Improving Elasticity: The Science of Aging Skin

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Although collagen changes from both chronologic aging and photoaging have been well studied, there is a dearth of research into the elastin component of the dermis. No products have been approved by the US Food and Drug Administration for either replacing elastin or stimulating its synthesis. Recently, a zinc complex was shown to increase dermal elastin staining, hypodermal fat, and epidermal thickness in animal studies. Histologic studies of the same zinc complex in humans have revealed increased deposition of functional elastin fibers following 10 days of use. In the clinical trials reported here, there was an increase in functional elastin, as well as improvements in fine lines and wrinkles. No adverse events were noted.

Collagen and elastin are the fibers that make up the dermal matrix. Cosmetic dermatologists have long used topical medications, fillers, and light-based and laser-based therapies to improve the loss of collagen that occurs in aging skin. However, until recently, no fillers or topical agents have been available to treat the loss of function of elastin, which is also an important feature of dermal photoaging. The loss of collagen, elastin, and other dermal matrix components translates into the wrinkled, sagging, fragile skin associated with chronologic aging and photoaging.

THE ROLE OF ELASTIN IN THE APPEARANCE OF AGING SKIN

Elastin is a resilient connective tissue in the extracellular matrix. Elastin fibers are found at the periphery of collagen bundles and endow the skin with rebounding properties. Tropoelastin molecules, which are precursors to elastin, bind covalently with cross-links to form elastin. Elastin fibers are assembled on bundles of microfibrils composed of fibrillin. The latter forms a template on which elastin is deposited.[1] Most elastin production is restricted to a narrow window of development. Elastogenesis increases dramatically during fetal life, peaks near birth and early neonatal life, decreases significantly thereafter, and is nearly nonexistent by maturity.

In contrast to collagen fibers, elastin fibers are present in various stages of maturity. Oxytalan fibers, the least mature elastin fibers, course perpendicularly from the dermal-epidermal junction to the top of the reticular dermis whereas elaunin fibers, the more mature elastin fibers, attach to a horizontal plexus of fibers found in the reticular dermis. Elaunin fibers are more mature because they have more elastin deposited on the fibrillin mesh. The most mature elastin fibers are unnamed and are found deeper in the reticular dermis.[1,2] This fibrous network running from the uppermost section of the papillary dermis to just beneath the basement membrane lends elasticity to young skin. As this network deteriorates with age, the loss of or damage to elastin fibers may play a significant role in skin sagging and loss of youthful resilience.[3,4]

Photoaging initially leads to hyperplasia of elastin fibers according to the level of UV exposure. Later, a degenerative

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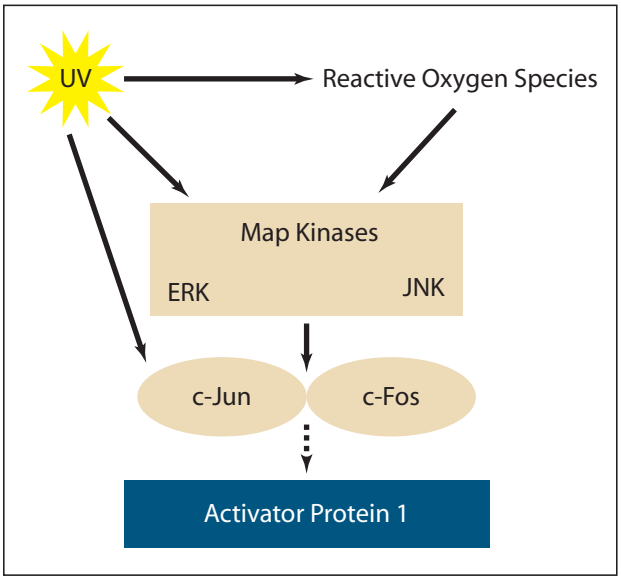
response occurs with resultant loss of skin elasticity.[5,6] When viewed by light microscopy, degraded elastin appears as an amorphous substance that accumulates in the papillary dermis.[1,7] The resultant elastosis, a hallmark of photoaged skin, is due to the breakdown of elastic fibers and loss of functional elastin. Defective or damaged elastin may lead to wrinkles, even in the absence of sun exposure and aging. A child with wrinkled skin syndrome was shown to have a deficiency of elastin fibers, which demonstrates the important contribution of elastin to skin integrity.[1]

Studies have demonstrated that, with aging, there is a reduction in the elastin content of protected areas of the skin. In a study of Egyptian subjects, the relative amount of elastin in the non–UV-exposed abdominal skin decreased significantly from 49.2%±0.6% in the first decade of life to 30.4%±0.8% in the ninth decade.[2] Another study on elastin content in the non–UV-exposed skin of the buttocks of 91 white subjects between 20 and 80 years of age showed a 51% reduction in elastin tissue.[8]



Complicated signaling cascade that leads to collagen degradation. ERK indicates extracellular signal–related kinase; JNK, c-Jun amino-terminal kinase.

MECHANISMS OF DERMAL AGING

Although chronologic aging and photoaging have often been considered to be separate processes, research indicates a potential overlap at the molecular and clinical levels.[9,11] There is substantial evidence that skin aging is mediated by direct absorption of UV radiation by chromophores in the skin leading to the production of reactive oxygen species (ROS).[10] ROS-mediated photochemical reactions can oxidize cutaneous proteins, lipids, and DNA. The Figure shows the complicated signaling cascade that leads to collagen degradation. UV radiation leads to the generation of ROS and the formation of the mitogen-activated protein kinases (MAPKs), extracellular signal–related kinase, and c-Jun amino-terminal kinase. This, in turn, leads to upregulation of the transcription factor c-Jun. When sufficient c-Jun is expressed to heterodimerize with c-Fos, activator protein 1 (AP-1) is produced.[9,10] AP-1 is a transcription factor that stimulates the matrix metalloproteinases (MMPs) and reduces type I procollagen, both of which are seen in chronologically aged and photoaged skin.[9,10] Findings reported by Varani et al[11] have suggested that both chronologically aged and photoaged skin also exhibit similar features, such as connective tissue alterations (eg, progressive loss of dermal fibroblasts, increased space between connective tissue fiber bundles, and increased disorganization of fiber bundles). In addition to the activation of AP-1 and the MMP cascade, matrix degradation is also mediated by inhibition of transforming growth factor β signaling.[12]

Recently, there has been interest in the contribution of glycation to skin aging. Protein damage by reducing sugars and other reactive carbonyl species leads to the formation of advanced glycation end products, which form covalent cross-links between proteins that can alter their structure and function. Advanced glycation end products have been shown to accumulate in tissues with a low turnover rate, including dermal collagen and elastin. At approximately 35 years of age, glycation of the dermis has been shown to begin; it then increases rapidly with age.[13] Although changes in dermal collagen are well studied, research on changes in dermal elastin is less extensive.

In a study designed to demonstrate differences between chronologically aged and photoaged elastic tissue, Bouissou et al[14] found that low–sun-exposed skin showed a disappearance of oxytalan fibers beginning at 30 years of age. By 40 years of age, there were no oxytalan fibers, and there was significant lysis of elastic fibers. In high–sun-exposed skin, the same age-related lesions were noted, but elastotic degeneration in the reticular and deep dermis was also seen. Chronologic aging appeared to be characterized by the disintegration of elastic fibers, whereas photoaging was characterized by thicker, elastotic fibers. The authors suggested that the lesions of chronologic aging may be due to proteases originating in fibroblasts and that the lesions of photoaging may be due to UV stimulation of fibroblasts. Scharffetter-Kochanek et al[15] have suggested that the AP-1 and MMP cascade may be operative in the characteristic elastin changes because MMP-2 has been shown to degrade both elastin and collagen.

Human leukocyte elastase (HLE) may play a role in elastin degradation. It has been shown that lysosyme binding to elastin fibers, which may be induced by UV exposure, may prevent their degradation by HLE. A study

by Seite et al[8] revealed that the elastolytic activity of HLE was reduced by up to 38% after lysosyme binding to areas of damaged elastin.

COSMETIC MANAGEMENT OF THE AGING DERMIS: FOCUS ON ELASTIN

Cosmetic dermatologists have long addressed collagen loss via collagen replacement injections or topical products that support the formation of new collagen. However, no products or procedures have been available to address the changes in elastin resulting in the characteristic loss of resilience seen in chronologically aged and photoaged skin.[16] Although many topical products contain collagen and elastin and claim to increase the levels of these fibers in the skin, topical applications of collagen and elastin have never convincingly been shown to penetrate the dermis.

ZINC COMPLEX FOR ELASTIN REPLACEMENT

Because it is so difficult for elastin to penetrate the skin, stimulating the dermis to make its own elastin is an option. A promising new approach for elastin replacement is based on the ability of a patented zinc complex to promote the formation of new, functional elastin.

Zinc has many structural roles in biological membranes, cell receptors, and proteins.[17] It has been shown to affect epidermal growth factor–stimulated intracellular signaling, and numerous studies also indicate that zinc possesses insulinlike effects.[18] As a potent inhibitor of protein tyrosine phosphatase, zinc increases protein tyrosine phosphorylation and activates intracellular signaling, including MAPK activity that is crucial for cosignaling in extracellular matrix production.[19] Epidermal growth factor receptor signaling can affect mitogenesis, apoptosis, enhanced cell motility, protein secretion, and differentiation or dedifferentiation, depending on cellular phenotype.[20] Zinc may potentially exert insulinlike effects in lipogenesis, glucose transport, and glucose oxidation in rat epididymal adipocytes.[21-23] Moreover, zinc potentiates the mitogenic signaling of insulin.[24] Evidence suggests that zinc may actually be involved in several steps of the insulin-signaling pathway, which serves cosignaling roles for extracellular matrix pathways as well.[25] Recent evidence shows that zinc may regulate the serine/threonine protein kinase known as mammalian target of rapamycin, which plays a key role in regulating cellular activity and size, as well as cellular phenotype.[26]

Thus, through a combination of well-defined cellular pathways, zinc can induce production of new functional elastin, as well as a shift away from more perturbed extracellular matrix components. These effects occur over a well-defined concentration range only. Consistent with the cosignaling pathways involved, moderate epidermal thickening and marked reversal of hypodermal fat atrophy will also occur over concentration ranges effective for elastin production.

CLINICAL STUDY 1

Patients and Methods

In a prospective, randomized, double-blind, vehicle-controlled clinical study, both eyes of each of 26 subjects received once-daily applications of either a zinc complex cream for the eye area or a copper peptide formulation. Subjects were healthy adult females aged 37 to 60 years who were regular users of eye creams. Clinical follow-up was at 1, 2, and 4 weeks. The primary end points were quantitative measures of improvements in elasticity: the snap test, measurement with a DermaLab® suction cup, and a blinded dermatologist assessment of aesthetic improvement.

In this study, snap-test time was used as a measure of functional elastin. Functional elastin is a long, healthy elastic fiber capable of rebounding following mechanical distension. Although there are products that may increase elastin fibers in the dermis, elastin fragments have not been demonstrated to restore skin firmness as functional elastin does.[16] The snap test determines the number of seconds needed for the skin to snap back to baseline after being pulled a specific distance. There was a 40% improvement in snap time (2.1 seconds) in the eyes treated with the zinc complex versus the copper peptide control as measured by the snap test ($P=.0026$, 1-way analysis of variance) conducted by 2 blinded observers.

Skin elasticity was also measured by a DermaLab suction cup elasticity module, which is a suction probe that raises the skin a measured distance by means of a vacuum. The differential negative pressure required to lift the skin a predetermined distance was used to express skin elasticity. Both skin retraction time and viscoelasticity (the elevation and retraction phases combined in 1 score) were measured. Negative values, reported as kilopascals, reflected improved skin elasticity conditions. Statistically significant improvements in these parameters were reported at weeks 2 and 4 ($P<.05$).

Results

Blinded dermatologist assessments, based on a score of 0 (none) to 9 (severe), determined that the zinc complex produced significantly greater improvements at week 4 in skin roughness, fine and coarse lines, laxity, puffiness, dark circles, and crepey and sunken appearance. As early as 1 week posttreatment, improvements were seen in coarse lines, puffiness, dark circles, and crepey and sunken appearance.

CLINICAL STUDY 2

Patients and Methods

An eye product containing zinc complex was evaluated in a randomized, double-blinded, vehicle-controlled study of 27 female subjects aged 36 to 50 years. The primary objective was to evaluate the safety of the product in subjects after 4 weeks of product use. The secondary objective was to evaluate the efficacy of the product in improving the appearance of fine lines and wrinkles around the eyes.

Subjects were evaluated at baseline by means of a Nova meter to determine skin surface moisture. Subjects then had silicone replicas taken in the crow's-feet area of each eye as a baseline measurement of efficacy in reduction of fine lines and wrinkles in these areas. Participants were randomly assigned a test product to use on each eye. Follow-up was at 2 and 4 weeks.

Results

A significant smoothing of crow's-feet wrinkles was seen at day 14, with reduced number and depth of wrinkles in this area. This significant smoothing effect continued through the study's end at day 28. The Table shows the results obtained with the zinc complex eye product from baseline to day 28. All were statistically significant ($P<.01$). The subjects also noted improvements. Overall improvement in the eye area was noted by 78%; tighter, firmer skin, 70%; and reduced fine lines, 74%.

SUMMARY

Increased understanding of the processes underlying the dermal changes of both chronologic aging and photoaging is leading to new developments in cosmetic dermatology. Until recently, our ability to replace damaged or lost elastin has not paralleled our ability to replace or repair collagen.

Blinded Dermatologist Assessment of Zinc Complex Eye Gel at 28 Days*

29% decrease in fine lines and wrinkles
37% decrease in coarse wrinkles
43% decrease in undereye laxity
30% decrease in undereye puffiness
21% decrease in undereye dark circles

*$P<.01$.

A zinc complex has been shown in histologic, animal, and clinical studies to improve the resilience of chronologically aged or photoaged skin by increasing elastin synthesis. These pilot studies appear extremely promising and should be repeated in larger populations.

In addition, it would be interesting to study the effects of the zinc complex on the production of elastic tissue in other organs, as well as on nonexposed areas of skin, such as on the abdomen of pregnant women, where a loss of elasticity may occur.

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