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 ORIGINAL ARTICLE

Retinol: The Ideal Retinoid for Cosmetic Solutions

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ABSTRACT

Retinoids are a mainstay of dermatologic therapy. Although prescription retinoids are more potent than over the counter retinoids, when properly formulated cosmetic retinoids offer consumers an easily accessible, reasonably priced therapeutic option. Retinol has been shown to improve fine lines and wrinkles, hyperpigmentation, skin roughness, and the appearance of photoaged skin. The efficacy and tolerability of retinol makes it preferable to prescription retinoids as many patients are intolerant of these more potent forms. In this review, we will discuss the pharmacokinetics of retinol and the clinical studies confirming its efficacy, tolerability, and safety with long-term use.

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INTRODUCTION

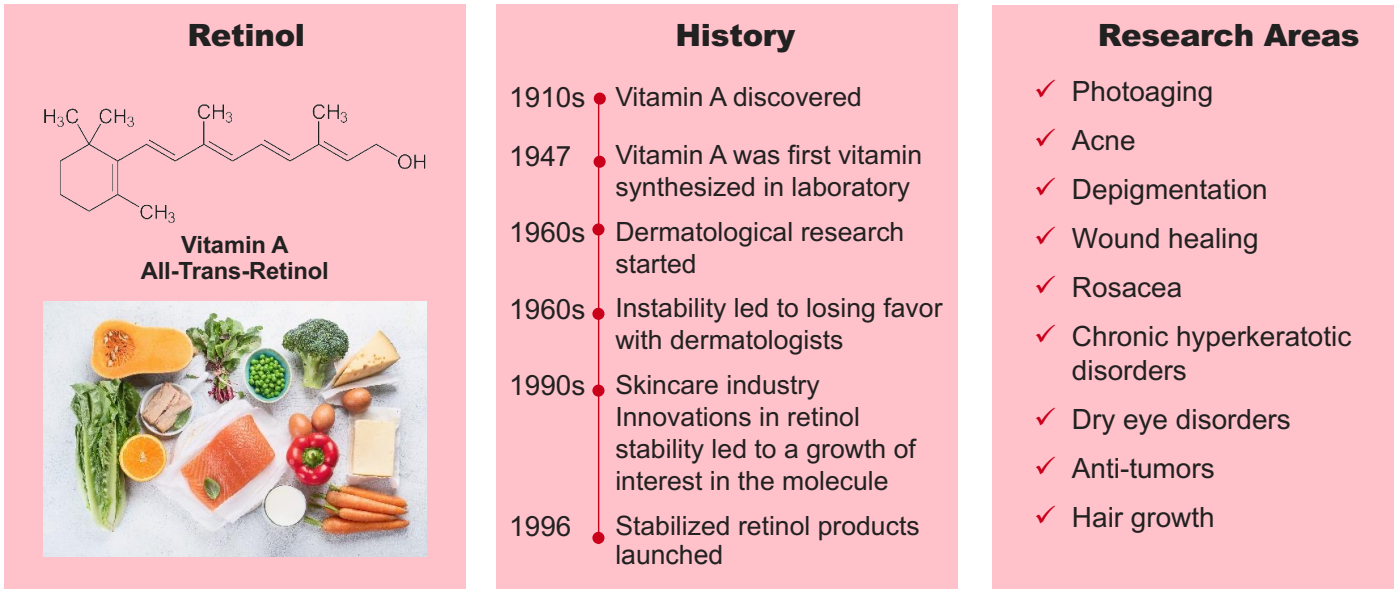
Retinol, or all-trans retinol, was the first vitamin to be synthesized in a laboratory. Methods of synthesis came from the work of David Adrianne van Dorf and Jozef Ferdinand Arens in 1947.[3]

Research into the effects of topical retinol on skin was started in the early 1960's by Albert Kligman and others, but instability of the molecule prevented it from reaching its full potential. It was not until the 1990's that cosmetic chemists were able to stabilize retinol in formulation leading to a resurgence of research on this molecule.[4] in addition to retinol, a variety of retinol derivatives referred to as retinoids, were developed and commercialized for topical application. Topical retinoids have been used as pharmacotherapy for acne, psoriasis, hyperkeratotic disorders, rosacea, and as anti-aging agents (Figure 1). In this review, we will focus on the cosmetic retinoids and make the case for retinol as the ideal retinoid for treating aging skin.

Skin aging is a result of the cumulative effects of intrinsic and extrinsic aging. Intrinsic aging, or natural aging, is a progressive degeneration of the skin over time and causes skin to be pale, thin, fragile, dry, and finely wrinkled. Extrinsic aging is a result of exposure to a variety of factors referred to as the exposome.[5] The exposome includes environmental factors such as ultraviolet light, infrared and visible light, pollution, and cigarette smoking and internal factors like nutrition, sleep, and stress. While all these play a role, ultraviolet light has the most profound effect on skins appearance. Photoaged skin has a distinct phenotype characterized by a deep coarse wrinkling, laxity, mottled hyperpigmentation, lentigines, leathery appearance, telangiectasia, and sallowness. Oxidative stress plays a central role in both intrinsic and extrinsic aging but is greatly upregulated by UV exposure.[6] Chromophores in the skin produce an array of reactive oxygen species (ROS) upon exposure to UV light that are toxic at high concentrations. The oxidative stress that ensues triggers downstream signaling that induces collagen breakdown by metalloproteinases (MMPs) and reduces collagen production.[7] This collagen deficit impairs the mechanical and functional properties of the dermis resulting in exaggerated skin wrinkling. Melanin pigments are photoprotective and upregulated by UV exposure causing mottled hyperpigmentation and lentigines. The appearance of aging skin is a primary cosmetic concern and there is a rise in consumer demand for affordable and accessible topical treatments. This has led to an increasing investment in research and development by major cosmetic companies in search of effective over the counter skincare solutions.

The efficacy of retinoic acid or tretinoin for treating aging skin was confirmed in the hairless mouse model and in clinical trials in the 1980's. Histologic evaluation of mice irradiated with UV and treated with tretinoin showed a significantly wider zone of reconstructed dermal collagen in the papillary dermis when compared to vehicle controls.[8] Several small studies published at this time demonstrate tretinoin improves

FIGURE 1. Vitamin A in dermatological research.



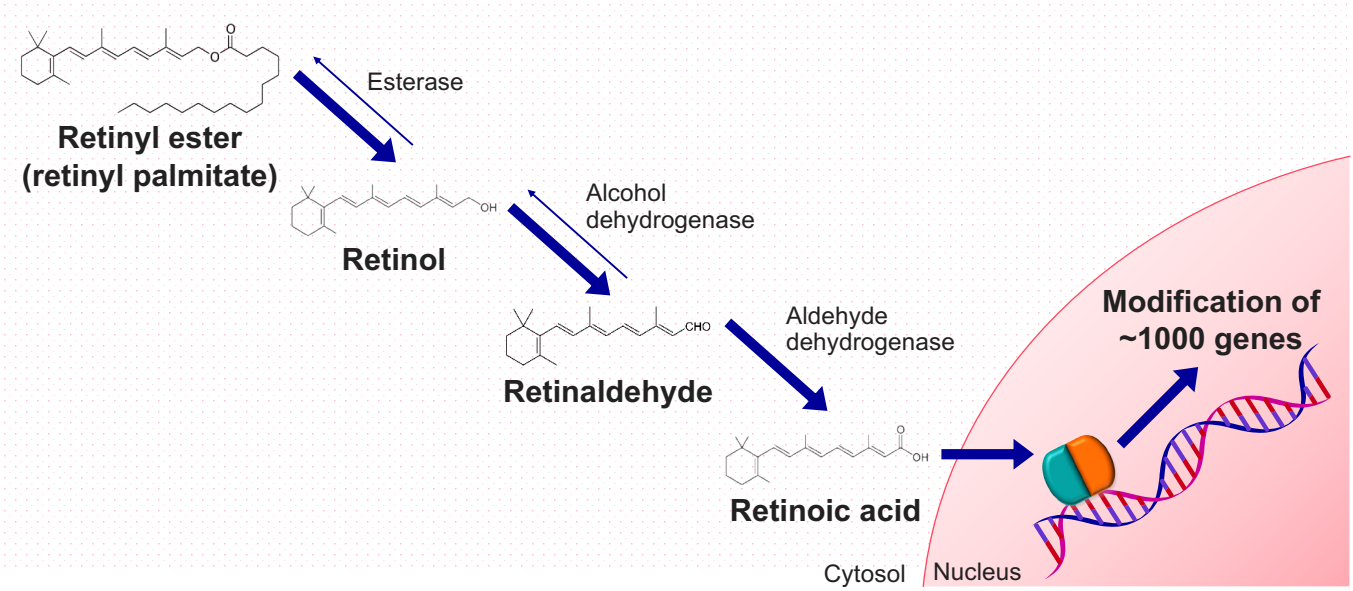
skin roughness, dyspigmentation, and softens fine lines and wrinkles.[9,10] Subsequently, a pivotal double-blind, vehicle-controlled study confirmed the anti-aging effects of tretinoin.[11] This study and others that followed ultimately led to tretinoin 0.05% emollient cream being the first prescription topical approved for the treatment for aging skin in 1995.[12] In view of the fact that several formulations of tretinoin were already FDA-approved for the treatment of acne, this retinoid remains available today only by prescription.

Despite its anti-aging benefits, the clinical use of tretinoin has been limited by its propensity to cause skin irritation or retinoid dermatitis. Retinoid dermatitis is characterized by redness, peeling, and flaking and is believed to be a result of applying supraphysiologic amounts of retinoic acid to the skin.[13] Retinoic acid upregulates heparin-binding epidermal growth factor (HB-EGF) and amphiregulin. These serve as ligands for epidermal growth factor receptor (EGF-R) and cause proliferation of basal keratinocytes, epidermal hyperplasia, and stratum corneum desquamation. Subsequent disruption of the skin barrier by tretinoin causes cytokine release and erythema. Although retinoid dermatitis is viewed as an indicator of efficacy and penetration, it is probably not related to the anti-aging benefits that occur primarily in the dermis. Retinoid dermatitis limits the use of topical tretinoin in many patients so identifying non-irritating alternatives is essential.

Over-the-counter formulations containing vitamin A are now widely available. There are three basic forms of vitamin A used in these cosmetic products including retinyl esters, retinol, and retinaldehyde. The rationale supporting their use comes from our understanding of the metabolism of vitamin A in the skin. (Figure 2).[14] When retinyl esters, such as retinyl palmitate, are applied to the skin, they are hydrolyzed to retinol. Retinol is subsequently oxidized to retinaldehyde, which is then irreversibly oxidized to retinoic acid, the active form of vitamin A in the skin. Thus, skin has the inherent capability to utilize a variety of topically applied precursor molecules and convert them to retinoic acid. It is also of interest that when retinol is applied to the skin, only a small amount is converted to retinoic acid while the majority is esterified with fatty acids, such as palmitic acid, stearic acid, and oleic acid.[15] These retinyl esters serve as a natural storage form for vitamin A and can be reconstituted back to retinol through hydrolysis. The conversion of retinol to retinoic acid is tightly regulated to maintain relatively low levels of retinoic acid. This helps mitigate irritation with topical retinol and provides cells with retinoic acid only when its needed.

Retinyl esters, retinol, and retinaldehyde differ in their efficacy, potency, and irritation profile (Figure 3). Retinyl esters are the most stable but least potent of all topical retinoids. They are least likely to cause retinoid dermatitis and are favored by some cosmetic chemists due to their stability and safety profile. Retinol and retinaldehyde are more potent than retinyl esters. They are inherently more unstable than retinyl esters although innovations in formulation techniques have allowed their stabilization. Retinol and retinaldehyde are more irritating

FIGURE 2. Vitamin A metabolism and action.



than retinyl esters but far less likely than topical tretinoin to cause retinoid dermatitis.[16] It is also of interest that retinol has been shown to penetrate human skin more readily than retinyl palmitate, retinaldehyde, and retinoic acid, although retinol did not produce erythema in this study.[17] Irritation potential with retinol is also concentration-dependent and can be minimized by delivering stabilized low-concentration retinol.[18]

Commercially available over the counter retinols differ vastly. Most retinols are formulated with concentrations of 0.04%–1% retinol, although few are labeled with this information. Intuitively, it might seem reasonable to assume that higher concentration retinols are more effective, but there are other formulation parameters that affect potency and efficacy. In a comparative study, retinol bioactivity as indicated by cellular retinoic acid binding protein II (CRABP II) expression, was greater with stabilized 0.1% retinol versus prestige brand 0.2% and 1.0% retinols.[19] Delivery systems such microsponges and liposomes have been used to deliver retinol to the skin and have an effect on potency, efficacy and tolerability.[20] Modern advances in formulation science and analytical stability techniques have enabled the use of consumer-friendly

FIGURE 3. Retinoids relative potency, irritation potential, and stability.

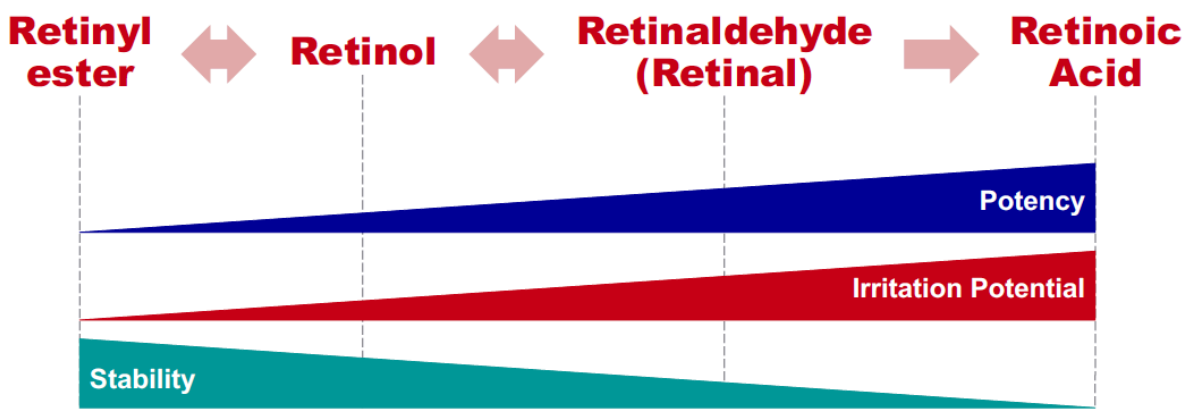
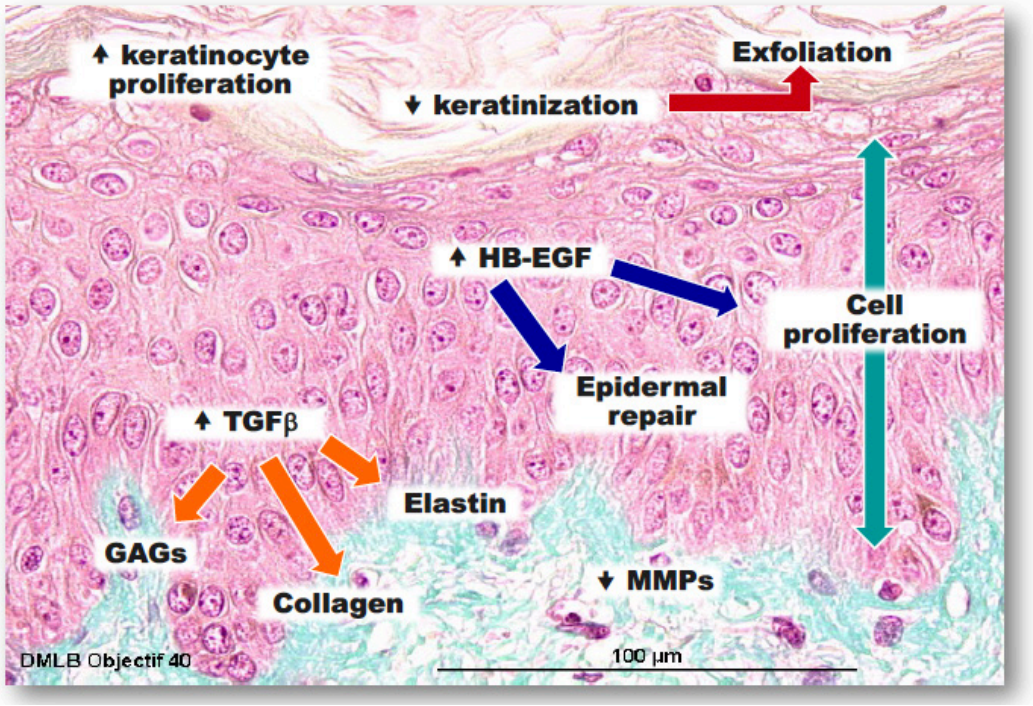


FIGURE 4. Mechanism of action.

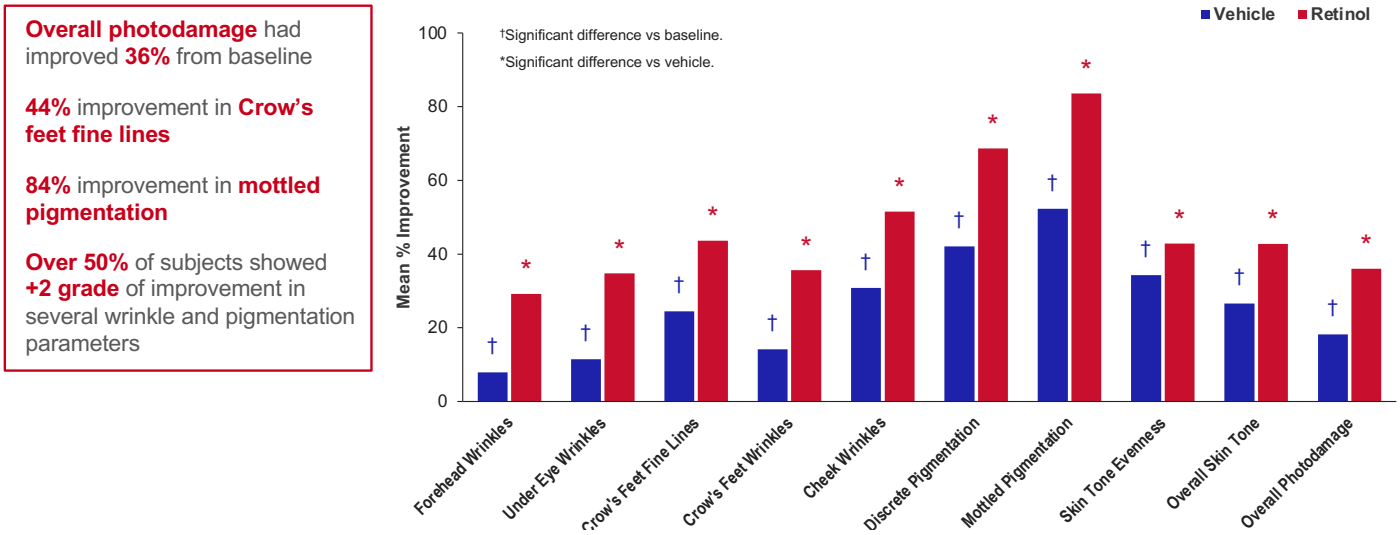


packaging such as airless pumps and tubes with a useful shelf-life of 2 years. Packaging in jars is a technical hurdle that has been achieved but requires rigorous formulation development and testing.

The biologic effects of all retinoids are dependent on their ability to bind to cytoplasmic and nuclear receptors.[21] Within the cytoplasm, retinol and retinaldehyde bind to cellular retinol binding protein (CRBP). Although the role of this cytoplasmic receptor is not completely understood, it is believed that it serves to facilitate the conversion of retinol to retinaldehyde and retinaldehyde to retinoic acid. Retinoic acid binds to cellular retinoic acid binding protein (CRABP), of which there are two isomers, CRABPI and CRABPII. Binding of retinoic acid to CRABPII facilitates translocation of retinoic acid into the nucleus. To regulate gene transcription, retinoic acid must bind to nuclear receptors that are members of the steroid-thyroid hormone superfamily. There are two unique families of nuclear receptors, retinoic acid receptors (RARs), and retinoid X receptors (RXRs). There are three isoforms of RARs and RXRs, α, β, and γ. The epidermis expresses primarily RARγ/RXRα, making this heterodimer important in cutaneous signaling.[22] Retinoic acid binds to RARγ within the keratinocyte nucleus, which then forms a heterodimer with RXRα. Once formed, this retinoid-receptor heterodimer complex binds to specific DNA elements known as retinoic acid response elements (RAREs). These elements reside in the promoter region of target genes and stimulate (no 2) transcription of mRNA and ultimately protein synthesis. In addition, retinoids have indirect effects that result from downregulation of genes that do not contain RAREs in their promoter region.[23] Retinoic acid is known to antagonize transcription factors activator protein-1 (AP-1) and nuclear factor kappa beta (NF-κβ).[24] AP-1 increases synthesis of metalloproteinases that break down collagen and concomitantly causes a reduction in collagen synthesis. NF-κβ triggers production of a variety of inflammatory mediators that contribute to skin aging. The anti-aging benefits of retinoids have been attributed, in part, to their ability to down-regulate these transcription factors.

The cellular and molecular effects of retinol have been studied extensively and confirm its bioactivity in the epidermis and dermis (Figure 4). Topical application of 1.6% retinol under occlusion induces epidermal thickening and enhances expression of CRABPII mRNA like tretinoin 0.025%.[25] Retinol treatment resulted in less erythema and skin irritation compared to tretinoin in this study. An ex vivo study using human skin explants demonstrated that 0.1% retinol induced CRABPII and HBEGF gene expression, increased keratinocyte proliferation and epidermal thickness.[26] In this study, human

FIGURE 5. Clinical results of stabilized 0.1% retinol with long-term use (52 weeks) compared to vehicle control.



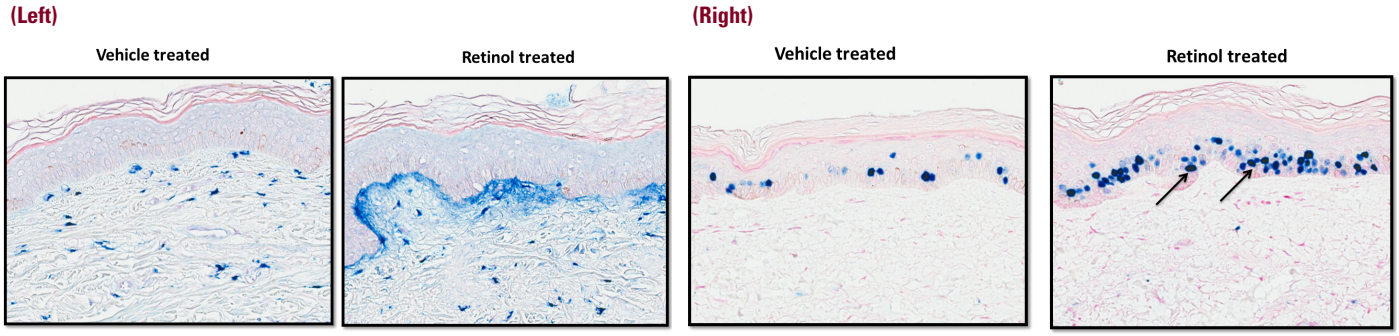
volunteers who applied the 0.1% retinol formulation for 36 weeks showed improvement in all major aging signs assessed including wrinkles under the eyes, fine lines, and tone evenness compared to placebo control. Moreover, tryptophan fluorescence, a non-invasive indicator of epidermal thickness, increased in the active-treated group and not in the placebo-treated group indicating cell proliferation was accelerated in vivo. Retinol 0.1% applied to a monolayer of epidermal keratinocytes increased gene expression of all three forms of hyaluronic acid synthases (HAS) and increased hyaluronic acid production in human skin equivalents.[27] Subjects treated with the same 0.1% retinol demonstrated an increase in hyaluronic acid accumulation in the epidermis compared to those treated with vehicle.

The dermal effects of retinol have also been confirmed. Retinol 0.04% lotion applied three times a week for 24 weeks to the forearm significantly increased glycosaminoglycan expression and procollagen 1 immunostaining in naturally aged skin.[28] Clinical assessment resulted in significant improvement in fine wrinkling score between retinol-treated and vehicle-treated groups. In a comparative study, tretinoin 0.1%, retinol 0.1%, and vehicle were applied to forearm skin once weekly under occlusion for four weeks.[29] Genes for collagen type 1 and collagen type 3 were upregulated with both retinoids and increases in procollagen I and procollagen III protein expression observed mostly in the papillary dermis. Application of 1% retinol to naturally aged skin was shown to increase fibroblast growth and collagen synthesis while decreasing matrix metalloproteinases.[30] In addition having collagen boosting effects, retinol has also been shown to increase elastin fiber formation.[31] Retinol 0.04% added to cultured dermal fibroblasts resulted in an increase in elastin protein synthesis and elastin fiber formation. Application of the same retinol 0.04% to human skin explants confirmed an elastin fiber network on biopsy using Luna staining. Thus, it appears that retinol confers similar benefits to retinoic acid on skin with less irritation.

Clinical studies confirm the benefits of retinol on aging skin. An eight-week, double-blind, split-face, vehicle-controlled randomized study was conducted on female subjects with moderate photodamage.[18] Subjects applied 0.1% stabilized retinol or vehicle for eight weeks to each side of the face. Retinol treatment resulted in a progressive improvement over time with significant improvement over vehicle in all wrinkle parameters, pigmentation, elasticity, firmness, and overall photodamage at eight weeks. The test retinol was well tolerated with no erythema, scaliness, or edema noted. Improvement was seen in the vehicle-treated group but far less than the active group and is believed to be due to the moisturizing effects of the vehicle containing glycerin and the passive lightening that occurs during the winter months.

Studies have also confirmed that topical retinol remains beneficial with long-term use. In a one-year, double-blind,

FIGURE 6. (Left) Procollagen and (Right) Ki67 expression changes at 52 weeks.



vehicle-controlled trial, 0.1% stabilized retinol outperformed vehicle at ameliorating all parameters aging including cheek wrinkles, crow's feet, under-eye wrinkles, discrete pigmentation, mottled pigmentation, and overall skin tone from weeks 24 through the end of the 52-week study (Figure 5). Retinol treated patients experienced a 44% improvement in crow's feet and 84% improvement in pigmentation over baseline at the end of the study. Over 50% of the patients treated with retinol experience a 2+ grade improvement in many aging skin parameters. This retinol formulation was well tolerated with no adverse events reported by any of the 62 subjects who participated in the study. Biopsies were performed on 12 subjects to address the question of whether the skin remains responsive to topical retinol over an extended period of time. Retinol-treated photoaged skin showed an increased expression of type 1 procollagen at 52 weeks, indicating long-term benefits of retinol on collagen production (Figure 6). Ki67 staining in basal keratinocytes, an indicator of epidermal proliferation, was increased in the retinol-treated group at the end of the study. Expression of hyaluronan both in the dermis and viable layers of the epidermis was also increased compared to vehicle control. This study indicates that long-term use of retinol induces biological responses that improve the appearance of photoaged skin and that the skin remains responsive to topical retinoids even with prolonged use.

The evolution of cosmetic retinols has afforded consumers effective over the counter solutions to address a variety of cosmetic concerns.The data presented here support the notion that retinol-containing cosmeceuticals are not only effective alternatives to retinoic acid but may actually be preferrable since they are more well tolerated and readily available. While some products contain only pure retinol, others contain additional ingredients that provide skin benefits. Topical retinols are inherently well tolerated but some formulations include ingredients like bisabalol or glycerin that reduce the possibility of irritation and dryness. Dermatologists need to familiarize themselves with the nuances of retinols so they can best advise their patients on proper product selection.

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