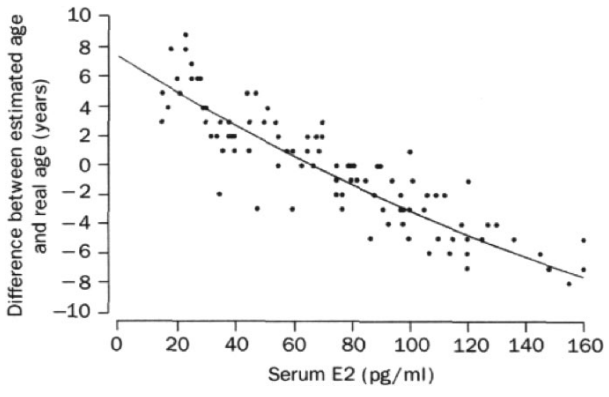

Figure 1 Serum estradiol levels in relation to the difference between estimated age and real age in 100 perimenopausal women[12]

Several studies have criticized the WHI for prematurely drawing conclusions on the safety profile of estrogen and progesterone replacement therapy among postmenopausal women.[20–24] For example, the WHI published that HRT in postmenopausal women exhibited a significant increase in risk for cardiovascular disease (CVD); however, the study failed to recognize and highlight the influence of age and onset of menopause in this population of women. A second analysis was conducted on the dataset and showed that CVD events with postmenopausal women on HRT were at significantly less risk than initially described, even suggesting that the risk of perimenopausal women on HRT had low risk of CVD events and all-cause mortality was not increased.[20] Furthermore, in response to the results shown by the WHI, two studies, KEEPS and ELITE, were published with the purpose of evaluating the HRT safety in early postmenopausal women. Both studies showed no change in adverse effects due to CVD, and KEEPS specifically showed no increased risk for breast cancer as well.[21,22] Lastly, the WHI writing group states, themselves, that the findings from this study should not be extrapolated to other doses and types of hormone replacement as only specific dosages were studied, which further narrows the application of these results.[24]

Following the WHI, which highlighted the potential problems of estrogen therapy in postmenopausal women, many studies have been published in support of the use of estrogen therapy in high-risk women. In a meta-analysis of nine cohort studies and one RCT, breast cancer survivors using estrogen replacement therapy (ERT) experienced no increased risk of breast cancer recurrence and had significantly fewer deaths compared to non-ERT users.[25] Another study, which spanned 7.6 years, showed that there was no increased risk in future breast cancer

development in BRCA1 carriers, post-oophorectomy, who were using HRT compared to non-users. This further confirms that estrogen replacement does not increase the risk of breast cancer, even among high-risk populations.[26]

Lastly, bioidentical estrogen replacement has been shown to be superior to replacement with synthetic estrogens, such as conjugated equine estrogens (CEE). In a recently published study by Zeng in 2018, CEE led to an increased risk of breast cancer development (hazard ratio [HR]: 1.49), while bioidentical estrogens led to a deceased risk of breast cancer development (HR: 0.65).[27]

The negative findings of the WHI have caused great concern about the safety profile of HRT. However, after a closer examination of the WHI and subsequent studies on the risk profile of synthetic and bioidentical HRT, it becomes clear that when used appropriately, HRT with estrogens and progestins can safely and effectively manage postmenopausal females.

Progesterones

Synthetic progesterones are associated with many unfavorable side effects, including weight gain, hypertension, and impaired glucose metabolism. These adverse effects are the result of high affinity binding between this synthetic hormone and mineralocorticoid and glucocorticoid receptors. Bioidentical progesterone, on the other hand, binds the glucocorticoid and mineralocorticoid receptor with a lower affinity than synthetic progesterone, thereby decreasing the risk for the aforementioned side effects.[28–30] Furthermore, bioidentical progesterone is less likely to lower high-density lipoprotein (HDL) than synthetic progesterone[28] and is associated with a lower risk for breast cancer when combined with bioidentical estrogens compared to their synthetic counterparts.[31,32]

Testosterone

Despite much fear surrounding the use of testosterone cream and the perceived risk for developing prostate cancer or benign prostate hypertrophy, there is no clinical evidence that it increases the risk of these diseases.[33] In fact, recent studies have failed to confirm a relationship between testosterone levels and the risk for prostate cancer.[34–36] Moreover increased risk for prostate cancer, greater 5-year biochemical relapse rates, and higher Gleason scores have been associated with low testosterone levels.[34,37] With respect to testosterone levels and cardiovascular disease, several studies suggest that low testosterone levels are associated with an increased risk of atherosclerosis.[38–44] Studies have also demonstrated that testosterone replacement in deficient males is not as dangerous as once believed.[45,46] A recent study of 3,422 military service members, retirees, and their dependents, aged 40–64, highlighted this point. This study demonstrated that men replacing testosterone had an improved cardiovascular event-free survival and a lower incidence of coronary artery disease at 17-month follow-up ($P = 0.004$ and 0.008, respectively).[45] Moreover among 46 men with a history of chronic, stable angina, time to exercise-induced myocardial ischemia was longer among the testosterone treated group compared to the placebo group, with the prolonged effect more significant in men with lower baseline testosterone concentrations.[46]

Contraindications for hormonal replacement therapy

Absolute contraindications to HRT include estrogen receptor positive breast cancer, endometrial cancer, undiagnosed abnormal uterine bleeding, active thromboembolic disease, and a history of malignant melanoma, which is believed by some to be driven by estrogens.[47]

Relative contraindications to HRT include chronic liver disease, severe hypertriglyceridemia, endometriosis, previous thromboembolic disease, and gallbladder disease.[48] Under appropriate circumstances and with physician supervision, hormonal replacement can be not only safe but also beneficial. Furthermore, it is clear that hormonal replacement with bioidentical hormones has been shown to have a superior safety profile when compared to synthetic hormones.

Methods

In order to determine the role of hormone replacement therapy in anti-aging medicine, articles were found through searching PubMed and Google Scholar. Search terms included estrogen, progesterone, testosterone, DHEA, OR human growth hormone AND replacement OR therapy AND skin OR skin thickness OR wrinkles OR appearance OR cosmetic. The first, second, and third authors discussed the articles generated with the senior author, who offered his guidance and expertise on the subject field to dictate which articles we included. It was decided to focus attention on those articles with outcomes focusing on wrinkles, assessed clinically, and skin thickness, assessed through ultrasound imagery and skin biopsies. An additional emphasis was placed on randomized, placebo-controlled, clinical trials.

Through this literature search and discussion, we gathered eight articles on the aesthetic benefits of estrogen replacement,[13,48–51,53–,55] six articles on the anti-aging benefits of topical estrogens,[52,56–60] one article on the benefits of progesterone replacement,[13] two articles on the benefit of testosterone replacement,[15,62] one article on the benefit of oral DHEA replacement, four articles on the benefits of topical DHEA,[16,64–66] and one article on the benefits of HGH replacement.[18]

Hormonal replacement and skin benefits

Estrogens

The anti-aging benefits of estrogen replacement therapy have been well established with previous research. Studies dating

back to the 1980s have demonstrated that ERT can increase skin thickness in both the dermal and epidermal layers,[13,14] increase epidermal hydration and skin elasticity,[13,51,52] reduce wrinkles,[53] increase the level of vascularization,[14,51,52] and enhance the quantity and quality of collagen.[48,49]

In a prospective, randomized, double-blind, placebo-controlled study, Sator *et al*. randomized 40 postmenopausal women (average age of 51) to 2 mg 17B estradiol/10 mg dydrogesterone for 7 months. This study found that 7 months of HRT improved skin elasticity and increased skin thickness, as assessed by cutometer and high frequency ultrasound (US), respectively.[48] In another randomized, double-blind, placebo-controlled study, Maheux *et al*.[53] demonstrated that oral estrogen replacement significantly increased the skin thickness, assessed through US and skin biopsy.

While several studies have reported the positive benefits of estrogen replacement on the skin, such as those discussed previously, a few studies reported a lack of cosmetic improvement with this treatment. These studies, however, often have limitations due to study design and/or sample population. In a study by Owen *et al*.,[54] 116 postmenopausal women were randomized to treatment with 0.45 mg oral CEE or transdermal estradiol (50 μg daily), both with micronized progesterone (200 mg daily), or placebo for 4 years. In this study, HRT failed to demonstrate an improvement in skin wrinkling, by clinical assessment, and rigidity, by durometer. However, the study authors acknowledge that it is possible that they were underpowered to detect a difference with HRT, that HRT positively affects skin parameters that were not measured, or that the relatively low dose of HRT used was not sufficient enough to yield visible results.

Furthermore, in a double-blind, placebo-controlled study, 485 women, on average 5 years post-menopausal, were randomized to receive estradiol or vehicle for 48 weeks. The study failed to demonstrate that low-dose estrogen replacement therapy improved mild to moderate age-related facial skin changes, assessed clinically. However, the results of this study are limited, as the dose of estrogen replacement was much lower than doses used in previous, positive studies. Additionally, the study population was on average 5 years postmenopausal, suggesting there may be added benefit to initiating hormone replacement therapy among newly menopausal or perimenopausal females.[55]

Topical application of estrogens has also been shown to have anti-aging benefits. Topical estrogen has been shown to increase collagen fibers,[51,52] increase skin thickness,[56,57] increase skin laxity,[56–58] and treat fine wrinkles.[55] Varila *et al*.[52] demonstrated that a 6-month course of topical estrogen increases the collagen content, as measured by skin hydroxyproline, and causes an increase in collagen synthesis, as measured by the increase of the carboxyterminal propeptide of human type I procollagen and of the amino terminal propeptide of human type III procollagen. Similarly, the first National Health and Nutrition Examination Survey (NHANES I) confirmed the ability of topical estrogens to improve the appearance of wrinkles through the assessment of 3,875 postmenopausal women.[60] Furthermore, a recent, double-blind, randomized pilot study found that topical estrogen applied for 14 weeks to the face was found to statistically improve dryness, skin laxity, atrophy, and dullness, as well as increase fibroblast estrogen receptor staining in skin biopsies.[58] Adverse effects of topical estrogen creams are uncommon and mild. Reported side effects include temporary breast tenderness and redness at the site of the hormone cream administration. Systemic effects are not reported to be shown by most studies.[61]

Progesterone

Estrogen therapy is often supplemented by progesterone in order to protect the endometrial lining, and studies have demonstrated the positive skin benefits of this progesterone replacement. Subjects supplemented with both estrogen and progesterone exhibited an increase in skin surface lipids, which was not seen among subjects supplemented with only estrogen. This reflects progesterone's ability to stimulate sebaceous gland activity. Subjects perceived this increase in skin surface lipids positively, believing it to create a more youthful glow.[13]

Testosterone

Testosterone replacement has demonstrated success in thickening skin of postmenopausal women. Dating back to 1983, Brincat *et al*.[62] concluded that postmenopausal women on hormone replacement therapy with estrogen and testosterone had a collagen content 48% higher compared to the content measured in untreated women, stratified by age. Moreover estrogen and testosterone replacement has been shown to increase type III collagen.[15]

DHEA

DHEA has shown to have positive skin benefits when supplemented both orally and topically. Specifically, supplementation

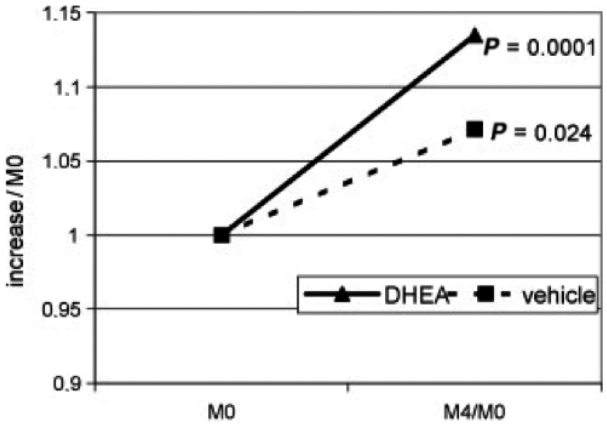

Figure 2 Skin thickness following 4 months of topical DHEA vs. vehicle[16]

with 50 mg of DHEA confers many positive benefits on the skin of both men and women aged 60–79 years. Specifically, oral DHEA improved skin status, particularly in women, in terms of hydration, epidermal thickness, sebum production, and pigmentation.[63] Moreover 4 months of topical DHEA has been shown to increase the rate of sebum production, which was correlated with enhanced skin brightness and increased skin thickness (Fig. 2).[16] Similarly, topical application of DHEA over 4 weeks increased collagen production through inhibiting ultraviolet (UV)-induced MMP-1 production and the UV-induced decrease of procollagen synthesis.[64,65] Moreover in a placebo-controlled, randomized, prospective study of 75 postmenopausal women, El-Alfy *et al.*[66] demonstrated that not only does topical DHEA increase procollagen levels but also increases heat shock protein, leading to stimulation of collagen fibers. Both topical and oral DHEA may cause mild acne, seborrhea, hirsutism, and ankle swelling.[65,67]

Human growth hormone

Low levels of human growth hormone (HGH) are commonly seen in older age. Studies have suggested that low levels of HGH are associated with decreased skin thickness and supplementing deficient individuals with HGH can help to thicken skin. For example, among GH deficient elderly men, skin thickness decreased to 94% of baseline after 18 months in the control group, while the experimental group, which received HGH replacement, experienced a 4% increase in skin thickness.[17] Similarly, a study by Rudman *et al.*[18] demonstrated that HGH replacement for 6 months significantly increased skin thickness by 7% among men over 60 years.

Limitations

While comprehensive, this literature review was not conducted in a systematic manner and, therefore, suffers from selection bias. Moreover the studies supporting the use of HRT for anti-aging purposes did not use bioidentical hormone therapy. As a result, our support of HRT with bioidentical hormones is based on studies supporting the anti-aging benefits of HRT as well as the superiority of bioidentical compared with synthetic hormones.

Conclusion

Hormone replacement with bioidentical hormones is a safe and effective way to prevent skin aging. While negative studies do exist, specifically on the skin benefits of estrogen and progesterone replacement therapy, they are often limited in their study design and/or study population. From our literature review and clinical experience, we recommend the use of hormonal replacement with bioidentical hormones at doses tailored to each patient that aim to restore normal blood values. There is evidence that treatment should begin in the years immediately surrounding menopause or andropause, as this more adequately maintains constant hormone levels, rather than replacing a deficient state. Furthermore, combination of oral and topical estrogens and DHEA may further enhance cosmetic outcomes, as studies have demonstrated both to be effective on their own for thickening skin and improvement of wrinkles. If this approach is taken, the senior author believes blood levels of these hormones should be monitored at regular intervals. In summary, declining hormone levels are often the cause of many age-related signs and symptoms of the skin, and HRT may provide a means to prevent hormonal decline and its negative cosmetic side effects.

Questions (answers provided after references)

1 Thin, wrinkled, and sagging skin is the result of:
- a decrease in quality of collagen
- b decrease in quantity of collagen
- c increase in metalloproteases
- d alteration in keratinocyte shape
- e all of the above

2 True or False**:** Estrogens decrease by 10% in the first 5 years following menopause.

3 Which of the following is not a known role of estrogen?
- a acts as a natural oxidant
- b increases blood flow
- c stimulates fibroblasts
- d inhibits metalloproteases

4 True or False: Studies have shown that BRCA1 carriers have a much higher likelihood of developing breast cancer if they receive hormone replacement therapy.

5 True or False: Bioidentical estrogens do not increase the risk of breast cancer development

6 True or False: Bioidentical progesterone binds the glucocorticoid and mineralocorticoid receptor more strongly than synthetic progesterone

7 True or False: Synthetic progesterone impacts HDL cholesterol more than bioidentical progesterone.

8 True or False**:** Prostate cancer, higher Gleason scores, and 5-year chemical relapse rates are associated with higher testosterone levels.

9 True or False: Topical estrogens are able to increase the collagen content of skin

10 True or False: Topical DHEA increases skin thickness by stimulating heat shock protein.

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Answers to Questions

1) e
2) False
3) c
4) False
5) True
6) False
7) True
8) False
9) True
10) True

