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The molecular mechanism of glycation. Harmful effects of advanced glycation end products (AGEs) on the skin

Molekularny mechanizm glikacji. Szkodliwe oddziaływania zaawansowanych produktów końcowych glikacji (AGEs) na skórę

ABSTRACT

Non-enzymatic glycosylation, commonly known as glycation, is a physiological process that may be intensified by endogenous and exogenous factors. The accumulation of advanced glycation end products (AGEs) effects negatively the aging process of the skin, modifying the biochemical, structural, and morphological properties of the skin.

The study aimed to describe the mechanisms and effects of AGEs on the cells of the epidermis, dermis, vascular endothelium, as well as extracellular matrix proteins and intercellular lipids.

Scientific research is being conducted to find substances that effectively inhibit the glycation process and the accompanying glycooxidation.

Keywords: glycation, advanced glycation end products, AGEs, hyperglycemia

STRESZCZENIE

Glikozylacja nieenzymatyczna, zwana powszechnie glikacją jest procesem fizjologicznym, który może ulegać nasileniu pod wpływem czynników endogennych i egzogennych. Akumulacja zaawansowanych produktów końcowych glikacji (AGEs, *advanced glycation end products*) wywiera negatywny wpływ na proces starzenia się skóry, modyfikując jej właściwości biochemiczne, strukturalne i morfologiczne.

Celem pracy było opisanie mechanizmów oraz efektów oddziaływania AGEs na komórki naskórka, skóry właściwej, śródbłonka naczyniowego, a także na białka macierzy zewnątrzkomórkowej i lipidy międzykomórkowe.

Wciąż prowadzone są badania naukowe w poszukiwaniu substancji skutecznie hamujących proces glikacji oraz towarzyszącej jej glikooksydacji.

Słowa kluczowe: glikacja, zaawansowane produkty końcowe glikacji, AGEs, hiperglikemia

INTRODUCTION

Glycation and the formation of its advanced end products (AGE) is a physiological process that occurs in all tissues and body fluids. It is one of the main molecular mechanisms that play an important role in the aging process of the skin because an accumulation of AGEs in the body increases with age. Particular intensification of glycation occurs under the influence of endogenous factors, in conditions of hyperglycemia and insulin resistance, renal failure, or inflammatory diseases. Moreover, diet and lifestyle are also important.

The pathological effect of the accumulation of these harmful metabolic products is related to their ability to disrupt the functioning of skin cells by binding to the receptor on their surface, activation of inflammation, and cross-linking of extracellular matrix proteins [1, 2].

MECHANISM OF NON-ENZYMATIC GLYCATION

The term non-enzymatic glycation refers to the Maillard reaction between sugars, most commonly the aldehyde group of glucose or the keto group of fructose, and the primary free amino groups of proteins, lipids and nucleic acids. In contrast to the enzymatic reaction of glycosylation, non-enzymatic glycation is spontaneous and, occurs in a randomly, disrupts the functioning and structure of cells. The effect of the glycation process is the formation of advanced end products - a group of diverse compounds, referred to as AGEs. So far, several types have been identified, including pentosidine, pyrraline, argpyrimidine, carboxymethyllysine, and imidazole derivatives [3, 4].

The process of non-enzymatic glycosylation of proteins is complicated and involves multi-step. The first phase is the reaction between the carbonyl or aldehyde group of the sugar and the free amino groups of proteins, lipids, peptides, and nucleic acids, resulting in the formation of an unstable Schiff base. At this stage, it is possible to reverse the reaction by lowering the glucose concentration in the body. Then, within a few weeks, as a result of intramolecular rearrangement, a more stable Amadori product, so-called an early glycation product with a chemically reactive free carbony group, is formed. Proteins with a short half-life undergo these processes, and the equilibrium of the reaction occurs after about 28 days. Proteins with a long half-life bear further transformations. Depending on the pH of the environment, these reactions may include oxidation, dehydration, condensation, and fragmentation with other amino groups, resulting in the formation of stable AGEs [2, 5-7] (Fig. 1).

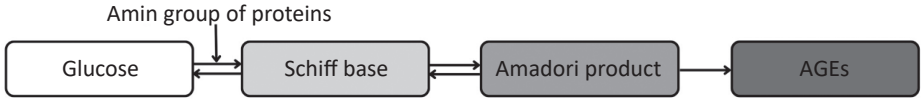

Fig. 1 Stages of formation of advanced AGEs glycation end products
Source: Own study based on [2]

In a properly functioning body, most AGEs are broken down and eliminated. Proteins modified as a result of AGEs are degraded in proteasomes, i.e. enzyme complexes, located in the cytoplasm and cell nucleus, and then they are released and excreted with urine [5].

DIET – AN EXOGENIC SOURCE OF AGES

Glycation end-products also occur naturally in food (dAGEs, dietary glycation end-products). The high level of dAGEs has been shown in sweetened food products, products rich in monosaccharides and those of animal origin, especially in beef, high-fat and long-ripening cheeses. Cereals, legumes, fruits and vegetables have the lowest level of dAGEs.

AGEs obtained from the food are protolysed as a result of the action of digestive enzymes, and intestinal bacterial flora. About 80% of aAGEs is absorbed by diffusion, the rest is excreted in the faeces. Absorbed compounds are accumulated in tissues or excreted with urine [5].

The amount of these unfavorable compounds may increase depending on the method of food heating treatment. Processes such as grilling, frying and baking increase the amount of dAGEs to a greater extent than steaming and stewing [1].

The intensification of the glycation process in the body can also be caused by smoking. Scientific reports have proved that the glutotoxin present in tobacco smoke is able to induce the production of AGEs significantly faster than glucose [8].

The glycation process can be slowed down by limiting the consumption of foods high in sugars and refined carbohydrates. Studies have shown that herbs and spices such as cinnamon, oregano, allspice, and clove are able to inhibit the endogenous production of AGEs, especially those induced by fructose [3]. High hopes are also put in fruits rich in polyphenols with antioxidant properties, such as grapes, blueberries, cherries, and cranberries [4].

ACTION OF AGEs

The indirect pathogenic effect of AGEs on cells is related to their ability to bind to transmembrane receptors for advanced glycation endproducts (RAGEs) [1].

The presence of RAGEs receptors was demonstrated on the surface of skin cells, keratinocytes, melanocytes, fibroblasts and dendritic cells, but also, among others, on the surface of endothelial cells, monocytes, and T lymphocytes [9].

RAGEs receptors show increased expression in areas exposed to solar radiation. In these areas, increased solar elastosis of the skin was observed, which may suggest that ultraviolet (UV) radiation intensifies oxidative stress and accelerates the formation of AGEs, or that glycation is an additional mechanism that sensitizes cells to photoaging. Many studies reported reduced viability AGEs exposed fibroblasts and keratinocytes after UVA irradiation of the skin. Moreover, pentonysine, which is one of the end products of glycation, has a photosensitizing effect, causing an increased production of reactive oxygen species (ROS) [10, 11].

The interaction with the receptors modifies the biochemical, structural, morphological and functional properties of the cell (Table 1). A variety of molecular pathways that trigger inflammation, immune response, cell proliferation, or genes expression can be activated. An example may be a mechanism in which, as a result of the interaction between AGEs and the receptor, the cell signaling pathway is initiated, resulting

Table 1 Effect of AGEs on cells, proteins, and extracellular lipids: ↑ increase ↓ decrease

Type of cells	Mechanisms of action	Effect
Keratinocytes	↓ proliferation ↑ cellular apoptosis ↓ intercellular adhesion ↑ production of pro-inflammatory factors ↑ ROS	– disturbance of the turn-over time cycle – thinning of the epidermis – loss of tightness of the epidermal barrier ↓ hydration
Intercellular lipids	↓ epidermal lipid synthesis ↓ ceramide synthase expression	– increasing the permeability of the epidermal barrier – changing the pH of the epidermis
Fibroblasts	↓ proliferation ↓ migration ↑ cellular apoptosis ↑ amount of ROS ↓ synthesis of extracellular matrix cells	– disappearance of support elements – loss of skin elasticity – thinning of the skin ↑ visibility of wrinkles ↓ hydration
Melanocytes	↑ tyrosinase activity ↑ MITF ↑ melanogenesis ↑ production of pro-inflammatory cytokines	– color disorders – induction of inflammation
SALT immune system cells	↑ proliferation ↑ chemotaxis ↑ concentration of pro-inflammatory factors TNFα, IL-1, IL-6 ↓ number of T lymphocytes	– induction of inflammation – impaired immune competence of cells ↑ skin reactivity
Extracellular matrix proteins	– change in spatial conformation of proteins – intermolecular cross-linking ↑ resistance to degradation by MMP	– slowing down the wound healing process ↑ stiffness ↓ resistance to mechanical damage ↑ visibility of wrinkles
Vascular endothelial cells	↑ vascular permeability ↑ vessel stiffness	– telangiectasias – inflammations

Source: Own elaboration based on [9, 16]

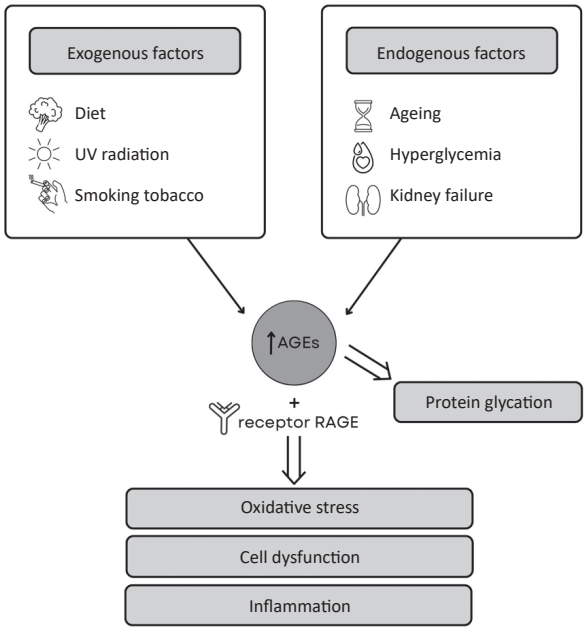

Fig. 2 Simplified diagram of mechanism of action of AGEs
Source: Own elaboration based on [1, 3]

in the intracellular production of reactive oxygen species (ROS) and the activation of pro-inflammatory transcription factors, inducing the expression of cytokines IL-1, and TNF, which all together cause inflammation. Binding of AGEs to the RAGE receptor also leads to oxidative stress by activating nicotinamide adenine dinucleotide phosphate (NAPDH), an compound responsible for the production of reactive oxygen species, and reducing the activity of superoxide dismutase (Fig. 2). At the same time, the oxidation process promotes the formation of new advanced glycation end products. This phenomenon is referred to as glycooxidation [1, 12].

The direct effect of AGEs on the proteins of the extracellular matrix is related to the structural change of proteins, their cross-linking and the disturbance of support functions (Fig. 2). Additional, strong intra- and intermolecular cross-links are formed. AGEs accumulating in the structures of the dermis significantly affect the tissues, thus accelerating the aging process of the skin [3, 13].

Keratinocytes

The binding of AGEs to the RAGEs receptor, located on the surface of keratinocytes, leads to their dysfunction. There is an increase in the production of pro-inflammatory mediators, inhibition of cell growth, reduction of intercellular adhesion, and induction of cellular apoptosis. Impairment of proliferation is associated with stopping the cell division cycle by blocking the transition of cells into the mitosis phase. Proteins of the keratinocyte cytoskeleton are modified and thus the correct shape if the cell is not maintained. These processes result in the loss of tightness, disruption of barrier functions, and thinning of the epidermis, which may result in the formation of numerous inflammations and acceleration of the skin aging process [10, 14].

Intercellular lipids

As a result of the disturbance of intracellular processes of keratinocytes, the synthesis of lipids is also disturbed. Under the influence of AGEs, there is a significant change in the ratio of the components of the intercellular binder. The glycation process reduces the expression of ceramide synthase, which results in a decrease in the content of ceramides and

cholesterol. The function of filaggrin, which is a precursor for natural moisturizing factors (NMF), is also disturbed. These mechanisms lead to a decrease in the amount of synthesized lipids and homeostasis disorders, and thus a weakening of the protective functions of the skin barrier, its increased permeability and changes in pH. This may worsen the condition of the skin with atopic or contact dermatitis and increase the risk of fungal and bacterial infection [15- 17].

Melanocytes

As a result of the action of glycation end products, the function of melanocytes is disturbed, along with the intensification of their apoptosis. AGEs increase the production of melanin without increasing the number of pigment cells. The level of microphthalmia-associated transcription factor (MITF), which is the main regulator of the melanocyte cell cycle, increases. The synthesis and enzymatic activity of tyrosinase are also enhanced, which may result in pigmentation disorders. Stimulated by the end products of advanced glycation, melanocytes secrete pro-inflammatory cytokines, affecting other cells present in the skin, including keratinocytes, dendritic cells, lymphocytes, and fibroblasts [18].

Fibroblasts

The functions of fibroblasts, which are the source of collagen fibers, elastin, hyaluronic acid and proteoglycans, are disturbed under the influence of AGEs. The shape of the cell and its distribution in the skin are modified. There is a decrease in the activity of fibroblasts, and a reduction in their metabolic and proliferative abilities. The number of extracellular matrix components produced, primarily collagen and elastin, decrease. The quantity and quality of hyaluronic acid produced by fibroblasts is also reduced. As a result of these changes, the supporting elements disappear, the skin loses elasticity and thins, which leads to increased visibility of wrinkles, and loss of hydration [3, 9].

Extracellular matrix proteins

AGEs have the ability to produce cross-links between proteins, negatively affecting the properties of connective tissue. This process is particularly important for proteins with a long half-life, such as collagen, elastin and fibronectin. As a result of the intensification of the glycation process, additional intramolecular and intermolecular cross-links are formed in collagen and fibrils thicken. Cross-linking of collagen fibers results in the weakening of their supporting properties, stiffening, and reduction of elasticity. As a result of modification of the side chains of collagen amino acids, the charge of the molecule changes, which inhibits proper reaction with other cells and matrix proteins [19]. Glycated collagen is highly resistant to degradation by matrix metalloproteinases, which makes it difficult to remove old fibers and replace them with newly synthesized ones. Its ability to bind water in tissues also changes. The effect of cross-linking of connective tissue proteins is the loss of elasticity, increased visibility of wrinkles and slower wound healing process [2, 3, 10, 20, 21].

Vascular endothelial cells

Glycation end products react with specific RAGE receptors located on endothelial cells and vascular smooth muscle cells. The supraphysiological concentration of glucose in the blood leads to an imbalance between vasodilating factors, which results in reduced blood flow and tissue hypoxia [22]. The collagen present in the walls of blood vessels stiffens, vascular reactivity decreases and blood pressure increases, which increases the likelihood of numerous telangiectasias. The change in the structure of blood vessels hinders gas exchange and supply cells with essential nutrients [23].

Cells of the immune system

Receptors for AGEs are found on the surface of many immune cells, including monocytes, macrophages, Langerhans cells and T lymphocytes. The ability to bind glycation end products is a potential immunomodulatory factor. Langerhans cells responsible for the induction of the immune response and associated with keratinocytes, in conditions of hyperglycemia, induce the development of inflammation. An increased amount of pro-inflammatory cytokines are released and oxidative stress is increased. In the state of elevated glucose concentration, the growth of T lymphocytes and their proliferation is inhibited. As a result of mitochondrial stress and damage to deoxyribonucleic acid (DNA), the efficiency of immune cells and their immunological competence decrease. Stimulation and dysfunction of the immune system cells may result in increased skin reactivity and the formation of local tissue inflammation, which will exacerbate the course of acne vulgaris, psoriasis, or atopic dermatitis [9].

SUMMARY

It is believed that glycation is one of the processes that significantly affect the course of skin aging. The pathological effect of AGEs, both indirectly on the cell and directly on the proteins of the extracellular matrix, leads to disturbances in skin homeostasis. Signaling pathways are activated, ROS production is increased as well as the development of inflamation is observed. These mechanisms cause a cascade of events, resulting in a decrease in skin density, loss of elasticity, and disruption of the skin-epidermal barrier function. As a result of these changes, the course of dermatoses such as acne vulgaris, psoriasis, atopic dermatitis, or skin allergies may worsen. In order to inhibit the glycation process, and at the same time delay the aging process of the skin, the supply of sugars in the diet should be reduced as much as possible. Comprehensive action should also include proper care that neutralizes the effects of free radicals and protects the skin against UV radiation.

The glycation process also has a significant impact on the condition of the entire body, especially in the case of people suffering from diabetes. The level of AGEs can be monitored by diagnostic tests performed from venous blood - fructosamine and glycated hemoglobin. Modern methods also provide the possibility of non-invasive assessment of AGEs accumulation in the skin, using autofluorescence caused by the accumulation of these products. However, this type diagnostic devices are available only in specialized laboratories and health centers.

Currently, numerous scientific studies are focused on the search for a substance that would effectively inhibit the process of glycation and the accompanying glycooxidation and would weaken the adverse effects of these mechanisms.

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