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Aging – what's new?

Starzenie – co nowego?

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Słowa kluczowe

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S u m m a r y

Skin aging is a natural process, which consists in reducing the biological activity of body's cells, slowing down regenerative processes and loss of adaptability. The decisive role is played by genetic factors and associated with them external factors, such as: UV radiation, environmental pollution, smoking, improper care and internal factors connected with hormonal regulation disorders, poor nutrition and vitamin deficiencies. We can distinguish endogenous and exogenous skin aging.

Some of these changes can be eliminated and prevented, but unfortunately together with the passage of time, there are distinctive symptoms of aging, such as: an excess of the skin on upper eyelids, "crow's feet" in side corners of the eye, clearly marked nasolabial folds, transverse forehead creases and frown lines, prolapse of the nose's tip, less clearly marked line of the mandible, neck wrinkles, visible horizontal bands of platysma, prolapse of side parts of cheeks, thinning of the skin and subcutaneous tissue atrophy contributing to clear wrinkles and skin laxity and much more. Substances, which effectively prevent aging of the skin, include: vitamin A and its derivatives, UVA and UVB protective filters, hydroxyl acids (especially glycolic acid, because of its smallest molecule), antioxidants, hormone-substances and hyaluronic acid. Non-invasive (non-surgical) rejuvenating programs include: superficial chemical peelings, local retinoids, botulinum toxin, filling, volumetry, threads, mesotherapy, rollcit, microdermabrasion, lasers and much more.

S t r e s z c z e n i e

Starzenie się skóry jest naturalnym procesem polegającym na zmniejszeniu biologicznej aktywności komórek organizmu, spowolnieniu procesów regeneracyjnych i utracie zdolności adaptacyjnych ustroju. Decydującą rolę odgrywają tu czynniki genetyczne oraz współdziałające z nimi czynniki zewnętrzne, takie jak: promieniowanie UV, skażenie środowiska, palenie papierosów, niewłaściwa pielęgnacja i czynniki wewnętrzne, związane z zaburzeniami regulacji hormonalnej, nieprawidłowym odżywianiem i niedoborami witamin. Starzenie się skóry możemy podzielić na: wewnątrz- i zewnątrzpochodne.

Część z tych zmian można wyeliminować, części zapobiegać, ale niestety wraz z upływem czasu pojawiają się charakterystyczne oznaki starzenia, takie jak: nadmiar skóry powiek górnych, „kurze łapki” w bocznych kątach oka, wyraźnie zaznaczone fałdy nosowo-wargowe, poprzeczne zmarszczki czoła i zmarszczki marsowe, opadanie końca nosa; mniej wyraźnie zaznaczona linia żuchwy; zmarszczki szyi; widoczne poziome pasma mięśnia szerokiego szyi; opadanie bocznych części policzków.

Do substancji, które skutecznie przeciwdziałają procesowi starzenia się skóry, zaliczamy: witaminę A i jej pochodne, filtry ochronne UVA i UVB, hydroksykwas (w szczególności kwas glikolowy z uwagi na jego najmniejszą cząsteczkę), przeciwutleniające (antyoksydanty), substancje hormonopodobne, a także kwas hialuronowy. Nieinwazyjne (niechirurgiczne) programy odmładzające obejmują m.in.: powierzchniowe peelingi chemiczne, retinoidy miejscowe, toksynę botulinową, wypełnienia, wolumetrię, nici, mezoterapię, Roll-Cit, mikrodermabrazję, laseroterapię i wiele innych.

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INTRODUCTION

Skin aging is a natural process, which consists in reducing the biological activity of body's cells, slowing down regenerative processes and loss of adaptability.

The decisive role is played by genetic factors and associated with them external factors, such as: UV radiation, environmental pollution, smoking, improper care and internal factors connected with hormonal regula-

tion disorders, poor nutrition and vitamin deficiencies. We can distinguish endogenous and exogenous skin aging (1-3).

AGING IN THE AREA OF EPIDERMIS

Around living layers of the epidermis, we can observe an atrophy, which is caused by a decrease in the ability of proliferation of keratinocytes. Stratum corneum is more and more thick. The "turnover" can be prolonged even twice. Simultaneously, the number of melanocytes, which group themselves and create lentigines or disappear from certain places causing colored spots, decreases. The number of Langerhans cells is reduced by 50%. There is also a decrease in the secretion of sebum what dries the skin. It contributes to changes of the hydro-lipid composition, and consequently to change the pH of the skin. It becomes more acid, and this means that the epidermis is less resistant to adverse effects of external environment and microorganisms. Moreover, the decrease in sebum secretion causes the enlargement of glands, which favors the formation of sebaceous adenoma. The sensitivity to exogenous substances, i.e. soaps, detergents and UV radiation, increases. It causes the reduction of the skin's ability to slow down TEWL. Synthesis of vitamin D₃ is also reduced (1, 4, 5).

AGING IN THE AREA OF DERMAL-EPIDERMAL JUNCTION

The dermal-epidermal junction flattens. Adhesion of the skin to dermis is also reduced (1, 4, 5).

AGING OF THE SKIN WITHIN THE DERMIS

Within the dermis, there is a decrease in the number and size of fibroblasts. Consumption of oxygen decreases and there is a reduction of intracellular ATP. This causes deterioration in the ability of protein synthesis with a significant reduction in the ability of passage into interior of cells. It causes the reduction in the number of macrophages, and the loss of hyaluronic acid and dermatan sulfate. Water-binding capacity is weakened by the proteoglycan gel.

Elastin fibers disappear in the papillary layer of the skin, but they become hypertrophied in a reticular layer what leads to the formation of senile elastosis. There is a reduction in the synthesis of collagen and proteoglycans and to impair of angiogenesis, that is, the formation of new blood vessels what results in the formation of wrinkles and furrows, decreased flexibility and increased sensitivity of the skin (1, 6).

AGING OF THE SKIN APPENDAGES

There is a decrease in sweat glands what reduces the sweat secretion. Nails, just like the skin, are subject to aging. Their recovery process slows down, the plate becomes thickened, there are longitudinal furrows, a nail becomes more brittle. The deterioration of the nail's condition is affected by many factors, among other, drying chemical agents, radiation, etc. (1, 7).

Endogenous factors affect the endogenous skin aging. Aging is a genetically determined process, which causes a decrease of skin's flexibility. It becomes dry and thinner, but remains smooth. During this process, we can observe atrophic lesions, i.e. thinning of the epidermis, flaccidity, mimic wrinkles. There are two theories that explain changes in cells, tissues and organs of an aging body. The first is so-called programming theory, which says that so-called gerontogenes are responsible for aging. On the other hand, disorders of cell renewal are responsible for the endogenous aging. Somatic cells have a limited ability to divide. This is so-called Hayflick number or cellular aging. It has been proved that the combination of senescent cells with young cells evokes in these young cells degenerative symptoms. This means that gerontogenes work dominantly. Cell regeneration disorder occurs by the inhibition of cell division, influence of genes on the connective tissue metabolism, e.g. degradation of collagen, apoptosis disorders. The second theory is a "stochastic" theory, which assumes that the aging of cells is associated with biochemical abnormalities, causing their dysfunction (1, 7).

The most important biochemical disorders include:

- excessive formation of oxygen radicals, which damage proteins and DNA,
- amino-acid racemization,
- non-enzymatic glycosylation.

As a result of these molecular and cellular disorders, there are changes in the function of tissues and organs, including the skin. It leads to abnormal response to external stimuli, epidermal barrier dysfunction, as well as disorders of immunological reactions and production of sweat and sebum. There is a decrease of mechanical protection of the skin, reduction in the production of vitamin D₃, as well as the thermoregulation disorder. One of the endogenous factors affecting the skin aging process is hormones. The fact that estrogens and androgens deficiency results in degradation of collagen, dryness, loss of elasticity, loss of epidermis and formation of wrinkles was documented (7-10).

Theories of the endogenous skin aging:

1. Theory of biochemical disturbances in the area of aging skin.

It is assumed that the aging process is connected with a damage of its function due to excess production of free oxygen radicals, which damage proteins and DNA of cells. During the excessive accumulation, an oxidative stress occurs. With age, there is also the racemization process, i.e. changes of D-amino acids form to L-amino acids resulting in changes in the composition of proteins. There is also non-enzymatic glycosylation, which leads to an incorrect cross-linking of collagen fibers and other proteins and causes a reduction in the barrier function of the skin (7).

2. Theory of a limited number of cell divisions – so-called Hayflick theory.

It assumes that the ability of cells to divide is limited and decreases with age. After exceeding the number

of cell divisions programmed in the genetic material, this cell dies. There is also a decrease in the activity of telomerase, which is an enzyme responsible for replication of telomeres that during each division are shortened. As a result of this process, the transcription and apoptosis process are precluded, which means the death of particular cell (7, 8).

3. Gene theory.

It assumes that the longest duration of life is a genetically determined characteristic. According to this theory, aging does not depend solely on external factors. Generic material of cells include genes that are responsible for the speed of aging (1, 7).

MENOPAUSE AND THE EFFECTS OF ESTROGENS ON THE PROCESS OF SKIN AGING

Menopause is an absence of menstruation sustained for over a year caused by the ovarian failure. The lack of estrogens effects on the metabolism of skin cells leading to changes in a content of collagen and a decrease in skin flexibility, as well as a decrease in the synthesis of hyaluronic acid and glycosaminoglycan concentration. The effect of this situation is a reduction in hydration, dry skin and a drop of skin tension.

During the menopause, there is a significant influence of estrogens on the skin's condition. Along with the decrease in their level, there are changes mainly in the form of loss of elasticity, thinning and skin's density loss (11).

SOMATOPAUSE

With increasing age, there is also a decline of growth hormone secretion and it is connected with symptoms of aging. The action of this hormone can be easily observed in people, who have the growth hormone deficiency. The skin of these persons is dry, flaccid and thin, due to a reduction of water and collagen in its content. There is also a reduction in the sweat secretion by sweat glands, which have growth hormone receptors. It contributes to a disorder of thermoregulation and degrading the physical capacity. The skin becomes cool especially in distal parts of limbs. Moreover, growth hormone deficiency causes reduction in lean body mass, i.e. bone and muscle atrophy (11).

IMPACT OF FREE RADICALS

Free radicals (reactive forms of the oxygen) are produced in our body during metabolic processes, i.e. digestion, blood circulation, energy production. These are molecules with an unpaired electron. Each molecule tends to have on its orbit a pair of electrons. In order to obtain this pair, free radicals collect the electron from cell membranes what initiates a chain reaction. There are more and more of free electrons, which have the potential to damage cells. Damage of cell nucleus's DNA causes disorders of DNA translation what weakens the ability of cells to self-repair and regeneration and increases the aging process (8, 12).

EXOGENOUS FACTORS AFFECTING THE SKIN AGING PROCESS

Factors that accelerate the skin aging process are:

- UV radiation,
- cigarette smoking,
- pollution of the external environment.

Ultraviolet radiation is a primary factor responsible for the formation of changes occurring in the skin with age within the area exposed to light. Changes occurring within the facial skin are dependent on environmental factors in 80%. Biological effects, triggered in the skin, depend on the length of radiation, and thus are associated in a greater or lesser extent with the specific UV spectrum. Initially, it was believed that the main role in photo-aging of the skin is played by UVB radiation. Nowadays, it is known that both UVA and UVB radiations induce a number of degenerative changes in the skin, acting like immunosuppressants and have carcinogenic properties (13).

Radiation with a shorter wavelength (UVB) is mainly absorbed in the skin and acts on the contained therein keratinocytes and Langerhans cells, while the longer radiation (UVA) penetrates deeper areas, so it also influences within the dermis on fibroblasts, dendritic cells, endothelial cells of vessels and inflammatory cells of infiltration (lymphocytes, monocytes, granulocytes). UVA exerts its action in the skin in the indirect way through induction of free radicals, especially singlet oxygen, which can then cause among other: lipid peroxidation, activation of transcription factors, increase in the metalloproteinases' expression and damage of single strands of a cellular DNA and DNA of mitochondria. Although, UVB also has the ability to induce free radicals, its main mechanism of action consists in the direct damaging of cell's DNA. Under the influence of UVB, characteristic mutations in the DNA are produced: C → T, CC → TT. Due to increased exposure to natural UV radiation (the sun) and the excessive use of artificial sources of UV radiation (solariums), more and more often we meet with photo-aging and precancerous and cancerous changes.

Even small daily doses of UVA cause thickening of the stratum corneum and the whole epidermis, as well as the formation of cellular infiltration under the epidermis. This skin over-exposed to ultraviolet radiation has a dry, earthy appearance with small wrinkles and numerous thick furrows. The facial skin often has an image resembling popular degeneration accompanied with multiple horny cysts and open blackheads (Favre-Rachouhot disease). Other changes are numerous telangiectasia and uneven pigmentation manifested in the form of freckles, lentigines on the face and spot discolorations on the skin of trunk and limbs (*hypomelanosis guttata*). The epidermis may be subject to atrophy or conversely, may be exceeded in relation to the skin protected against radiation. Keratinocytes often ripen asynchronously. Moreover, we can observe atypical cells in the histological image. Melanocytes are unevenly distributed along the basal layer and their

number increases. There is a clear decrease in the number of Langerhans cells (13, 14).

UVA radiation clearly impacts on the connective tissue stroma, induces metalloproteinase causing matrix proteolysis and degradation of collagen fibers. Chronic solar radiation leads to degeneration of connective tissue stroma. This phenomenon is known as the solar elastosis and involves deposition of abnormal and amorphous material at the border of papillary and reticular layer of the skin. Furthermore, in contrast to the chronologically aged skin with a reduced number of cells, in the skin damaged by solar radiation, we can observe a large number of infiltration cells under the epidermis, mainly lymphocytes (so-called dermatoheliosis).

Collagen and elastin fibers are subject to degenerative changes. Blood vessels become dilated and sinuous, there is a thickening of the intima, and petechiae are frequently founded. Immunological and regenerative abilities of the skin are weakened. Chronic activity of the UV radiation causes numerous benign lesions in the skin, such as seborrheic keratosis, pigmented lesions, as well as precancerous changes (actinic keratosis). Skin cancers occur more often than in the case of skin protected from excessive sun exposure (15, 16).

Clinical changes in solar aging of the skin:

- telangiectasia,
- petechiae,
- whiteheads,
- solar blackheads,
- overgrowth of sebaceous glands,
- small wrinkles,
- deep furrows,
- sponginess of the skin,
- irregularity and roughness of the surface,
- lentigines,
- uneven coloration of the skin “mottled pigmentation”,
- discoloration of the seborrheic keratosis,
- skin cancers: basal cell carcinoma and squamous-cell carcinoma.

Histological changes in the solar aging of the skin:

- thickening of the stratum corneum,
- thickening or atrophy of the epidermis,
- uneven ripening of keratinocytes,
- atypia of keratinocytes,
- sunburn cells,
- atypia of cell nuclei,
- thickening of a basement membrane,
- uneven distribution of melanocytes along the basement membrane,
- melanocytic hyperplasia,
- reduction of Langerhans cells,
- degeneration of elastic fibers,
- degeneration of collagen fibers,
- vasodilation,
- thickening of vessel walls,
- lymphocytic infiltrations under the epidermis (fig. 1-5) (16).



Fig. 1. Cornu cutaneum on the ear.

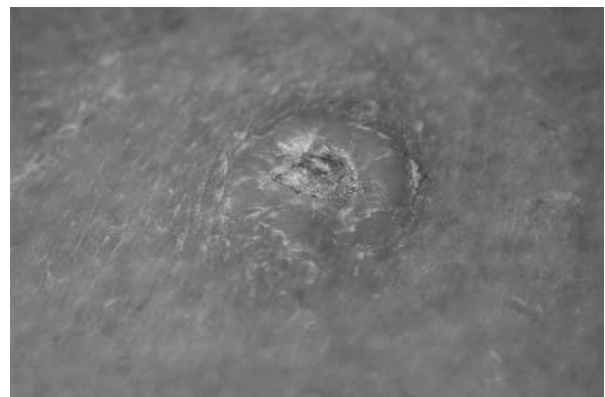


Fig. 2. Keratoacanthoma.



Fig. 3. Photoaging on the face.

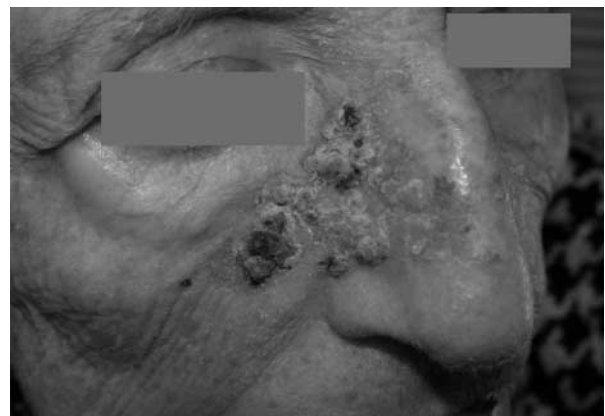


Fig. 4. Carcinoma spinocellulare on the nose.

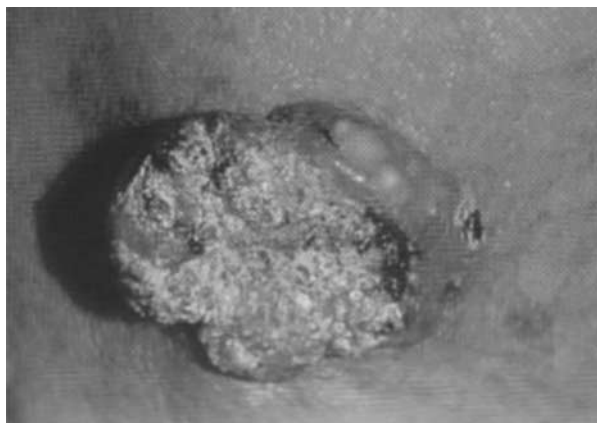


Fig. 5. Carcinoma spinocellulare on the cheek.

TREATMENT AND PREVENTION

In order to counteract skin aging, we should impact on all process in advance by the use of products with biologically active substances (cosmeceuticals). Some of these changes can be eliminated and prevented, but unfortunately together with the passage of time, there are distinctive symptoms of aging. Changes observed on the face in the next decades of life are:

1. 30 years – an excess of the skin on upper eyelids (ptosis of upper eyelids), “crow’s feet” in side corners of the eye.
2. 40 years – clearly marked nasolabial folds (furrows from the nose wing to the corner of mouth); transverse forehead creases and frown lines (vertical between eyebrows).
3. 50 years – prolapse of the nose’s tip, less clearly marked line of the mandible, neck wrinkles, visible horizontal bands of platysma, prolapse of side parts of cheeks.
4. 60-80 years – thinning of the skin and subcutaneous tissue atrophy contributing to clear wrinkles and skin laxity (1, 3).

The slowdown in these processes can be achieved by proper diet, exercises, appropriate skin care program, as well as coping with the stress of everyday life. Cosmetology created a new type of cosmetics for women – called the cosmeceuticals (creams-medicines). They counteract skin aging by its protection from the damaging effect of ultraviolet radiation and environmental pollutions. In order to maintain the skin in good condition, it should be systematically nursed and supplemented by appropriately selected treatments and biologically active ingredient, which at therapeutic concentrations reach the deepest layers of the epidermis acting regenerative, nourishing and protective. Thanks to these actions, the skin is hydrated, elastic and free of stains.

To select appropriate cosmetics/cosmeceuticals, we need to understand mechanisms of their action and look at the processes of skin aging. Without this knowledge, buying cosmetics is a kind of expensive hoppy and does not produce intended results. For example, the retinol needs to be activated only in the

epidermis for effective work, otherwise it is decayed when exposed to light and air. Moreover, the use of this ingredient in creams requires the use of advanced technologies.

Substances, which effectively prevent aging of the skin, include: vitamin A and its derivatives, UVA and UVB protective filters, hydroxyl acids (especially glycolic acid, because of its smallest molecule), antioxidants – encourage protective and regenerative mechanisms – mainly vitamin C at a concentration of at least 10%, krill oil, zinc, vitamin D, seabuckthorn berry oil, cocoa, red isoflavones, hormone-substances, e.g. soybean – so-called phytoestrogens, hyaluronic acid, which is a strongly water-binding in the connective tissue substance (it fills spaces between collagen fibers and maintains the elasticity of the skin), mucopolysaccharides, chondroitin sulfate – a substance conditioning the skin moisturizing (water-binding) (4, 8, 17).

Non-invasive (non-surgical) rejuvenating programs: Superficial chemical peelings:

- alpha-hydroxy acids and/or hydroquinones,
- beta-hydroxy acids,
- local retinoids (in the form of peeling or long-term therapy, tazarotene, adapalene).

Locally used retinoids influence on the structure and morphology of the skin through the induction of keratinocytes’ proliferation. They also inhibit the abnormal desquamation process of keratinocytes. The increase in the speed of cellular turnover causes the acceleration of the growth and differentiation of hair follicles what limits their occlusion. The increased proliferation mainly concerns basal and spinous layers of the epidermis. In the acne, we have to deal with hyperproliferation accompanied by overproduction of tonofilaments, desmosomes and keratin K6 and K16. Locally applied retinoids cause that the size of keratinocytes and their adhesion are reduced. Degradation of desmosomes causes thinning of the epidermal stratum corneum, decrease in the number of tonofilaments and growth of autolysis of keratinocytes (17, 18).

- Botulinum toxin,
- filling, volumetry, threads,
- mesotherapy, rollcit,
- micro-dermabrasion,
- non-ablative laser/IPL,
- CuBr laser (578 nm),
- pulsatile dye laser (585-600 nm),
- N-lite laser (585 nm),
- IPL (500-1100 nm),
- Nd: YAG (1064 nm),
- CoolTouch (1320 nm).

FILLERS

These are biological or artificial preparations served in the form of subcutaneous or intradermal injections in order to model contours of the face, filling of wrinkles and lip enlargement. Biological preparations include _patient’s own adipose tissue, hyaluronic acid, collagen.

Collagen preparation for the wrinkles smoothing were used for the first time in the 80s. The collagen is a protein of animal origin, hence the possibility of allergic reactions in about 10% of patients. Currently, collagen preparations are selected by synthetic substances, which do not cause allergies.

Autogenic fat graft is taken under local anesthesia from the abdomen, hips or buttocks by a special probe. Then, it is separated and clear fat cells are injected in a desired location (nasolabial folds, lips, frown lines etc.). The treatment must be repeated after the period from 4 weeks to 3 months, because a part of the fat is absorbed.

Hyaluronic acid is a polysaccharide having the same composition in all living organisms, hence its use does not require skin tests. Non-animal hyaluronic acid is most commonly used in the aesthetic medicine. It is a preparation in the form of a gel undergoing a natural biodegradation. It does not cause allergic reactions. The treatment is connected with inserting a preparation by a thin needle subcutaneously or intracutaneously in order to fill superficial or deep wrinkles of the skin. Its effect maintains from 6 to 12 months.

Artificial substances include among other Gore-Tex, polyacrylamide (Aquamid from the Contura Company). Aquamid have the form of a gel. It composes of 97.5% of water and 2.5% of polyacrylamide. It is biocompatible, does not cause allergic reactions. The effect obtained after the injection is final – this preparation is not absorbed and does not move. This treatment carried out with or without a local anesthesia is connected with the introduction of a gel by a thin needle in the subcutaneous layer of the skin. It is not appropriate for the correction of fine wrinkles. Administration of fillers can cause temporary swelling, redness, ache in the injection site (4, 9).

BOTULINUM TOXIN

It is the strongest known biological toxin, which is produced by an anaerobic rod of the *Clostridium botulinum*. There are seven antigenic serotypes (from A to G), of which only the neurotoxin type A is used in the medicine. In the aesthetic medicine, doses up to 200 units are used during the treatment. Action of the toxin consists in blocking of nerve impulses' conduc-

tion to muscle cells. It causes a temporary paralysis of a flaccid muscle, loosening of the skin located above this muscle, and as a result – smoothing of wrinkles. Indications in the aesthetic medicine are: wrinkles between eyebrows (frown lines), horizontal forehead creases, crow's feet, nasolabial folds, neck wrinkles. This is an ambulatory treatment carried out without the anesthesia. Insulin syringes 1 ml or 2.5 ml with the needle 30G are used for injections. There are subcutaneous or intramuscular injections. The effect is visible after two-three days after the treatment. The final effect is obtained after 10-14 days and lasts for 4-8 months (4, 7).

GENERAL RETINOIDS

Due to the effect of the DNA's transcription, retinoids modify the growth and differentiation of cells and have immunomodulatory and antitumor activity. Cellular mechanism of this phenomenon consists in the intracellular RAR-dependent isomerization of the isotretinoine. Moreover, retinoid inhibits the cell cycle in a manner independent from receptors and stimulates apoptosis of sebocytes without induction of a similar phenomenon in keratinocytes. It also blocks a synthesis of lipids through inhabiting of terminal differentiation, dependant on the RAR and RXR, as well as reduces the production of androgens by blocking the 3 alpha-hydroxysteroid activity of the retinol dehydrogenase. Anti-inflammatory activity mainly consists in inhabiting of neutrophils' migration by the reduction of MMP expression (collagenase, gelatinase, stromelysin, matrilysin). Derivatives of vitamin A also inhabit the transcription factor AP-1 by blocking extracellular matrix metalloproteinases that rebuild and decay the skin's matrix. Inhibition of the cellular matrix reconstruction, as well as the growth of mucopolysaccharides synthesis, collagen and fibronectin and inhibition of collagenase have a great importance in the reduction of scarring what is a unique feature of vitamin A's derivatives.

The following scheme is recommended in the treatment of skin aging: 2 times a year for 2-3 months 20 mg/day, eventually 5 mg/day in a continuous therapy, without a time limitation (6, 19).

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