22 Photoaging - Retinoids, Alpha Hydroxy Acids, and Antioxidants

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Introduction: Relevance and Treatment Effects

The recognition that excessive exposure to sunlight can damage skin has been with us since antiquity.

Song of Solomon

"Do not stare at me because I am dark,
Because I am darkened by the sun.
My mother's sons are angry with me
And made me take care of the vineyards;
My own vineyard have I neglected."

Sunlight-induced "premature aging" has been recorded in dermatological literature since the end of the nineteenth century [1,2]. However, only in recent decades has the extent of the ultraviolet (UV) radiation-induced dermal connective tissue changes and its divergences from that of chronologic or intrinsic aging been appreciated [3–7]. These studies have made it clear that "premature aging" is a misnomer and have led to the coining of the new term of photoaging [8]. Even more recently, it has become possible to ameliorate some of the visible and histological features of photoaged skin, such as wrinkles, roughness, irregular pigmentation and collagen loss. This chapter will only address topical treatments that can be self-administered by the patient at home, rather than the more drastic chemical peels and laser "re-surfacing" performed by dermatologists.

The treatment of photoaged skin has attained prominence owing, in large part, to the youth obsessed culture of the 1980s and the realization that people are living longer, have more leisure time, and reach advanced ages in better physical condition than ever before. The desire to look better is an understandable development.

The major topical treatments for photoaging fall into three classes: retinoids, alpha hydroxy acids (AHAs) and antioxidants. The first evidence that it was possible to partially reverse photoaging surfaced during treatment with all-trans-retinoic acid (RA) of post-adolescent acne in woman. In addi-

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1 As recounted from the Bible by Frederick Urbach, M.D. at the meeting in Utrecht, The Netherlands honoring Jan Van der Leun, Ph.D.

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tion to improvement of the acne, the women reported that their skin felt smoother and was less wrinkled (A.M. Kligman, unpublished observations). These observations prompted a clinical study that demonstrated amelioration of sunlight induced epidermal atrophy, dysplasia, keratoses and dispigmenta-
tions [9]. Among other findings were new collagen deposition and increased vascularity. Subsequent double-blind, vehicle-controlled studies confirmed the earlier findings [10-12]. Griffiths and Voorhees [13] have compiled a more complete review.

Prior to the human clinical studies, experiments with photoaged hairless mice demonstrated that topical RA treatment induced the deposition and synthesis of new collagen in the subepidermal dermis [14, 15]. In addition, increased synthesis of elastin and fibronectin as well as a reduction of UV-induced glycosaminoglycans (GAGs) was reported [16]. Confirmation of these findings came from a number of other laboratories [17-19]. It was also reported that, as in humans, wrinkles were partially effaced by RA in these animals [17, 18]. Similar enhanced collagen synthesis and wrinkle effacement was seen with 13-cis-RA [17]. Retinol, the parent retinoid (vitamin A), has been shown to cause epidermal hyperplasia [20] and to normalize Rhino mouse utriculi (L.H. Kligman, unpublished observations) as does RA. Final validation of the hairless mouse model occurred when it was shown that all-
trans RA increased collagen synthesis in human photoaged skin [11, 21, 22].

The AHA, glycolic acid, was reported in the 1970s and 1980s to ameliorate xerotic and hyperkeratotic skin conditions [23, 24]. Recently, glycolic acid has been recommended as a skin peeling agent at 50-70% concentrations and at lower concentrations (5-10%) to reduce superficial wrinkling in photoaged skin [25]. More recently, a β-hydroxy acid (salicylic acid) has been reported to have similar effects [26]. Other AHAs suggested for photoaged skin include lactic, citric, pyruvic and gluconic acids, with glycolic and lactic being the most commonly used. A number of clinical studies have reported that they are efficacious in reducing fine lines and in smoothing photoaged skin [27-29]. The sole double-blind, vehicle-controlled study compared 8% glycolic and lactic acid creams [30]. A very modest effect was reported in reducing mottled pigmentation, wrinkling and roughness on the forearms of patients. It should be noted that forearms respond less well than facial areas, even with tretinoin [31].

With regard to the repair of dermal connective tissue photodamage, little in the way of formal studies has been reported for AHAs. Increases in GAGs have been reported [27, 32]. The significance of this is unknown since UV radiation alone will increase GAGs [4, 5]. There have been no studies exam-
ing collagen synthesis in vivo. One in vitro study, using human fibroblasts, reports that glycolic acid added to the growth medium had a stimulating ef-
fect on collagen [33]. Extrapolation of the in vitro glycolic acid concentra-
tions to those used topically is not possible. Moreover, no calculation of in-
tercellular pools was made, and details were unavailable as to how radiolabel incorporation was normalized to cell protein and DNA content. Examination of collagen synthesis in the photoaged mouse model treated with 10% glyco-
lic acid, 12% ammonium lactate and 20% lactic acid failed to show histologi-
cal or biochemical differences compared with untreated or vehicle controls.