A dermatologist's opinion on hormone therapy and skin aging

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The Taylor et al. study in this issue suggests that long-term hormone replacement therapy helps prevent skin aging. All patients interested in preventing skin aging should regularly use sunscreens, retinoids, and oral or topical antioxidants. (Fertil Steril® 2005;84:289–90. ©2005 by American Society for Reproductive Medicine.)

I commend Dr. Wolff and colleagues (1) on performing this study as I have long believed that I can tell by looking at a postmenopausal woman whether she is receiving hormone therapy (HT). I believe it was so important that I included a chapter in my textbook *Cosmetic Dermatology: Principles and Practice* on the subject and I frequently put postmenopausal women who are not on HT on topical estrogens for facial skin care. This study by Dr. Taylor et al., although small, indicates that long-term hormonal therapy can indeed prevent skin aging in women. This is not surprising, as estrogen plays many important roles in the skin. Keratinocytes, Langerhans cells, melanocytes, sebaceous glands, and fibroblasts are under hormonal influence (2). In addition, decreased estrogen levels result in a decreased capillary blood flow velocity to the skin.

WHAT IS SKIN AGING?

Wrinkles are thought to be caused by changes in the dermal tissue, which is composed of fibroblasts. Older skin has been shown in multiple studies to have decreased amounts of collagen, elastin, and hyaluronic acid. Much research has gone into how to prevent the loss of these three main components of the dermis. Although dermal fillers containing collagen (Cosmoderm, Cosmoplast) and hyaluronic acid (Captique, Restylane, and Hylaform) have been developed to replace these components in the skin, much interest has focused on preventing the loss of these vital components. Skin aging seems to accelerate after menopause. It is known that the decline in skin collagen that occurs with aging occurs at a greater rate during the first few years after menopause. In fact, some 30% of skin collagen is lost in the first 5 years after menopause with an average decline of 2.1% per postmenopausal year during a period of 20 years (3).

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WHAT CAN BE DONE TO PREVENT AGING?

Retinoids

Retinoic acid, a naturally occurring derivative of vitamin A, has long been known to improve wrinkled skin. A plethora of clinical trials confirmed early observations that those treated with retinoids for acne had less photoaging than those not treated with retinoids, and resulted in Food and Drug Administration approval of Renova (Johnson and Johnson, Los Angeles, CA) and Avage (Allergan, Irvine, CA) for this purpose. More recently, evidence suggests that retinoids also play a role in the *prevention* of aging. This occurs because of its inhibitory effects on damaging metalloproteinases. Ultraviolet (UV)-B exposure dramatically up-regulates the production of several collagen-degrading enzymes known as matrix metalloproteinases (MMPs). Activation of the MMP genes results in production of collagenase, gelatinase, and stromelysin, which have been shown to fully degrade skin collagen (4, 5). Fisher et al. (6) demonstrated that application of tretinoin (a retinoid) inhibits the induction of all three of these harmful MMPs.

In addition to increasing levels of destructive enzymes such as collagenase, UV exposure has also been shown to decrease collagen production. Fisher et al. (7) demonstrated that expression of type I and III collagen is substantially reduced within 24 hours after a single UV exposure. Pretreatment of the skin with all-*trans* retinoic acid was shown to inhibit this loss of procollagen synthesis. Therefore, pretreatment of the skin with topical retinoids, when used consistently, is likely to be beneficial in preventing as well as treating photodamage (8).

Antioxidants

The free radical theory of aging, proposed in 1956 (9), is one of the most widely accepted theories to explain the cause of aging (10). Free radicals lead to inflammation, damaged

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DNA, and damaged cell membranes, which, in turn, leads to the activation of MMPs, directly and by activating ERK and JNK genes (11). Therefore, free radicals alone can cause the production of collagenase and the breakdown of collagen, even in the absence of UV exposure.

The use of antioxidants to prevent photoaging and the breakdown of collagen, elastin, and hyaluronic acid has become very popular in the dermatology and skin care fields. Numerous studies have supported the use of green tea (12), vitamin C, vitamin E, coenzyme Q10, idebenone, lutein, lycopene, and genistein to prevent photoaging. Antioxidants can be applied topically or taken orally with varying effects based on the formulations and presence of other ingredients. Many skin care lines offer vitamins and skin care products that contain these ingredients. Vitamin C may have the added benefit of increasing collagen synthesis; however, it is a molecule that is difficult to stabilize and proper formulation is essential to achieve efficacy (13).

Estrogen also may play a role in maintaining collagen and hyaluronic acid. Both estrogen and androgen receptors have been identified on dermal fibroblasts and epidermal keratinocytes (14). In fact, the naturally occurring estrogen, 17β-E_2 and a close stereoisomer, 17α-E_2, were found to be as effective as all-*trans* retinoic acid in stimulating the development of new connective repair zones in photodamaged skin of mice, which resulted in a skin thickening response. The increase in skin thickness among patients receiving hormone therapy has also been reported in other studies using differing measurement techniques (15, 16).

It is currently believed that these skin thickness changes seen with aging are due to hormonal effects on collagen (17), elastic fibers (18), and dermal hyaluronic acid content (19). In 1983, Brincat et al. (3) found that women on HT had a skin collagen content that was 48% higher than women not on HT. Varila et al. (20) found an increase of collagen I among patients treated with HT, whereas Savvas et al. (21) reported an increase in collagen type III. However, the exact role of estrogen on collagen synthesis is not known and not all studies agree. One study looking at the effect of estrogen alone or combined with progestin on the amount and synthesis of skin collagen in postmenopausal women did not show a stimulatory effect on collagen synthesis (22).

SUMMARY

Prevention of skin aging is a concern of many patients. All of the preventative recommendations focus on preserving collagen, hyaluronic acid, and elastic tissue. Several studies, including this one by Dr. Wolff's group, have demonstrated that HT may help prevent the rapid aging seen after menopause. Antioxidants, retinoids, and sunscreens should also be used in all patients to prevent aging.

REFERENCES

1. Wolff EF, Narayan D, Taylor HS. Long-term effects of hormone therapy on skin rigidity and wrinkles. Fertil Steril 2005;84:285–8.
2. Sator PG, 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.
3. 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.
4. Fisher GJ, Wang ZQ, Datta SC, Varani J, Kang S, Voorhees JJ. Pathophysiology of premature skin aging induced by ultraviolet light. N Engl J Med 1997;337:1419–28.
5. Fligiel SE, Varani J, Datta SC, Kang S, Fisher GJ, Voorhees JJ. Collagen degradation in aged/photodamaged skin in vivo and after exposure to matrix metalloproteinase-1 in vitro. J Invest Dermatol 2003;120:842–8.
6. Fisher GJ, Datta SC, Talwar HS, Wang ZQ, Varani J, Kang S, et al. Molecular basis of sun-induced premature skin ageing and retinoid antagonism. Nature 1996;379:335–9.
7. Fisher GJ, Datta S, Wang Z, Li XY, Quan T, Chung JH, et al. c-Jun-dependent inhibition of cutaneous procollagen transcription following ultraviolet irradiation is reversed by all-trans retinoic acid. J Clin Invest 2000;106:663–70.
8. Fisher GJ, Talwar HS, Lin J, Voorhees JJ. Molecular mechanisms of photoaging in human skin in vivo and their prevention by all-trans retinoic acid. Photochem Photobiol 1999;69:154–7.
9. Harman D. Aging: a theory based on free radical and radiation chemistry. J Gerontol 1956;11:298–300.
10. Pelle E, Maes D, Padulo GA, Kim EK, Smith WP. An in vitro model to test relative antioxidant potential: ultraviolet-induced lipid peroxidation in liposomes. Arch Biochem Biophys 1990;283:234–40.
11. Kang S, Chung JH, Lee JH, Fisher GJ, Wan YS, Duell EA, et al. Topical N-acetyl cysteine and genistein prevent ultraviolet-light-induced signaling that leads to photoaging in human skin in vivo. J Invest Dermatol 2003;120:835–41.
12. Katiyar SK. Skin photoprotection by green tea: antioxidant and immunomodulatory effects. Curr Drug Targets Immune Endocr Metabol Disord 2003;3:234–42.
13. Nusgens BV, Humbert P, Rougier A, Colige AC, Haftek M, Lambert CA, et al. Topically applied vitamin C enhances the mRNA level of collagens I and III, their processing enzymes and tissue inhibitor of matrix metalloproteinase 1 in the human dermis. J Invest Dermatol 2001;116:853–9.
14. MacLean AB, Nicol LA, Hodgins MB. Immunohistochemical localization of estrogen receptors in the vulva and vagina. J Reprod Med 1990;35:1015–6.
15. Brincat M, Yuen AW, Studd JW, Montgomery J, Magos AL, Savvas M. Response of skin thickness and metacarpal index to estradiol therapy in postmenopausal women. Obstet Gynecol 1987;70:538–41.
16. Punnonen R, Vilska S, Rauramo L. Skinfold thickness and long-term post-menopausal hormone therapy. Maturitas 1984;5:259–62.
17. Castelo-Branco C, Duran M, Gonzalez-Merlo J. Skin collagen changes related to age and hormone replacement therapy. Maturitas 1992;15:113–9.
18. Punnonen R, Vaajalahti P, Teisala K. Local oestriol treatment improves the structure of elastic fibers in the skin of postmenopausal women. Ann Chir Gynaecol Suppl 1987;202:39–41.
19. Bentley JP, Brenner RM, Linstedt AD, West NB, Carlisle KS, Rokosova BC, et al. Increased hyaluronate and collagen biosynthesis and fibroblast estrogen receptors in macaque sex skin. J Invest Dermatol 1986;87:668–73.
20. Varila E, Rantala I, Oikarinen A, Risteli J, Reunala T, Oksanen H, et al. The effect of topical oestradiol on skin collagen of postmenopausal women. Br J Obstet Gynaecol 1995;102:985–9.
21. 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.
22. Haapasaari KM, Raudaskoski T, Kallioinen M, Suvanto-Luukkonen E, Kauppila A, Laara E, et al. Systemic therapy with estrogen or estrogen with progestin has no effect on skin collagen in postmenopausal women. Maturitas 1997;27:153–62.