Review article / Artykuł przeglądowy

Amanda Zielińska[1]
Anna Kamm[1,2] 0000-0002-4560-7645
Aleksandra Dąbrowska[1,2]

[1] *University of Health in Gdańsk, 80-335 Gdańsk, Pelplińska Street 7*
+48 58 769 08 10 *anna.kamm@kamelia.pl*
[2] *Department of Medical Chemistry, Medical University of Gdansk, 80-211 Gdańsk, Dębinki Street 1*
+48 58 349 10 70 *aleksandra89dabrowska@gmail.com*

Sposób cytowania / Cite Zielińska A, Kamm A, Dąbrowska A. Processes in the human skin responsible for its aging. *Aesth Cosmetol Med.* 2022;11(2):75-80. https://doi.org./10.52336/acm.2022.010

Processes in the human skin responsible for its aging

Procesy zachodzące w ludzkiej skórze odpowiadające za jej starzenie

ABSTRACT

With reaching biological maturity, the skin, like other organs, undergoes aging processes. They are mainly related to the regenerative processes of cells being slowed down, as well as their reduced biological activity. The above-mentioned molecular mechanisms at the cellular level have a significant impact on the phenotypic signs of skin aging. They cause typical morphological changes within each layer of the skin's integument. The characteristic appearance of aging skin is a clinical manifestation of changes within it.

The aim of the article is to present the molecular mechanisms that occur during the skin aging process.

There is no doubt that the aging phenomenon should be considered as the interaction of many factors of various etymology.

Keywords: skin aging, menopause, free radicals, antioxidants, photoaging skin of the skin, ultrafiolet radiation, glycation

STRESZCZENIE

Skóra wraz z osiągnięciem dojrzałości biologicznej, podobnie jak inne narządy, ulega procesom starzenia. Wiąże się to przede wszystkim ze spowolnieniem procesów regeneracyjnych komórek oraz ich zmniejszoną aktywnością biologiczną.

Mechanizmy molekularne zachodzące na poziomie komórkowym mają istotny wpływ na fenotypowe oznaki starzenia skóry. Pociągają one za sobą typowe zmiany morfologiczne w obrębie każdej z warstw powłoki skórnej. Charakterystyczny wygląd skóry starzejącej się stanowi manifestację kliniczną przemian zachodzących w jej obrębie.

Celem artykułu było przybliżenie niektórych mechanizmów molekularnych, które zachodzą podczas procesu starzenia się skóry.

Dokładne mechanizmy molekularne leżące u podstaw starzenia organizmu nie są jednoznacznie określone, przez co funkcjonuje wiele teorii tłumaczących ten złożony i wieloletni proces. Nie ulega wątpliwości, że zjawisko starzenia należy rozpatrywać jako wypadkową interakcji wielu czynników o zróżnicowanej etymologii.

Słowa kluczowe: starzenie skóry, menopauza, wolne rodniki, antyoksydanty, fotostarzenie, promieniowanie ultrafioletowe, glikacja

INTRODUCTION

The aging of the organism is a complex, complicated, and inevitably progressive process inherent in human physiology. The consequences of aging are changes both at the cellular and tissue levels, as well as aberrations affecting all organs and their systems. In the course of physiological skin aging, a gradual reduction in the number of keratinocytes is observed at the level of the epidermis. The phenomenon of atrophy affects all layers of the epithelium except the dead

stratum corneum, where no changes in the number of corneocytes are noted. The ubiquitous atrophy is also accompanied by a reduction in the division activity of the cells of the reproductive layer. The population of Langerhans cells and melanocytes is reduced. The connective tissue of the dermis is also overwhelmed by atrophy, where its cellular components and the components of the extracellular matrix are diminishing. The resting fibroblasts synthesize supporting collagen fibers and elastic fibers with less and less efficiency. Apart from the decreasing number of newly formed protein fibers, the already existing ones are subject to degeneration. In the histological description of individual skin layers presented above, the changes occur with age, mainly of a degenerative nature, except in areas of the skin exposed to ultraviolet UV radiation, in which the features of hyperplasia predominate. The accumulation of various types of damage translates into impaired functionality and biological activity of cells, as well as a reduction in their regenerative potential, which gradually loses their ability to renew. The exact molecular mechanisms underlying the aging of the organism are not clearly defined, which is why there are many theories explaining this complicated and long-term process [1-4].

SKIN STRUCTURE

The skin is a group of several types of tissues closely related to each other and performing synchronized activities. Importantly, the extent of the skin's surface and its location makes it the largest and most externally located human organ. As part of the common shell, it separates the interior of the body from the environment, allowing it to maintain its homeostasis.

There are three main layers within the skin:

- epidermis,
- dermis,
- subcutaneous tissue [1, 5, 6].

Each of the layers is diverse, which is related to the different types of tissues that make them up. The epidermis is built up of epithelial tissue, dermis, and subcutaneous tissue - connective tissues [1, 5].

The outermost, border layer of the skin is the epidermis, formed by the constantly renewing multilayer keratinizing planar epithelium. Keratinocytes lie directly in the basal membrane to which they are firmly bound by hemidesmosomes. The basal membrane is a cell-free structure, not divided into specific layers, composed mainly of proteins and glycoproteins - mainly type III, IV, VII collagen, and laminins. In addition, melanocytes, Merkel cells, and sometimes Langerhans cells are present. The presence of melanocytes guarantees the synthesis and storage of grains of the skin pigment - melanin. One melanocyte is assumed to provide mature melanin grains to approximately 30-40 keratinocytes, thereby forming an epidermal melanin unit. Langerhans cells belong to the population of dendritic cells, the key cell structures of the immune system. Thus, they participate in immune mechanisms, being responsible for the presentation of antigens to T lymphocytes [1, 2, 7].

The direct contact of the epidermis with the external environment makes it the first and most important barrier isolating the sensitive interior of the body against the influence of environmental aggressors [1-6].

The dermis is made up of connective tissue, the main mass of which, unlike the epidermis, is the extracellular matrix (ECM). The structure of the dermal matrix is based on two components - textured fibers and an essence devoid of any specific form. The latter is a mixture of inorganic substances, such as water and mineral salts, and organic substances: proteins, lipids, and carbohydrates. Among them, significant importance for the properties of the dermis is attributed to non-collagenic proteins, like fibronectin, laminin, and glycosaminoglycans (GAG), such as hyaluronic acid, which exhibits strong hygroscopic properties [1, 6, 8, 9].

A characteristic cell of the dermis is the fibroblast and its mature form - fibrocyte, responsible for the synthesis and degradation of collagen, elastin, and glycosaminoglycans [1, 2, 9].

There are three types of fibers: collagen, elastin, and mesh. They are primarily responsible for the mechanical properties of the skin, giving it the expected strength and elasticity. In terms of quantity, the majority of collagen fibers are 80% formed by type I collagen, they guarantee tissue resistance to damaging stimuli. In addition, together with glycosaminoglycans, they determine the degree of hydration of the dermis. It is worth mentioning that it is the connective tissue of the dermis that is one of the main water reservoirs for the entire body, it collects up to 20% of the water present in the body.

Turning to the properties of elastic fibers, they show the ability of stretching and then returning to their original length, which is the result of their irregular and non-parallel distribution. The main component of the above fibers is elastin.

The mesh fibers are actually also collagen fibers, but definitely thinner and mainly made of type III collagen. As all types of fibers collectively organize into a spatial network, they form a specific skin scaffold [1, 5, 6].

The basis of the subcutaneous tissue are adipocytes, arranged in larger clusters resembling lobules. Between the accumulated fat cells, there are partitions made of connective tissue, rich in nerves and blood vessels. At the same time, the hair follicles and secretory parts of the sweat glands penetrate the subcutaneous tissue [1, 2, 7].

In the histological description of individual skin layers presented above, changes occur due to endogenous and exogenous factors [4, 11, 12].

SKIN AGING

In the literature, the skin aging process is divided according to its cause:

- intrinsic aging induced by endogenous factors,
- exogenous aging induced by external factors.

Taking into account the above differentiation of the skin aging process, the following factors constitute its resultant, which together determine the complete image of mature skin [3, 10, 13].

Intrinsic aging - endogenous determinants of skin tissue aging

A reflection of the changes characteristic of the endogenous form of skin aging is the clinical picture of the skin not exposed to the destructive influence of UV radiation [4]. When analyzing the mechanisms governing the process of intrinsic aging of the skin, the following factors are attributed to the greatest contribution to their development: genetic conditions, the endogenous fraction of reactive oxygen species (ROS), and hormonal changes [5].

- Hayflick theory - telomere theory

As the most distal segments of chromosomes, telomeres shorten with each cell cycle. They consist of numerous repetitions of the characteristic sequence of deoxyribonucleic acid (DNA), thus protecting genes against damage during copying.

The reduction of telomeres, and thus the loss of the stability of the entire genome, is counteracted by telomerase - an enzyme of which expression decreases with age. The successive disappearance of telomerase, characterized by the ability to rebuild declining telomeres, contributes to disturbances in cell division while promoting the loss of vital information, which ultimately determines their death. Research highlights the role of omega-3 fatty acids in slowing down the process of telomere shortening. [7, 11, 12].

- Endogenous fraction of ROS

The primary source of endogenous reactive oxygen species are mitochondria - one of the most important organelles of all eukaryotic cells, including human skin. ROS generation is part of their physiology, strongly correlating with their function. As a result of the Krebs cycle occurring at the mitochondrial level, a portion of the energy is generated in the form of adenosine triphosphate (ATP) molecules, necessary for the proper functioning of cells [2, 13, 14].

In parallel to the oxidation of organic substrates, the reduction of molecular oxygen takes place, often incomplete to highly reactive intermediates such as ROS. About 4% of oxygen is converted into free radicals [1, 13].

It is worth noting that under the conditions of homeostasis, ROS play an important role as mediators and regulators of cellular processes, during signal transmission from cell to cell, inducing cell differentiation processes and apoptosis.

Undoubtedly, homeostasis between ROS and antioxidants plays a key role here. Prooxidative-antioxidant imbalance (oxidative stress), which increases with human biological maturity, is associated with mitochondrial dysfunction. At the same time, the level of physiologically present antioxidants in the body, such as superoxide dismutase, glutathione peroxidase, coenzyme Q10, or melatonin, is reduced [4, 11, 14].

Oxidative stress is associated with an increase in the amount of ROS, causing cell damage, including skin cells. Endogenous ROS, similarly to their extrinsic counterparts, interact with almost all components of skin cells, contributing to dysfunctional modification of cell membrane lipids, proteins, and cell DNA. The effects of these changes are discussed in the section on extrinsic aging [3, 7, 13].

- Menopausal aging - histological changes observed at the level of the epidermis, dermis, and subcutaneous tissue

The key influence on the functioning of the skin is exerted by sex steroid hormones - estrogens and androgens [1-4, 11, 14-16].

The consequence of menopause - a marked reduction in the amount of estrogen - intensifies the aging process of the skin. This is a consequence of the presence of estrogen receptors in almost all skin cells, additionally in peak amounts on the particularly exposed skin of the face [4, 11, 16].

There are two types of estrogen receptors: ERα and ERβ, the number of which depends not only on the body area but also on sex and age [4, 14, 16, 17].

Menopause and the resulting significant reduction in estrogen levels include changes in the skin in each of its three layers: epidermis, dermis, and subcutaneous tissue [7, 11].

The decrease of β-type estrogens in the menopausal period, and thus the lack of stimulation of estrogen-dependent receptors in the epidermis, increases the number of cytokines in cells, leading to disturbance of the epidermal cell proliferation process [4, 7, 11, 16].

The limited possibility of proliferation, accompanied by disturbances in the process of keratinocyte differentiation, translates into a reduction in the regenerative potential of the epidermis and, at the same time, worse healing. At the same time, the thin epithelium is tantamount to lowering the resistance of mature skin to external factors - mainly mechanical stimuli [2, 7].

Studies conducted with the use of estrogens have proven their influence on the level of the dermis, and the stimulation of fibroblasts for the synthesis of the components of the extracellular matrix. With a reduced level of estrogens, the efficiency of the above process is reduced, which results in a decrease in the amount of hyaluronic acid responsible for water binding. Chronic dryness often triggers itching and a feeling of tightening, emphasizes wrinkles and, in addition, promotes hypersensitivity reactions [1-7, 16, 18, 19].

The declining number of newly formed collagen support fibers and elastic elastin fibers also reflect the quenching activity of fibroblasts. The above process contributes to the accentuation of numerous fine lines and wrinkles, considered

to be the first signs of aging. It is worth noticing, however, that wrinkles caused by endogenous aging mechanisms are definitely shallower than those characterizing the skin exposed to exogenous factors [2, 11, 12, 20].

Estrogens also dilate blood vessels and affect angiogenesis. Due to the decreased level of estrogens, the nutrition and oxygenation of the tissues are reduced, thus making the skin pale [11, 16, 17].

Low estrogen levels during menopausal aging also contribute to the loss of adipose tissue, mainly on the temples, browbones, and cheeks. The consequence of this action is the change of the face oval [4, 7, 16, 17].

Importantly, estrogens are formed in the reaction pathway during androgen aromatization.

Natural steroid hormone (DHEA, Dehydroepiandrosterone), one of the adrenal androgens, also called the youth hormone, is metabolized into testosterone, estradiol, and estrone. Numerous studies have proven its beneficial effect on the condition of the skin, including the regulation of the work of sebaceous glands, hydration, elasticity, and elasticity [7, 18].

One of the most common problems in menopausal aging is skin lesions of uneven color, mainly on the skin of the face. These changes may occur at the level of the epidermis and the epidermal-cutaneous border during the abnormal grouping of melanocytes, which then increase their activity [3, 11, 14, 16].

The formation of hyperpigmentation is favored by fluctuations in hormones, especially estrogens and progesterone. The aforementioned hormones activate appropriate receptors located on melanocytes for the initiation of melanin synthesis. These discolorations are very often aggravated by ultraviolet radiation (UV) [1, 4, 14-18]. As demonstrated by the results of the research, niacinamide used at a concentration of 4% in the sunscreen preparation decreased the expression of DNA of methyltransferase 1 (DNMT1), the elevated level of which is observed in the case of melasma [21].

• Hormonal changes - growth hormone and melatonin

Growth hormone and melatonin are also worth mentioning when discussing hormone-dependent skin aging.

Growth hormone and insulin-like growth factor 1 (IGF-1) make up the somatopause process. As a result of this process, wound healing slows down, thermoregulation is impaired and connective tissue is more susceptible to glycation [7].

On the other hand, melatonin, which is most intensively secreted by the pineal gland with a decrease in light, and also during sleep, has a non-specific effect on the skin, acting as an antioxidant. The above aspect emphasizes the influence of the circadian rhythm on the biological processes taking place in cells. Melatonin levels decrease with age [7, 14]. Based on research reports, it is concluded that melatonin is 5 times more powerful antioxidant than glutathione. In a study conducted on an animal model, after the administration of melatonin, apart from the reduction of free radicals, a decrease in the expression of matrix metalloproteinases (MMP-1, Matrix metalloproteinase-1) as well as an increased expression of collagen VII in keratinocytes was observed [22].

• Glycation

The term glycation is associated with a multi-step process that occurs spontaneously without the involvement of enzymes, determining the formation of Advanced Glycation End--Product (AGE) products. It has a destructive effect on the structure of the skin's supporting proteins, especially collagen. The cause of this unfavorable process is an over-supply of simple sugars, mainly glucose, galactose, and fructose [7, 23].

During the non-enzymatic glycation reaction, simple sugar molecules can bind to DNA, lipids, amino acids, peptides, and proteins causing their modification. The process takes place as a result of an overstated supply of simple sugars. Another no less important cause of elevated blood glucose is cortisol - the stress hormone [21, 24].

Glucose, galactose, and fructose molecules most oftenly combine with proteins with a high number of free amine groups, such as lysine and arginine in their structure. There are three stages of the glycation reaction [25].

The fructose ketone group and the galactose or glucose aldehyde groups react with the amino group to form a Shiff base. If there is a decrease in the concentration of one of the above-mentioned sugars, the reaction is thus reversed. Otherwise, during the organism's increased exposure to sugar, we observe a slow rearrangement reaction resulting in the formation of an Amadori product with an active carbonyl group [22, 24].

This reaction is also reversible. However, if not inverted, it ultimately leads to the production of advanced irreversible glycation products. Then proteins, including collagen, undergo a series of Maillard reactions, i.e. oxidation, dehydration, fragmentation, and condensation with other amino groups. AGE products are brown, which is often manifested by yellowing of the skin [24, 26].

AGE products increase collagen cross-linking by creating cross-links. The formation of these bonds increases the stiffness of collagen fibers. The fibers become less susceptible to digestion by enzymes (proteases), as well as show reduced solubility and denaturability. These physical and chemical changes in collagen contribute to the aging process of the skin. Due to the increase in the amount of collagen, which is insoluble in aqueous solutions, its ability to retain water in the skin decreases. The result is a decrease in skin firmness and hydration [1, 19, 23].

Additionally, increasing the stiffness of collagen fibers lowers their tensile strength, and the fibers become brittle. In this way, their original support properties are abolished, which contributes in particular to the loss of elasticity observed in skin affected by aging [1-3, 6, 12]. In addition

to direct protein modifications, AGEs affect the function of whole cells through specific membrane receptors anchored on their surface. The binding of AGEs to receptors of advanced glycation reaction products (RAGE, *Receptor For Advanced Glycation End Products*) initiates cell signaling programs, including intracellular production of ROS and the activation of pro-inflammatory transcription factors, which triggers a cascade of reactions leading to the overexpression of genes encoding inflammation mediators [22- 25].

Extrinsic aging

Compared to other organs, the skin is more exposed to environmental factors, including solar radiation. In addition, air pollution, as well as tobacco smoke, are key exogenous factors. Due to the length and complexity of the topic, the most important determinant of extrinsic aging - ultraviolet radiation [1-3, 21] was discussed.

Destructive changes occurring in the skin under the influence of UV radiation are called photoaging. Importantly, it is estimated that this radiation is responsible for 80% of degenerative changes in the area of unprotected skin. The degenerative effect of UV radiation is related to the initiation of mechanisms responsible for mutagenesis, immunosuppression, and excessive production of ROS [14, 16, 21].

A series of abnormalities observed at individual skin levels are generated by the UVA band (wavelength 320-400 nm) and the UVB band (wavelength 290-320 nm).

It is worth noting that the biological effects caused by ultraviolet radiation are not noticeable only immediately after sun exposure. Some of them are distant and spread over time. UVA radiation, reaching the papillary and reticular layers of the dermis, destabilizes most of the cellular structures of the skin, as well as the intercellular matrix itself. On the other hand, UVB radiation covers the living layer of the epidermis, causing erythema, sunburn, and indirect pigmentation [2, 7, 27].

Both UVA and UVB radiation induce the formation of ROS, which are involved, inter alia, in lipid peroxidation. The mentioned reaction of lipids with ROS leads to modification of the physical properties of the cell membrane and, consequently, to its denaturation. Lipids, which are a component of the intercellular binder, are also oxidized, which contributes to the excessive escape of water from the epidermis, determining a decrease in its hydration. As a result, one of the representative clinical features of the senile skin phenotype is its chronic dryness with concomitant severe exfoliation [10, 16, 21].

The danger of overproduction of ROS is mainly due to their ability to interact with DNA molecules. Consequently, indirectly, UVA induces mutagenesis and tumorigenesis, similar to UVB. The link between carcinogenesis and photoaging determines the perception of any malignant changes as a representative symptom of mature skin. Considering the permeability of the UVA band, it is believed to play a major role in the pathomechanism of photoaging [16, 26, 28].

- Photoaging - histological changes observed at the level of the epidermis

The microscopic image of the exageed epidermis most reliably reflects the nature of the hypertrophic processes. Contrary to the physiological form of skin degeneration, it is characterized by a distinct thickening, especially noticeable at the level of the stratum corneum [5, 21, 29, 30].

The dryness of the thickened epidermis, which is felt together with the roughness, is the result of a drastic decrease in the quality of the hydrolipid coat and a decrease in the mucin content in the epithelium. Focusing on the transformation of skin appendages - the sebaceous glands are the most significant. Their clear hyperplasia is noted, with the accompanying permanent widening of their mouths, which gives the image of skin porosity [10, 26].

- Photoaging - histological changes observed at the level of the dermis

The interference of UVA rays destabilizes not only most of the dermal cell structures but also the intercellular matrix. Therefore, the process of photo-induced degeneration reaches the skin scaffold - cross-linked polymers of collagen and elastin. Activator protein 1 (AP-1) and matrix metalloproteinases (MMPs) are the main mediators of the degenerative pathways of extracellular matrix proteins, and in particular of type I and III procollagen. Physiologically, AP-1 acts as a nuclear transcription factor for MMPs belonging to the family of proteolytic enzymes that degrade dermal matrix components. AP-1 expression is enhanced by cytokines released by oxidatively damaged skin cells, which in turn affects the increased activity of metalloproteinases. Apart from the fragmentation of the existing support fibers by the mentioned MMPs, the process of neocolagenesis is disturbed in sun-damaged skin [21, 26, 29].

The role of vitamin C (ascorbic acid) in collagen biosynthesis, which is involved in the formation of collagen cross-links in the process of proline and lysine hydroxylation, should be emphasized. At the same time, ascorbic acid, which has antioxidant properties, directly stimulates collagen synthesis, activating its transcription and stabilizing procollagen mRNA. As evidenced by in vitro studies on fibroblasts, as well as numerous clinical trials with the use of cosmetic preparations with vitamin C, with a double-blind test [31].

- Photoaging - elastose

One of the most representative symptoms of photoaging skin (never identified in the obscured skin) is the synthesis of abnormal elastin, devoid of its original function. The clinical manifestation of solar elastosis is changed like hyperplasia in the form of lumps and nodules palpable under the skin. At particularly advanced stages, the famous symptom called "farmer's neck" may appear, manifested by the presence of specific diamond-shaped patterns on the skin of the nape of the neck, chronically exposed to sunlight [7, 21, 28].

The specificity of the morphological changes that arise is assumed to be the foundation for identifying the form of skin aging. The features of atrophy dominate in the histological picture of end staging. On the other hand, hypertrophic changes occurring predominantly remain reserved for the skin affected by extrinsic aging [3, 11, 28].

Although the skin matured in the course of individual types of aging is characterized by certain morphological differences, eventually these changes overlap [2, 3].

SUMMARY

The skin aging process is impossible to stop, but the knowledge of the mechanisms taking place in the body allows for the early implementation of preventive measures and slowing down the dynamics of this complex process.

The involvement of reactive oxygen species in the etiopathogenesis of aging, both external and internal, justify supplying the body with antioxidants neutralizing ROS. Also, a diet focused on the elimination of sugars slows down the dynamics of AGEs accumulation, delaying the appearance of the first signs of aging.

In turn, leading an unhygienic lifestyle can also cause premature hormonal aging. It should also be emphasized the importance of photoprotection, which allows for minimizing the effects of skin aging, depending on exposure to UV radiation.

To prevent premature skin aging, preventive measures to minimize endogenous and exogenous factors are necessary, based on an appropriate lifestyle, physical activity, regular hormone tests, and skincare. It seems ideal to combine proper home care with regular anti-aging treatments.

REFERENCES / LITERATURA

1. Błaszczyk M. *Histologia dla kosmetologów*. Nysa: Oficyna Wydawnicza PWSZ; 2013.
2. Kołodziejczak A. *Kosmetologia tom 1*. Warszawa: Wyd. PZWL; 2019.
3. Kozieł-Resich L, Niemyska K. Rodzaje oraz przyczyny starzenia się skóry. *Kosmetologia Estetyczna*. 2020;9(1):17-22.
4. Lizak A, Załęska I, Matuła A, et al. Molekularne mechanizmy starzenia się skóry w okresie menopauzy. *Kosmetologia Estetyczna*. 2019;8(2):229-235.
5. Sawicki W, Malejczyk J. *Histologia*. Warszawa: Wyd. PZWL; 2019.
6. Draelos ZD, Pugliese PT. *Fizjologia skóry – teoria i praktyka*. Wrocław: MedPharm; 2014.
7. Trommer H, Neubert RHH. Overcoming the Stratum Corneum: The Modulation of Skin Penetration. *Skin Pharmacol Physiol*. 2006;19(2):106-121.
8. Arda O, Göksügür N, Tüzün Y. Basic histological structure and functions of facial skin. *Clin Dermatol*. 2014;32(1):3-13.
9. Verdier-Sévrain S, Bonté F. Skin hydration: a review on its molecular mechanisms. *J Cosmet Dermatol*. 2007;6(2):75-82.
10. Zegarska B, Woźniak M. Przyczyny wewnątrzpochodnego starzenia się skóry. *Gerontol Pol*. 2006;14(4):153-139.
11. Olek-Hrab K, Hawrylak A. Wybrane zagadnienia z zakresu starzenia się skóry. *Postępy Dermatologii i Alergo*. 2008;5(25):226-234.
12. Wydro D. Starzenie się skóry – aspekty genetyczne, fizjologiczne i patomorfologiczne. *Acad Aesthetic Anti-Aging Med*. 2009;2:52-62.
13. Sies H. Oxidative eustress: On constant alert for redox homeostasiss. *Redox Biology*. 2021;41:101867.
14. Sarniak A, Lipińska J, Tytman K, Lipińska S. Endogenne mechanizmy powstawania reaktywnych form tlenu (ROS). *Postępy Hig Med Dośw*. 2016;70:1150-1165.
15. Michalak A, Krzeszowiak J, Markiewicz-Górka I. Starzenie się organizmu a stres oksydacyjny oraz zmniejszona sprawność systemów naprawczych. *Postępy Hig Med Dośw*. 2014;68:1483-1491.
16. Filoni A, Mariano M, Cameli N. Melasma: How hormones can modulate skin pigmentation. *Journal of Cosmetic Dermatology*. 2019;2:458-463. https://doi.org/10.1111/jocd.12877
17. Wojnowska D, Juszkiewicz-Borowiec M, Chodorowska G. Wpływ menopauzy na starzenie się skóry. *Postępy Dermatologii i Alergol*. 2006; 23:149-156.
18. LePillouer-Prost A, Kerob D, Nielsen M, et al. Skin and menopause: women's point of view. *Journal of the European Academy of Dermatology and Venereology*. 2020;34:267-269.
19. Verdier-Sévrain S, Bonté F. Skin hydration: a review on its molecular mechanisms. *J Cosmet Dermatol*. 2007;6:75-82.
20. Wołowiec J, Dadej I. Rola UVA w patologii skóry. *Postępy Dermatologii i Alergol*. 2003;20:170-175.
21. Campuzano-García A. E Torres-Alvarez B, Hernández-Blanco D, et al. DNA Methyltransferases in Malar Melasma and Their Modification by Sunscreen in Combination with 4% Niacinamide, 0.05% Retinoic Acid, or Placebo. *Bio Med Research International*. 2019;2019:1-7. https://doi.org/10.1155/2019/9068314
22. Rusanova I, Martinez Ruiz L, Florido J, et al. Protective Effects of Melatonin on the Skin: Future Perspectives. *International Journal of Molecular Sciences*. 2019;20(19):4948. https://doi.org/10.3390/ijms20194948
23. Perrone A, Giovino A, Benny J, et al. Advanced Glycation END Products (AGEs): Biochemistry, Singaling, Analytical Methods, and Epigenetic Effects. *Oxid Med Cell Longev*. 2020;2020:1-18. https://doi.org/10.1155/2020/3818196
24. Mackiewicz-Wysocka M, Araszkiewicz A, Wierusz-Wysocka B. Zaburzenia czynności skóry w cukrzycy. Część 1 – czynność komórek skóry. *Diabetol Klin*. 2014;3:108-116.
25. Strayer L. *Biochemia*. Warszawa: Wyd. Naukowe PWN; 2018.
26. Murray R, Granner D, Rodwell W. *Biochemia Harpera*. Warszawa: Wyd. PZWL; 2015.
27. Ferenc T, Pacholczyk M, Czernicki J. Wpływ słonecznego promieniowania ultrafioletowego (UV) na organizm człowieka. Część II: Mutagenne działanie promieniowania UV i naprawa uszkodzeń DNA. *Acta Balneol*. 2014;56:82-87.
28. Wolnicka-Głubisz A, Płonka P. Rola promieniowania UV w etiopatogenezie czerniaka skóry. *Współczesna Onkol*. 2007;11:419-424.

otrzymano / received: 12.01.2022 | poprawiono / corrected: 26.01.2022 | zaakceptowano / accepted: 07.02.2022