

LOCAL THERAPY AS BASIC ANTI-AGING PREVENTION

Nevia Delalle-Lozica

Dermalife Polyclinic for Dermatology and Venereology, Zagreb, Croatia

SUMMARY – Skin, the largest organ of the body, is the organ in which changes associated with aging are most visible. Intrinsic (chronologic) skin aging is characterized by atrophy of the skin with loss of elasticity and slowed metabolic activity. With superposition of environmental damage, particularly exposure to ultraviolet radiation (photodamage) on the intrinsic aging, the process results, at least initially, in hypertrophic repair response with thickened epidermis and increased melanogenesis. Even more striking changes occur in the dermis, i.e. massive elastosis (deposition of abnormal elastic fibers), collagen degeneration, and twisted, dilated microvasculature. Regular use of a sunscreen alone appears to allow for some repair as well as protection from further photodamage. Local anti-aging therapy has been shown to partially reverse the clinical and histologic changes induced by the combination of sunlight exposure and chronologic aging. Histologic changes in the epidermis and dermis noted after 12 months suggest repair of photodamage by reconstitution of rete pegs, repair of keratinocyte ultrastructural damage, more even distribution of melanocytes and melanin pigment, deposition of new papillary dermal collagen, and improvements in vasculature. Hyperkeratinization is normalized, while epidermal thickness and dermal glycosaminoglycan content are increased. Briefly, many of the unwanted changes can be improved by topical therapy.

Key words: *skin aging, photoaging, local therapy, hyaluronic acid, collagen UV rays, photoprotection, wrinkles, pigmentation*

Introduction

With natural aging, human skin becomes thin, lax, dry, loses its elasticity, looks lusterless and scaly, and finely wrinkled. There are internal and external factors affecting the skin. Internal aging is associated with progressive degenerative changes in the structure and function of the skin, i.e. chronologic aging, under the influence of genetic and hormonal factors. External factors also greatly influence the aging process, and the most important part is ultraviolet radiation, along with environmental pollution and modern lifestyle.

These effects entail reduction in the number of elastic and collagen fibers and blood flow, facial lines

become strong and prominent, with deepened wrinkles. Age spots and solar elastosis arise as melanocyte defense to aggressive sun exposure. Properly selected local therapy at the right time with adequate protection from external influences will not top the aging process, but will significantly delay the first signs of aging¹.

Efficacy of Local Therapy

Reduced amounts of hyaluronic acid occur with loss of connective tissue, resulting in wrinkled skin. Hyaluronic acid fills the connective tissue and is responsible for its strength. Mimic wrinkles occur because of frequent mimic muscle contractions, combined with the loss of elasticity. Static wrinkles are the result of photoaging combined with the loss and degeneration of collagen and elastic fibers. Thus, wrinkles are scar tissue formed due to the loss of tissue elasticity and cannot be

Correspondence to: *Nevia Delalle-Lozica, MD*, Dermalife Polyclinic for Dermatovenereology, Dermatosurgery, Dermato-Oncology and Anti-Aging Medicine, Ilica 203/I., HR-10000 Zagreb, Croatia

E-mail: nevia@dermalife.hr

removed by local preparations, but some of them can become shallower².

On the other hand, effective creams have numerous side effects and cosmetic companies cannot take the risk upon on themselves. The most common side effects are allergic reactions and pores characterized by clogging, redness, itching, powdery scaling, and sometimes burns. Some of these preparations can be recommended only by a physician. Active substances penetrate the skin, reaching the blood or lymphatic vessels by transepidermal or transfollicular route, however, in low concentrations, thus systemic side effects are very rare.

Efficacy of local preparation will depend on:

- 1) ability of active substance to release from the vehicle;
- 2) binding ability of individual active substances to specific structures of the skin;
- 3) absorption in different skin layers;
- 4) penetration; stratum corneum is the main barrier; epidermal enzymes: degradation of active substances: lipid layer: permeability of fat soluble active substances; size of active molecules; number and concentration of active molecules in the preparation; physicochemical properties;
- 5) resorption;
- 6) patient age: lower permeability in older patients;
- 7) skin thickness and density of hair follicles;
- 8) humidity and temperature; and
- 9) circulation.

It is necessary to estimate the skin before choosing local therapy, as well as before any dermatologic procedure. It is important to determine the phototype, thickness and quality of the skin, the presence of wrinkles and fine lines, and to distinguish mimic wrinkles and genetic lines of wrinkles due to aging. Then, changes attributed to the influence of UV rays, such as dyschromias, dermatoheliosis, premalignant lesions and other irregularities, should be verified.

The Goal of Local Therapy

The main goal of local anti-aging therapy is to preserve regeneration ability of the skin, to recover already damaged skin, and to replace the active ingredients that are missing or are present in a much lesser concentration

in older skin. Also, with topical anti-aging treatments it is possible to improve brightness of the skin, to remove fine wrinkles, to reduce irregular pigmentation and redness, and to improve the contour of the face³.

Methods

Primary prevention starts from the earliest youth and includes photoprotection, uniform and low-calorie diet, use of local products with anti-oxidant activity such as vitamins, minerals and some flavonoids, and regulation of physical activity. Secondary prevention starts after reporting the first signs of aging and best results are achieved using multiple methods and anti-aging products. To prevent the signs of aging skin to become ever more prominent, it is necessary to give enough active ingredients with moisturizing effects such as ceramides, hyaluronic and fatty acids, triglycerides, linoleic acid, glycerin and various other active ingredients. It is important to limit further sun exposure and daily apply preparations with high sun protection factor (SPF) throughout the year^{2,3}. Active substances that are commonly used in anti-aging preparations are alpha and beta hydroxy acids, vitamins A, C, E, B5, beta glucane, hyaluronic acid, CoQ10, C ester, alpha lipoic acid, aloe vera, jojoba, allantoin, essential oils, transretinoin (retin A), estrogen, growth hormone and melatonin³.

Moisturizers

Moisturizers are a key component of basic skin care, especially when there is alteration of the epidermal barrier and reduced water content in the epidermis. They are used to restore the barrier function of the epidermis, to cover tiny fissures in the skin, to provide a soothing protective film and increase the water content of the epidermis. Thus, they may slow evaporation of the skin moisture, thereby maintaining hydration and improving the appearance and tactile properties of dry and aging skin. They contain various combinations of emollients, occlusives, and humectants to achieve their beneficial effects, and there is an overwhelming number of formulations available. Newer products claim to have other properties such as anti-aging, skin-firming, anticellulite, and sun-protective effects⁴.

Protection with SPF

Changes induced by sunlight are the major factor causing alterations in the skin that contribute to the appearance of aging. Sunscreens and sun-blocking agents can prevent or retard these changes. These chemical sunscreens absorb various wavelengths of UV light and consequently allow for only a limited amount of light to enter the tissue. They can be classified according to their effectiveness in absorbing UVA *versus* UVB rays. Most common agents that protect against UVA are benzophenones, dibenzolmethanes or avobenzones including Parsol 1789. UVB protecting agents are para-aminobenzoic acid (PABA) with a great risk of contact sensitization, then PABA esters such as glyceryl PABA and padimate-O, cinnamates, salicylates and phenylbenzimidazole sulfonic acid. Physical blockers contain small particles that scatter, reflect, or absorb in the UV and visible range. Because some of these are absorbed, secondary oxygen radicals can be formed. Coating the particles with silicone absorbs these free radicals and is the basis of a product called Z-cote. The physical blockers include Zn oxide, titanium dioxide, iron oxide, kaolin and veterinary petrolatum. The value of SPF is the ratio of the time required to produce erythema through a sunscreen product to the time required to produce the same degree of erythema without the sunscreen.

Alfa hydroxy acids (α HA) represent a group of substances derived from natural products such as fruits (citric acid), milk (lactic acid), sugar cane (glycolic acid), apples (malic acid), and wine (tartaric acid). Their exact mechanism of action is unknown. These acids are exfoliants, i.e. substances that remove the upper layer of old, dead skin and stimulate the growth of smooth, evenly pigmented new skin (keratolysis or sloughing of excess stratum corneum). Alteration in the pH of the skin when the acids contact the epidermis causes irritation, with subsequent increased cell turnover rate and a renewed stratum corneum. Exposure to the acids may induce slight edema, which plumps the skin, reducing fine lines and wrinkles. These products are very effective on thin, dry and photodamaged skin in concentration of 5%-8% with pH 3-4^{5,6}.

Beta hydroxy acid (β HA) – Salicylic acid is a beta-hydroxy acid. It is a hydroxyl derivative of benzoic acid and represents a carboxylic acid attached to an aromatic alcohol, phenol. Salicylic acid is the only

member of the beta-hydroxy acid family, so named because the aromatic carboxylic acid has a hydroxy group in the beta position. Salicylic acid is derived from willow bark, wintergreen leaves and sweet birch. Salicylic acid as keratolytic also has an effect on prematurely aged skin due to exposure to UV rays from the sun. β HA causes softening of the horny layers and shedding of scales. It produces this desquamation by solubilizing the intercellular cement and enhances the shedding of corneocytes by decreasing cell-to-cell cohesion. It penetrates oil-laden hair follicle openings and, as a result, also helps in acne. The best results are achieved using β HA in a concentration of 2%-6% with pH 3-4⁷.

The main difference between α HA and β HA is their solubility. α HA's are soluble only in water and β HA in fat. β HA penetrates the pores filled with sebum, and peels dead cells (comedolytic effect) on fatty skin. Both types of acids increase the sensitivity to UV radiation, β HA even by 50%, so it is recommended always to combine these medicines with SPF-UVA and -UVB filters. Although β HA penetrates deeper than α HA, it is less irritative because of salicylic acid derived from acetylsalicylic acid (ASA) with anti-inflammatory effect. Caution is required in Fitzpatrick skin photo types IV-VI because of the side effects such as redness, itching, burning, and especially hyperpigmentation and scars.

α HA in a concentration of up to 30% may be an integral part of creams, foundations, moisturizers, cleansers or creams. It is recommended to use only one resource that contains α HA and combine it with a moisturizer to reduce irritative effect of the acid. Finished combined preparations with α HA are often ineffective and should be avoided. The cleansers containing α HA are not in contact with the skin long enough and there is no absorption and thus no action of active ingredients. Although the application of SPF creams is necessary with acid, combined preparations are not effective because the products with SPF are not stable with pH that is required for the stability and efficiency of α HA. That is the reason why creams with SPF have to be applied independently after the application of the acid. Because hydroxy acids increase susceptibility to sun damage, it is necessary to wear sunscreen during its use and for at least one week afterwards.

Antioxidants

Living in an oxygenated environment has required the evolution of effective cellular strategies to detect and detoxify metabolites of molecular oxygen known as reactive oxygen species. Today, there is a lot of appropriate and inappropriate production of oxidants in connection with the ability of the body to respond to oxidative stress against aging and prolonged life span.

There is increasing evidence that reactive oxygen species play a pivotal role in the process of aging. The skin as the outermost barrier of the body is exposed to various exogenous sources of oxidative stress. These are believed to be responsible for the extrinsic type of skin aging, photo-aging. It therefore seems reasonable to try to increase the levels of protective low molecular weight antioxidants through a diet rich in fruits and vegetables or by direct topical application. Indeed, various *in vitro* and animal studies have proved that low molecular weight antioxidants, especially vitamins C and E, ascorbate and tocopherol, as well as lipoic acid, exert protective effects against oxidative stress. However, controlled long-term studies on the efficacy of low molecular weight antioxidants in the prevention or treatment of skin aging in humans are still lacking.

To combat air pollution, many anti-aging cream products will include antioxidant vitamins. These vitamins are absorbed through the skin and fight the effects of free radicals. They create less harmful molecules or break the chain reaction caused by free radicals. It is known that excessive generation of free radicals (oxidative stress) leads to oxidative damage and the result is death of cells and tissues, and it underlies numerous skin diseases such as atopic dermatitis and psoriasis. During that process, hyaluronic acid becomes depolymerized and collagen oxidized, which stimulates photosensitivity and premature aging. The modern way of life certainly contributes to it.

The most common substances as an integral part of local preparations with antioxidant activity are vitamins A, C and E, selenium and zinc, carotenoids, i.e. beta-carotene, lycopene, lutein, astaxanthin, coenzyme Q, polyphenols, ginkgo biloba, silymarin, glutathione, L-cysteine, L-carnitine, melatonin hormone, kojic acid, pycnogenol, and allium sativum. In most preparations, these substances are unstable and cannot

penetrate the skin. The main role of these products is skin moisturizing, stimulation of new cell synthesis, and some of them have a whitening effect, improve circulation and stimulate collagen production.

One of the most largely used skin care ingredients is vitamin C. Skin care companies claim that vitamin C has powerful anti-aging properties for the skin. The scientific claims regarding wrinkle reducing and skin rejuvenation are impressive, but there is some controversy about the quality of the vitamin C being used, making some vitamin C products useless against aging. Vitamin C has the potential to help skin in two ways. One is the synthesis of collagen, which is a key structural protein of the skin. Adding vitamin C to skin cells significantly increases the synthesis of collagen. Second, vitamin C as an antioxidant reduces skin damage from pollution, sun, and other free radicals. The challenge is to deliver vitamin C properly into the skin cells. Vitamin C is unstable and unless it is in a dry form, its effects cannot be guaranteed. The presence of air or other oxidizing agents compromises its effectiveness. The challenge of making vitamin C beneficial to the skin is that it has to be prepared in a highly concentrated form. Even if it is concentrated, prepared properly free of oxidization, if not stored properly, the formulation will be ruined. To get maximum anti-aging results of vitamin C, it should be obtained exclusively from a highly trusted source. A yellowish tint is a sure sign that the formula has been oxidized.

Vitamin E acts as protector from UV rays, accelerates the healing process, and works synergistically with vitamin C, Co Q10, and selenium⁸⁻¹¹.

As an anti-aging product, collagen creams are practically useless. Collagen protein is necessary in order to maintain skin firmness, elasticity, and tone. Collagen loss also leads to the formation of wrinkles and fine lines. However, applying collagen topically with even the most expensive collagen cream will not make a difference. Only collagen that is naturally produced by the skin is effective in reducing the signs of aging. Collagen creams contain collagen from bovine and avian sources. The collagen molecules are too large to be absorbed by the skin. Even the 'bio-available' collagen forms are not effective. The skin care product that actually stimulates natural collagen production in the skin can be effective.

Coenzyme Q10 is a vitamin-like substance with antioxidant action. As an integral part of all cells, it participates in the creation of adenosine phosphate (ATP) and energy to stimulate the energy function of skin cells. The CoQ10 production decreases with aging. The question is how much of CoQ10 can be absorbed into the skin through local preparations, if talking about its impact on wrinkle reduction.

Polyphenols are flavonoids, which regenerate skin and mucous membranes, and resveratrol, which contains catechine and reduces DNA damage caused by the harmful influence of UV rays, suppresses tumor growth and has immunosuppressant action.

The skin is a target organ for various hormones, and **sex steroids** have a profound influence on the aging process¹³. A decrease in sex steroids thus induces impairment of those skin functions that are under hormonal control. Keratinocytes, Langerhans' cells, melanocytes, sebaceous glands, collagen content and the synthesis of hyaluronic acid, for example, are under hormonal influence. Topical application of estrogens has a positive effect on skin aging parameters. As an alternative treatment, phytohormones with structural similarity to 17 β -estradiol explaining their estrogen-like effects may be administered. However, isoflavonoids exhibit an inferior biological potency to synthetic estrogens. Although a large number of publications have documented the effects of sex hormones on the aging process, it is obvious that hormone replacement therapy should not be administered as an independent treatment for skin aging because of its large range of systemic side effects.

Melatonin is a hormone known as hormone of darkness and sleep. This hormone is synthesized in pineal gland from the amino acid tryptophan. The synthesis of this hormone is interrupted by light and its production decreases with age. Its effect has been shown in the process of wound healing; it reduces erythema when applied to the skin after sun exposure, and has a role in the protection against UV radiation. A group of scientists from Palermo have developed a noninvasive method based on the association of vitamin C 15% serum, melatonin as a human hormone, and resveratrol. When used together, they reduce morphological and histological skin disorders. The method was tested in more than 100 patients with photoaging, wrinkles,

melasma, solar keratosis and other signs of aging, with very encouraging results. They use vitamin C (serum of L-ascorbic acid, 15%) stabilized with *Vitis Vinifera*, melatonin and resveratrol. The passage of the active ingredients through the skin is facilitated by low pH to increase the concentration of L-ascorbic acid. In study group, treatment was specifically chosen according to each individual skin problem. To achieve the best skin penetration of active ingredients, a basic protocol was set up to reduce skin pH, thus enhancing the absorption of the preparations.

The basic protocol included:

- 1) skin purifying cleanser for skin acidification to pH 3.5,
- 2) purifying toner for in-depth skin cleaning, reducing pH to 3.2,
- 3) vitamin C 15% LAA serum where ascorbic acid is stabilized with *Vitis Vinifera*, and
- 4) restructuring cream with melatonin present at a concentration of 0.5% and stabilized with resveratrol, *Vitis Vinifera* and peptides in a multivitamin complex.

In solar keratosis and hyperpigmentation, exfoliating cream together with vitamin A cream may be added.

Important biological functions of the complex ingredients for the skin and all cellular tissues have been reported:

- antioxidant action opposing 'oxygen free radicals' stimulated by the same cellular metabolism and by smoke, UV light exposure and other pollutant attacks, as well as cellular aging;
- anti-inflammatory action by strengthening of the immune system;
- reinforcing cellular response to extra- and intracellular nociceptive stimuli; and
- noticeable action in the immune response modulation; intervening with an important antioxidant action in the body zones where an alteration of the cellular growth of tumor origin, dysplastic alteration and/or tissue atrophy is present.

The skin pH controlled system is promising in facilitating the skin health restoration and rejuvenation with high tolerance. Further clinical applications are still under study^{14,15}.

Retinaldehyde is the central molecule in the metabolism of natural retinoids with strong activity as pure retinoic acid, but without systemic effects, skin irritation or phototoxic reaction. Applied in local preparations, it has strong effects on photaging skin, which implies reduction of wrinkles and pigmentation, increased skin elasticity, improved skin tone and shine. In the 1980s, this product was used in the treatment of acne vulgaris. Then, in patients having applied the cream for a long time their skin was observed to have become smooth and pink (rosy glow), with uniform pigmentation and significantly reduced wrinkles. Since 1986, there have been numerous studies demonstrating that tretinoin (retinoic acid) is a locally safe and effective medicine for photodamaged skin.

Tretinoin is a form of vitamin A (trans retinoic acid) and today the best tested retinoid to reverse photoaging skin changes. The mechanism of action is unknown, but it may bind to a specific receptor that alerts the gene expression of the cell. Tretinoin is an integral part of numerous commercial products to slow the aging process of the skin and proven to stimulate collagen production. Therapy is most successful when a liberal amount of tretinoin 0.1% cream is applied to the skin daily. Tretinoin cream has an excellent safety record and local cutaneous irritation, pruritus, erythema and hypervitaminosis A are the only and rare side effects. The recommendation is to apply it overnight for one year and then every 3-4 days continuously in combination with moisturizing creams and SPF creams during the day to decrease sensitivity to UV radiation. In this period, mitotic activity of keratinocytes is accelerated (turnover) in the epidermis. Stratum corneum, which has previously become loose, turns compact, with increased deposition of mucinous substances (glycosaminoglycan, hyaluronic acid) that bind to a large amount of water. Also, atypical cells and microscopic actinic keratosis are eliminated, while total thickness of the epidermis is increased to the account of stratum granulosum. So, tretinoin affects the process of terminal differentiation of the epidermis, which leads to normalization of skin renewal. Initially it was believed that wrinkle smoothing occurs due to thickening of the epidermis, but histologic studies have proved that the epidermis returns to the initial state after several-week use of tretinoin, and the appearance of the skin continues improving

to reach maximum after 3 to 4 months. The main changes responsible for better skin appearance occur in the dermis. In papillary dermis, there is deposition of new collagen (type VII, a major component of anchored fibers), called reparation or reconstruction zone proved by immunohistochemical methods, procollagen markers. Collagen type I is multiplied (types I and III are most represented in the dermis). Formation of new blood vessels making the skin look pink ('rosy glow') has also been demonstrated^{16,17}. (Fig. 1)

Side Effects

Local anti-aging therapy could be a trigger for skin cancer due to permanent skin irritation and peeling of the protective surface layer of the skin. According to some studies, alpha hydroxy acids are the most dangerous products on the market. Hydroquinone, which was one of main bleaching topical agents, today is a forbidden substance in Europe and Asia. Despite its efficacy in treating hyperpigmentation, it has been demonstrated to be extremely toxic, and if penetrating below the outer layer into the dermis, it causes collagen fibers to thicken, leading to the possibly irreversible damage to the connective tissue in skin cartilage and premature aging. Furthermore, recent literature shows that it has carcinogenic effects.

Adverse side effects of hydroquinone include depigmentation or hyperpigmentation of the skin. It also causes ochronosis, a medical condition where the skin becomes dark and thick. A chronic user of hydroquinone may also start developing neurologic problems instantly.

Some products may cause skin irritation, rashes, burning, redness or scars. Also, side effects of anti-wrinkle creams include allergic reactions and pore clogging on the skin. As for allergic reactions, it is good to remember that the anti-aging industry is one of the areas of cosmetics that pushes the envelope in finding new compounds to prevent or reverse skin aging. Acne cosmetica is not an allergic reaction, but is caused by inclusion of comedogenic substances (sodium lauryl sulfate, isopropyl isostearate, isopropyl myristate, butyl stearate, hexadecyl alcohol, lauryl alcohol, oleic acid, lanolin and cocoa butter) that can be found in many cosmetic products¹⁸.

We have to be very careful with anti-aging products as well. Many of the products out there do not

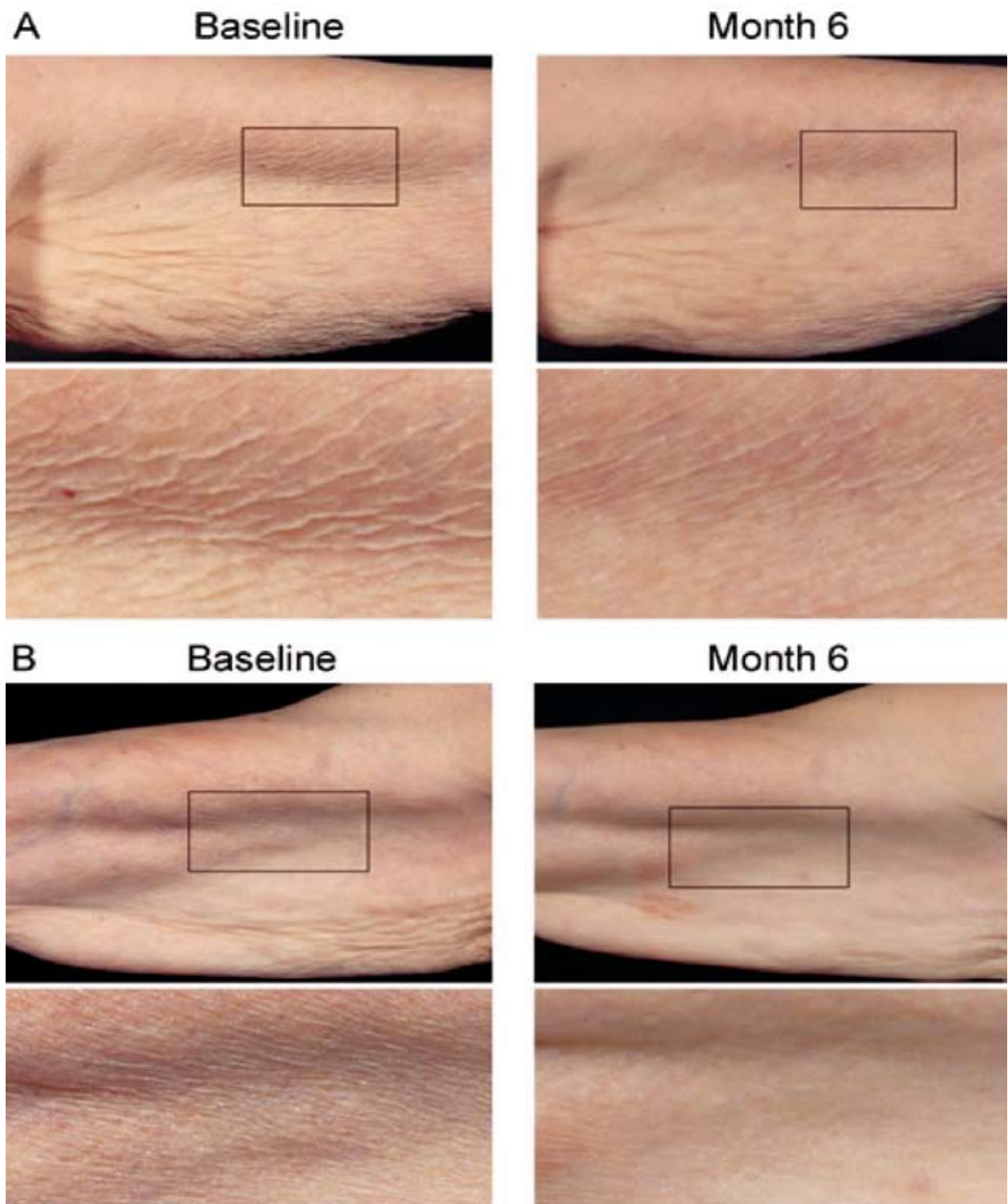


Fig. 1. Tretinoin cream – effects on ageing skin

lead to any favorable results. Some creams may be popular but they are ineffective because they cannot be absorbed properly by the skin.

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Sažetak

LOKALNA TERAPIJA KAO OSNOVNA PREVENCIJA PROTIV STARENJA

N. Delalle-Lozica

Koža je najveći organ našega tijela te su sve promjene povezane sa starenjem na njoj vrlo brzo uočljive. Unutarnje (kronološko) starenje obilježava atrofija kože i gubitak elasticiteta te usporena metabolička aktivnost. Pridodamo li i vanjske štetne učinke, prije svega izlaganje ultravioletnom zračenju (fotostarenje), proces rezultira hipertrofijom s posljedičnim zadebljanjem epidermisa i pojačanom melanogenezom. Još značajnije promjene se događaju u dermisu: masivna elastoza (taloženje abnormalnih elastičnih vlakana), degeneracija kolagena, poremećaj mikrovaskularizacije. Redovitom upotrebom lokalnih pripravaka sa zaštitnim faktorom protiv UV zraka moguće je ispraviti nastala oštećenja i svakako zaštititi kožu od daljnjih oštećenja. Dokazano je da lokalna terapija protiv starenja može u velikoj mjeri promijeniti i kliničku i histološku sliku promjena uzrokovanih izloženosti suncu i kronološkim starenjem. Do promjena u histološkoj slici u epidermisu i dermisu dolazi 12 mjeseci nakon primjene lokalnih pripravaka (rekonstitucija epitelnih nastavaka, reparacija ultrastrukturnih oštećenja na keratinocitima, distribucija melanocita i pigmenta, odlaganje novog kolagena u papilarnom dermisu i značajno poboljšanje vaskularizacije). Normalizira se hiperkeratinizacija, povećava debljina epidermisa i količina glikozaminoglikana u dermisu. Dakle, brojne neželjene promjene mogu se spriječiti, a nastale promjene se mogu ublažiti primjenom lokalne terapije.

Ključne riječi: *starenje kože, fotostarenje, lokalna terapija, hijaluronska kiselina, UV zrake, bore, pigmentacije*