Human skin: a mirror for estrogen action?

Human skin is a complex organ accounting for 15% of the total body weight of an adult. It provides the first line of defence against environmental stress including microorganisms, ultraviolet radiation, dehydration or physical damage, and regulates body temperature, water balance, excretion and the synthesis of vitamin D. Human skin is a heterogeneous tissue composed of three main layers, the epidermis, the dermis and the hypodermis. The keratinocytes of the epidermis proliferate and differentiate to form a waterproof keratinizing squamous epithelium, while the fibroblasts in the dermis form the connective tissue, synthesising collagens, reticular and elastic fibres and glycoproteins[1]. Within the dermis are blood and lymphatic vessels, and skin appendages e.g. sweat glands, hair follicles and sebaceous glands. The hypodermis is a subcutaneous layer composed of insulating fatty connective tissue and loose connective tissue; the predominant cell type is the adipocyte, although fibroblasts and macrophages may also be found.

With aging, human skin undergoes profound changes due to atrophy of the epidermis, dermis and hypodermis; this results in reduced thickness, an increase in number and depth of wrinkles, increased dryness, and decreased vascularity, firmness and elasticity[2]. Skin aging is also associated with impaired wound healing which can give rise to non-healing chronic wounds. Estrogen modulates all phases of wound healing reducing inflammation, accelerating re-epithelialisation, stimulating the formation of granulation tissue and regulating proteolysis[3]. Furthermore, postmenopausal women over the age of 65 have been shown to be at a lower risk of developing a venous ulcer or a pressure ulcer if they were taking estrogen replacement[4].

While a number of environmental factors including sun exposure and smoking can affect the rate at which age-associated skin changes take place, there is a plethora of evidence to suggest that onset of the menopause in women significantly accelerates it (reviewed[5-8]). The role of estrogen deficiency in the age-associated changes concomitant with the decline in the structural integrity and functional capacity of the skin is well recognized. In elderly females the decrease in skin thickness and collagen content correlates more closely with the period of estrogen deficiency than with chronological age[9,10] indeed the decrease in skin collagen parallels the reduction in bone mass observed in post-menopausal women[9].

Many of the reported effects of estrogen on aging human skin have stemmed from comparisons of post-menopausal women taking estrogen replacement with those who have not. While administration of estrogen clearly has positive effects on human skin by delaying or preventing symptoms associated with skin aging[5,11], understanding these effects is complicated by a number of factors. The majority of studies have been observational, and the use of different estrogen preparations and doses with, or without, the simultaneous use of progesterone or testosterone offers further complications. Thus, making true comparisons and conclusions pertaining to the isolated effects of estrogen are difficult.

The diverse functions of estrogen in a wide range of tissues in both sexes, including the bone, brain, skeletal muscle, adipose tissue, colon, vascular system and skin is now well recognized, and the loss of estrogen in postmenopausal women has a negative impact on many aspects of female health, leading to conditions such as osteoporosis and an increased risk of cardiovascular disease[12]. However, menopausal hormone therapy appears to offer a complex pattern of risks and benefits. The Women's Health Initiative (WHI) trial[13] reported an increased breast cancer risk when an estrogenic compound was combined with progestin, whereas estrogen alone can have protective effects. These studies led to a significant reevaluation of the risks and benefits of systemic hormone replacement therapy, with recommendations for its use limited to short-term treatment for the relief of menopausal symptoms. More than a decade later, while estrogen replacement for most newly menopausal women appears to be safe and effective[14], justifying the use of randomized clinical trials to assess the effects of systemic estrogen on skin is still difficult from a risk-benefit point of view.

The study on aging skin reported by Toz *et al* in this issue is different to previous studies, because they have compared a group of women undergoing hysterectomy directly with another group undergoing hysterectomy with bilateral salpingo-oophorectomy (BSO). Since absence of estrogen clearly reduces the possibility of breast and ovarian cancer, hysterectomy with bilateral oophorectomy (BSO) is associated with a significant reduction in risk for breast and ovarian cancer. Therefore, for women undergoing hysterectomy, the opportunity for an elective BSO may appear to be an attractive proposition. However, since 65% of hysterectomies are carried out on women between the ages of 35-54 years[15], if they also elect for a BSO, then this will equate to an early menopause and they will be estrogen deficient for a significant proportion of their life.

The study considers two groups of pre-menopausal women (41-47years) who have been age matched and well-controlled for BMI, smoking status, parity and hypertension (Table 1). In order to remove any potential observer bias, the skin parameters were scored by the same dermatologist, who was unaware of the oophorectomy status of the women. The women were evaluated preoperatively and then at 24 and 48 weeks after surgery. Three different skin parameters were assessed and using anatomical landmarks, ordinal scores of the jowl area, suborbital area and crow’s feet were evaluated and given a score for (i) wrinkling, (ii) laxity/sagging, and (iii) texture/dryness.

Intragroup analysis of women who had undergone oophorectomy demonstrated a significant deterioration in all three skin parameters at 24 and 48 weeks (Table 3), although sub-group analysis indicated there was no significant deterioration between 24 and 48 weeks. In contrast, intragroup analysis of the women who had undergone hysterectomy without oophorectomy showed no significant change in any of the parameters. The women also completed a Skindex-29 questionnaire[16], to particularly assess their dermatology-specific quality of life (QOL). Interestingly, scores on emotion and symptom subscales that related to their appearance and dry or

itchy skin were significantly higher in women who had undergone oophorectomy.

While these results are not surprising, this study highlights the rapid aging of skin in the absence of estrogen, with significant changes observed as early as 24 weeks of estrogen deprivation. What is not clear is whether this dramatic deterioration is an immediate response to estrogen withdrawal. A longer study would be useful to determine whether skin aging continues at a similar rate. Other useful parameters to evaluate would be changes in the skin appendages e.g. the hair follicle and the sebaceous gland. There is limited trichogram evidence to suggest that estrogen extends the growing phase of the hair cycle to promote hair growth[17], while a common treatment-related side effect of the use of aromatase inhibitors is scalp hair thinning[18]. More recently a study has described a link between the risk of female pattern hair loss and a polymorphism of the gene encoding aromatase[19]. However, there have been no studies of the effect of oophorectomy on the hair cycle of pre-menopausal women.

The consequence of these changes e.g. dryness, decreased firmness and elasticity and appearances of wrinkles is most apparent on the face and other sun-exposed areas. In Western societies, women consider the appearance of their skin and hair to reflect their general health and well-being, and a significant visible acceleration of skin aging may impact on their quality of life. While changes to the skin are often overlooked or considered of minor importance, in addition to these visual concerns, these marked changes may also have more serious implications on skin health such as pressure ulcers and venous leg ulcers, and integrity of the genitourinary tract. A recent cross-sectional study of 460 women aged 25-93 years has reported that a higher perceived age (PA) is significantly associated with a lower bone mineral density (BMD)/trabecular bone score (TBS) when controlled for chronological age[20]. Therefore, the effects on skin health should also be considered and the pre-menopausal patient made fully aware of the detrimental changes that will occur to the skin when considering the risk-benefit of an elective oophorectomy.

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