Tretinoin peel: a critical view*

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Abstract: The tretinoin peel, also known as retinoic acid peel, is a superficial peeling often performed in dermatological clinics in Brazil. The first study on this was published in 2001, by Cuce *et al*., as a treatment option for melasma. Since then, other studies have reported its applicability with reasonable methodology, although without a consistent scientific background and consensus. Topical tretinoin is used for the treatment of various dermatoses such as acne, melasma, scars, skin aging and non-melanoma skin cancer. The identification of retinoids cellular receptors was reported in 1987, but a direct cause-effect relation has not been established. This article reviews studies evaluating the use of topical tretinoin as agent for superficial chemical peel. Most of them have shown benefits in the treatment of melasma and skin aging. A better quality methodology in the study design, considering indication and intervention is indispensable regarding concentration, vehicle and treatment regimen (interval and number of applications). Additionally, more controlled and randomized studies comparing the treatment with tretinoin cream versus its use as a peeling agent, mainly for melasma and photoaging, are necessary.
Keywords: Chemexfoliation; Keratosis, actinic; Melanosis; Skin aging; Tretinoin

TRETINOIN OR ALL-TRANS RETINOIC ACID

The liposoluble vitamin A is essential to the human body and only available in the diet. Its molecule is an alcohol and therefore is called "retinol". It is absorbed by the small intestine, stored in the liver as retinyl esters (palmitate and ethyl propionate), or converted to active metabolites such as tretinoin, with an intermediate form called retinaldehyde. The conversion of retinol into retinyl esters and retinaldehyde is reversible, whereas the retinaldehyde to retinoic acid is irreversible.

Tretinoin or all-trans retinoic acid represents 50% of the active cellular form, with its metabolites (4-hydroxy-retinoic acid) and stereoisomers 9-cis-retinoic acid (alitretinoin) and 13-cis-retinoic acid (isotretinoin) making up the difference.[1]

Thus, in topical application, retinol, retinol esters, and retinaldehyde have to be converted to a more active form (tretinoin), whereas isotretinoin, alitretinoin, adapalene, tazarotene and seletinoid G are already applied in their active form.

The discovery of the receptors for retinoic acid in 1987 was the first demonstration of a retinoid-responsive transcription factor.[2,3]

Tretinoin activates three nuclear retinoic acid receptors (RAR-alpha, RAR-beta and RAR-gamma). The retinoic acid receptors (RARs) bind to regulatory regions in DNA called retinoic acid response elements (RAREs) or target sequences, and activate many gene transcriptions. Tretinoin may exert its clinical effects, at least in part, through activation of retinoid receptors.[4,5]

The binding profile of tretinoin differs from that of synthetic retinoids, such as adapalene, which binds preferentially to RAR-beta and RAR-gamma, and tazarotene, which binds to all 3 RARs but appears to lead to an effective gene expression only by RAR-beta and RAR-gamma.[6]

Topical tretinoin application before ultraviolet irradiation has been shown to prevent matrix metalloproteinase production and collagen degradation.[7]

Histologically, increased collagen types I, III and VII (dermal-epidermal anchoring fibrils) production can be seen, as well as reorganization of the dermal collagen into new woven bundles.[8]

Topical tretinoin has been shown to increase production of type I collagen by 80% in photoaged skin.[9]

It is thought that the increased collagen content indirectly stimulates normalization of the elastic tissue organization.[10]

Increased smoothness of skin or wrinkle effacement from tretinoin topical treatment results from epidermal hyperplasia, compaction of the stratum corneum, thickening of the granular layer and increased epidermal and dermal glycosaminoglycan deposition.

Tretinoin therapy has also been shown to improve wound healing. Animal studies have also shown tretinoin to have an effect on cytokeratin 16, which is an important modulator of the wound healing process.[11,12]

The retinoids show antiproliferative properties, promote cell differentiation, interfere with the tumor initiation process, re-

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duce the regulation of proto-oncogenes, and increase the expression of p53 and pro-apoptotic caspases. It is speculated that they have antioxidative effects and thereby decrease the number of sunburn cells, which are apoptotic keratinocytes. [13-15]

However, to date, a direct cause-and-effect relation has not been established.

Although the ability of topical tretinoin to improve clinical features of photoaging is firmly established, the mechanism by which this occurs needs further study.

Not all of the clinical features of photoaging respond equally to tretinoin. Among them, hyperpigmentation, surface roughness and fine wrinkles demonstrate the most consistent and significant improvement with tretinoin therapy. This positive response to topical tretinoin is due to improvement or repair in both the epidermal (hyperpigmentation and surface roughness) and dermal (fine wrinkles) components of photoaging.

TRETINOIN AND AGING SKIN

Skin aging is divided into intrinsic or chronological aging and extrinsic or photoaging. Extrinsic aging means overlapping environmental factors (mainly ultraviolet radiation, pollution, smoking, etc.) and lifestyle (stress) to intrinsic aging, which is enhanced through the following mechanisms: (i) telomere shortening; (ii) generation of reactive oxygen species (ROS) that damage the mitochondrial DNA and product matrix metalloproteinases (MMPs) that degrade the dermal extracellular matrix; (iii) mutation of the p53 tumor suppressor gene, that is, making the tumor-inducing and promoting the development of preneoplastic and neoplastic lesions and (iv) reduction of growth hormone and sex steroids. [16-18]

The changes are caused in part by cumulative endogenous damage due to the continuous formation of reactive oxygen species, which are normally generated by mitochondrial metabolism. [19]

Despite a strong antioxidant defense system, the damage generated by ROS's overproduction affects cellular constituents such as membranes, enzymes and DNA. [20]

Cellular stress accumulated over time potentially impacts cell metabolism and, consequently, tissue regeneration and function. The progressive loss of function impairs tissue physiology, as it is frequently observed in older skins. The diminished cutaneous microvasculature seen in older persons accounts for the progressive lower nutritional support in aging skin. [21] In addition, obstruction of vessels has been associated with disturbances of the normal architecture of the vascular plexus in the dermis. [20]

In intrinsic aging, morphologic changes in sun-protected skin include fine wrinkling and laxity; histology shows general atrophy of the extracellular matrix, including reduced elastin and elastic fiber disintegration. [22]

On the other hand in photoaging, histopathologic features include increased skin pigment production, loss of cellular polarity, atypical epidermal cells, skin thinning and atrophy, mild inflammatory infiltrate, degenerative changes in elastic tissue (elastosis) and decreased collagen tissue (reduced synthesis and increased degradation). [22,23]

The "hallmark" of the histopathology of photoaging is a change in dermal elastosis, which primarily consists of thickened, tangled, and granular amorphous elastic structures. These features are attributed to UV-mediated damage to dermal fibroblasts, which then produce abnormal elastin.

Actinic keratosis (AK) is a pre-neoplastic skin disease mainly caused by solar radiation in photoexposed areas. It is characterized by atypical proliferation of keratinocytes and has a high risk of transformation into squamous cell carcinoma.

The chronically sun-exposed skin has genomic damage that predispose to carcinogenesis. More than 40% of patients with a previous diagnosis of multiple AKs developed a non-melanoma skin cancers (NMSC) (squamous cell carcinoma or basal cell carcinoma), or a malignant melanoma (MM) during a follow-up period of 5 to 11 years.[24]

The appearance of AK configures the existence of a field of cancerization and early intervention can result in primary prevention of NMSC and MM.

A systematic review concluded that topical tretinoin improves photoaging despite causing irritation; it is considered the primary drug for the treatment of aged skin. [25]

Other retinoids at proper concentrations and formulated in an appropriate delivery vehicle might be useful. Regular use of broad-spectrum sunscreens is mandatory.

CHEMICAL PEELS AND TRETINOIN AS A PEELING AGENT

Chemical peels not only improve skin appearance but also cause histologic changes such as improvement of epidermal atrophy and atypia, as well as deposition of new subepidermal collagen. [26,27]

Chemical face peels are generally classified according to the depth of penetration and its effect into: superficial (epidermal granular layer to the epidermal basal layer), medium (papillary dermis to upper reticular dermis), and deep (mid reticular dermis). [28,29]

Clinical improvement is proportionate to the depth of penetration. In superficial peels there is a need for sequential application to achieve the expected result. When compared to other peels, the healing process occurs faster and it is considered safer. Whereas, medium and deep peels are performed in a single application with a prolonged period for epithelization, implicating in more risks of infection.

In 2001, a case series with 15 participants investigated clinical and histologic modifications of the skin after five sessions of tretinoin peeling. The procedures were performed twice a month in concentrations of 1-5%. The study showed good clinical and histologic results applying the peel with 6 to 8 hours in contact to the skin in patients with skin types I to IV, with a quick achievement of lightening of melasma in photoaged skin over 2.5 weeks. [30]

One year later, these same authors (Cucé *et al*.) recommended the use of 5% tretinoin peel once a week, in three applications. At that time, Kligman commented this publication questioning stability and the advantage of such a high concentration. In fact, Kligman had previously stated that applying a 0.25% tretinoin in a solution of 50% ethanol and 50% polyethylene glycol every night was analogous to superficial chemical peels. This approach was named "rapid retinization" of photoaged facial skin. [31,32]

In a reply to Kligman´s statements, Cucé and Bertino wrote that their intent was to investigte an accurate concentration of tretinoin applied as a peeling agent, not as daily use, as performed in Kligman´s study. [33]

In 2004, one study demonstrated that 1% tretinoin peel was probably as effective in the reduction of the pigmentation in melasma in dark-skinned patients as the standard peel, using 70% glycolic acid.[34]

Topical retinoic acid applied daily to the skin produces modifications in the epidermis with dispersion of melanin.[35,36] It is possible that tretinoin peel, which is classified as a superficial peel, can induce the same modifications with the advantage of being faster and less cumbersome for the treatment of patients with melasma.[30,37]

In addition, 1% tretinoin peel provided the results in a relatively shorter period, that is, 12 weeks as opposed to the daily treatment with 0.1% tretinoin cream, which required 24 weeks to achieve the same outcomes.[38,39]

In comparison with 70% glycolic acid peel, the 1% tretinoin peel was less irritating and therefore better tolerated. As for effectiveness, both treatments reduced pigmentation, with no difference between the agents.[34]

Recently, in 2010, another study was published on the treatment of melasma by using 10% tretinoin peel. The clinical evaluation found moderate to intense improvement of this condition in all patients. This peel was suggested as an alternative modality in the treatment of melasma, considering tolerability and efficacy with no adverse events.[40]

In 2011, it was performed a double-blind, randomized study using 5% and 10% tretinoin peels in 30 subjects aged between 25 and 59 years and phototypes III and IV. It was concluded that the treatment was effective and safe for melasma, with no difference between the concentrations.[41]

Despite these reports about the efficacy and safety of tretinoin peels in high concentrations, only a few studies quantify the concentration of the drug retained in the various layers of the skin *in vivo*. Currently an experimental study assessed *in vitro* penetration of tretinoin at 0.25%, 1% and 5% concentrations, in cream and solution of ethanol and propylene glycol in equal parts. Regarding the viable epidermis, there was a greater retention of the drug when it was conveyed to 5% solution.[42]

However there is still a debate about the advantage of highly concentrated tretinoin peel versus its continuous use at low concentrations. A study from 2015 showed that most of the tretinoin peel was retained in the stratum corneum.[44] This might explain why tretinoin peels do not cause burning, stinging, pain or irritation at such high concentrations – which is commonly seen in home use of commercial formulations of the same agent at low concentrations. This very superficial retention of tretinoin peel implies that its only effect is an exfoliation of the stratum corneum, without action on the RAR of viable keratinocytes from the deeper layers of the epidermis.[31,43,44] Therefore the sequential peels effect may not be similar to daily use of standard concentrations of tretinoin cream for melasma and photoaging.

Many reports attest efficacy of tretinoin for repairing photodamaged skin, and promoting wound healing.[45-49]

A randomized and comparative study showed that, despite being safe and effective, the use of low-dose oral isotretinoin was not superior to topical 0.05% tretinoin cream every other night, for the treatment of advanced photoaging.[50]

For patients with extensive actinic keratosis and diffuse photodamage, peel is more practical than current therapies for individual lesions.

Given the limits of tretinoin peels, one should identify their real benefits not only in the treatment of melasma, but also in photoaging, pre-neoplastic and neoplastic actinic lesions (field cancerization). Additionally it is essential to investigate the ideal concentration, vehicle and standardization of application (range and number) for a particular treatment. For this purpose it is necessary more controlled, randomized and comparative studies between the gold standard tretinoin cream treatment versus its use as a peeling agent. ❑

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