ACCSCIENCE PUBLISHING

Eurasian Journal of Medicine and Oncology

REVIEW ARTICLE

Non-enzymatic glycation of proteins: Mechanisms and roles in biological aging and the pathogenesis of metabolic and neurodegenerative diseases

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Abstract

Global societies are currently facing a significant demographic challenge characterized by progressive aging and an increase in age-related pathological processes. One of the fundamental mechanisms underlying biological aging and the development of modern non-communicable diseases is the accumulation of harmful metabolic by-products. Particular importance is attributed to advanced glycation end products, which are formed through the non-enzymatic glycation of proteins. This process occurs when reducing sugars, primarily glucose, react with free primary amino groups of N-terminal amino acids or lysine residues. This chemical pathway, known as the Maillard reaction, results in the formation of permanent, pathological cross-links between proteins. These modifications not only alter individual protein structures but also significantly alter the physicochemical properties of the extracellular matrix, leading to tissue stiffness and loss of physiological function. Scientific evidence indicates that glycation plays a critical role in the pathogenesis of a wide spectrum of chronic conditions, including Alzheimer's disease, atherosclerosis, diabetic nephropathy, heart failure, sarcopenia, and chronic lung diseases. Understanding the dynamics of these molecular interactions is essential for developing novel therapeutic strategies aimed at slowing down the aging process and mitigating metabolic complications in geriatric patients.

Keywords: Glycation; Protein; Biological aging; Carboxymethyllysine; Advanced glycation end products; Maillard reaction

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Citation: Jabłońska-Trypuć A, Gil M, Cudowski A. Non-enzymatic glycation of proteins: Mechanisms and roles in biological aging and the pathogenesis of metabolic and neurodegenerative diseases. *Eurasian J Med Oncol*. 2026;10(2):025510528. doi: 10.36922/EJMO025510528

Received: December 18, 2025

Revised: February 21, 2026

Accepted: March 30, 2026

Published online: May 4, 2026

1. Introduction

Gerontological hypotheses relate organismal aging to changes occurring either in dividing cells (e.g., fibroblasts), post-mitotic cells (e.g., neurons), or in the extracellular matrix (ECM; e.g., collagen of connective tissue).[1] Another classification of gerontological hypotheses distinguishes between aging as a genetically programmed process and aging as a consequence of the accumulation of harmful metabolic by-products.[2] Such compounds include, among others, products formed during non-enzymatic glycation of proteins.[3]

A process clearly associated with the aging of organisms is glycation, where cross-linked structures accumulate over time due to the binding of sugars to proteins, forming advanced glycation end products (AGEs).[4] This biochemical process leads directly to the stiffening of proteins and the loss of their elasticity, which in turn results in cutaneous aging, manifested by loss of elasticity and wrinkle formation.

It should be noted that the accumulation of AGEs is not merely a marker of disease but a fundamental driver of chronological aging. Unlike enzymatic processes, glycation is a stochastic event that progressively modifies long-lived structural proteins, leading to interstitial stiffening of the ECM and altered mechanotransduction in aging cells.[5] A hallmark of biological aging is the collapse of proteostasis—the cell's ability to maintain, refold, or degrade proteins. Non-enzymatic glycation targets long-lived structural proteins, creating irreversible cross-links that render them resistant to the 26S proteasome and autophagy–lysosomal degradation pathways.[6] By disrupting proteostasis, AGEs accelerate tissue functional decline independent of overt metabolic disease.[7] Furthermore, persistent activation of the receptor for AGEs (RAGE) contributes to "inflammaging"—the chronic, low-grade systemic inflammation that characterizes advanced age. In aging tissues, this signaling induces a senescence-associated secretory phenotype in fibroblasts and endothelial cells, leading to a self-perpetuating cycle of tissue degradation and impaired regenerative capacity, independent of glycemic status.[8]

Glycation and glycosylation are distinct biochemical processes involving the attachment of sugars to macromolecules. Glycation is a non-enzymatic, spontaneous reaction, whereas glycosylation is enzyme-mediated.[9] Glycation involves a direct chemical reaction between a reducing monosaccharide, most commonly glucose, and a free primary amino group of a protein. As a result of glycation, glycated products are formed.[4,10] This process occurs spontaneously in living organisms, and its products accumulate in tissues with age,[11] supporting its role in organismal aging.

A key role is played by AGEs and their interactions with specific cell types. Since 1992, the term "glycation" has been used to describe non-enzymatic reactions involving the attachment of sugars to proteins, regardless of whether a glycosidic bond is formed. A glycation product can be either a glycoside (i.e., a glycoprotein) or a non-enzymatic reaction product that is not a glycoside, such as glycohemoglobin. In practice, the term "glycation" is used to describe the non-enzymatic addition of sugars to proteins in order to distinguish this process from enzymatic glycosylation. The enzymatic addition of sugars to proteins by glycosidic bonds is still commonly referred to as glycosylation.[4,12]

2. Molecular mechanism of non-enzymatic glycation of proteins

Proteins in the body undergo multiple post-translational modifications. Some of these modifications occur via enzymatic reactions, while others occur non-enzymatically. The latter includes non-enzymatic glycation of proteins. This mainly concerns proteins with a high content of free amino groups, especially those containing lysine residues.[10] Early glycation is initiated by the formation of a bond between the carbonyl group of reducing sugars (e.g., glucose, galactose, or fructose) and the amino group of an amino acid. This reaction initially yields a labile Schiff base (aldimine) (Figure 1).[10]

The transformation of the relatively stable Amadori product into highly reactive intermediate dicarbonyls occurs through two primary routes: oxidative cleavage (glycoxidation) and non-oxidative dehydration. Under physiological conditions, the Amadori product undergoes 1,2-enolization followed by dehydration to form 3-deoxyglucosone. Alternatively, in the presence of transition metals or reactive oxygen species, it may undergo oxidative fragmentation to produce glyoxal or methylglyoxal. Unlike the preceding Schiff base formation, these rearrangements are effectively irreversible. These dicarbonyls then act as potent electrophiles, rapidly reacting with amino groups on adjacent proteins to form permanent, irreversible AGE cross-links over a timeframe of weeks to months (Table 1).[13]

This reaction is readily reversible upon reduction of glucose concentration. After a few weeks, this compound undergoes a slow rearrangement via the Amadori reaction, and the resulting product is a reactive carbonyl-containing compound. The products of the Amadori rearrangement can assume cyclic pyranose or furanose conformations. This reaction is also reversible, and chemical equilibrium is typically reached within approximately 28 days. Such processes primarily occur in proteins with relatively short half-lives. Proteins that remain in the body longer undergo further transformations (e.g., oxidation, dehydration, fragmentation, and condensation with other amino groups), collectively referred to as the Maillard reaction. This process leads to the formation of AGEs. They are stable products and are formed in irreversible reactions. Their characteristic feature is a brownish coloration. Some of them exhibit distinct spectrophotometric properties, including fluorescence at specific wavelengths (observed in approximately 10% of glycation products), and the ability

Table 1. Timeline and reversibility of the stages of non-enzymatic glycation of proteins

Stage	Reaction type	Reversibility	Timeline	Key intermediate
Early	Nucleophilic addition	Highly reversible	Minutes/hours	Schiff base
Intermediate	Isomerization	Slowly reversible	Days	Amadori product
Late	Dehydration/oxidation	Irreversible	Weeks	Dicarbonyls
Final	Cross-linking	Irreversible	Months/years	Advanced glycation end products (pentosidine)

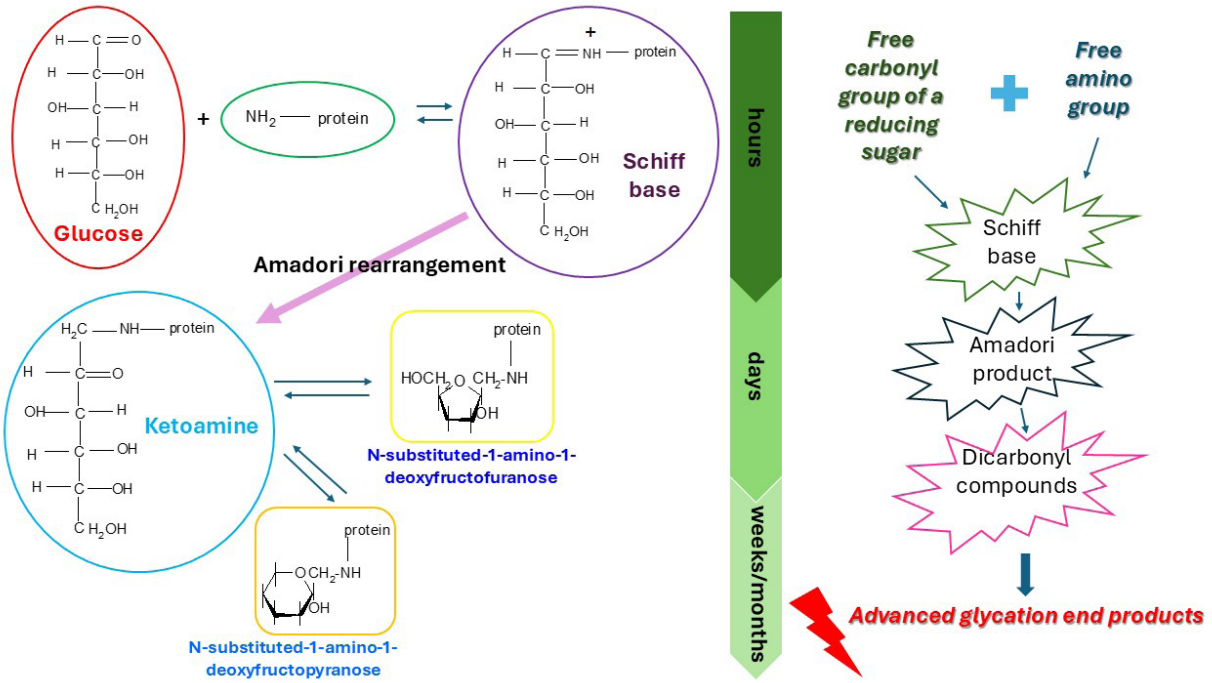

Figure 1. Non-enzymatic glycation of proteins. The initial phase begins with the reaction of a reducing sugar with a protein amino group under physiological conditions. A reversible Schiff base (aldimine) is formed through interaction between the carbonyl group of the sugar and the amino group of the protein. Once the Schiff base is formed, it undergoes an intramolecular rearrangement involving migration of the protonated amine group within the sugar moiety, facilitating the formation of a stable ketoamine linkage between the sugar and the protein. This rearrangement converts the intermediate Schiff base into a more stable Amadori product. Amadori products subsequently undergo oxidation, dehydration, and further rearrangements, leading to the formation of advanced glycation end products. These irreversible changes promote the accumulation of structurally and functionally altered, heterogeneous protein adducts. Image created by the authors.

to form cross-links between proteins. AGEs include, among others, furoyl-furanyl-imidazole, carboxymethyllysine (CML), pyrraline, and pentosidine (Figure 2).[14]

Under physiological conditions, non-enzymatic glycation occurs during the aging process of the organism. The glycation reaction is not enzyme-catalyzed, and its rate depends mainly on two factors: (i) the concentration of reactants and (ii) the duration of their interaction.[15] The participation of AGEs is crucial, among others, in altering the structure of the ECM. With age, the content of AGEs in tissues and body fluids increases. The probable cause of this condition is their reduced clearance from the body. This may be due to the age-related decline in the efficiency of tissue remodeling mechanisms.[16,17]

3. Functional changes of glycated proteins

Research indicates that there are two primary reasons why non-enzymatic glycation is of concern. First, many proteins—particularly antibodies modified to form Amadori products—exhibit impaired function; for example, immunoglobulin (Ig) G exhibits reduced binding and neutralization of bacterial toxins, such as streptolysin.[18] The second reason relates to the high stability of certain glycated proteins, which limits their removal through normal protein turnover mechanisms.[12]

Although the abundance of $-NH_2$ groups provides a chemical template for glycation, the functional impact is dictated by the local residue microenvironment and the protein turnover rate. In proteins such as IgG, glycation is not randomly distributed; residues located in the hypervariable regions of the Fab fragment are particularly susceptible. When these specific residues undergo conversion from Amadori products to AGEs, they can physically block antigen recognition or induce steric hindrance that prevents Fc receptor binding.[19] Furthermore, the pKa of specific lysine residues can be lowered by adjacent basic amino acids, making them more nucleophilic and thus more susceptible to early glycation than less reactive lysine residues elsewhere in the proteome. This explains why proteins with long physiological half-lives—such as type I collagen—accumulate damage that causes mechanical stiffness, whereas proteins with short half-lives may be degraded before Amadori products mature into functionally detrimental AGEs.[4,19]

One of the earliest observations regarding the effects of AGEs on protein function was the increased cross-linking of ECM components. Collagen, as a long-lived protein, undergoes glycation, resulting in an increased number of cross-links in its structure,[20] which leads to increased stiffness of collagen fibers, decreased solubility, and reduced susceptibility to enzymatic digestion. Studies using scanning microscopy have shown that collagen with increased pentosidine content (one of the AGEs) exhibits fibril thickening.[21] Glycated collagen, in addition

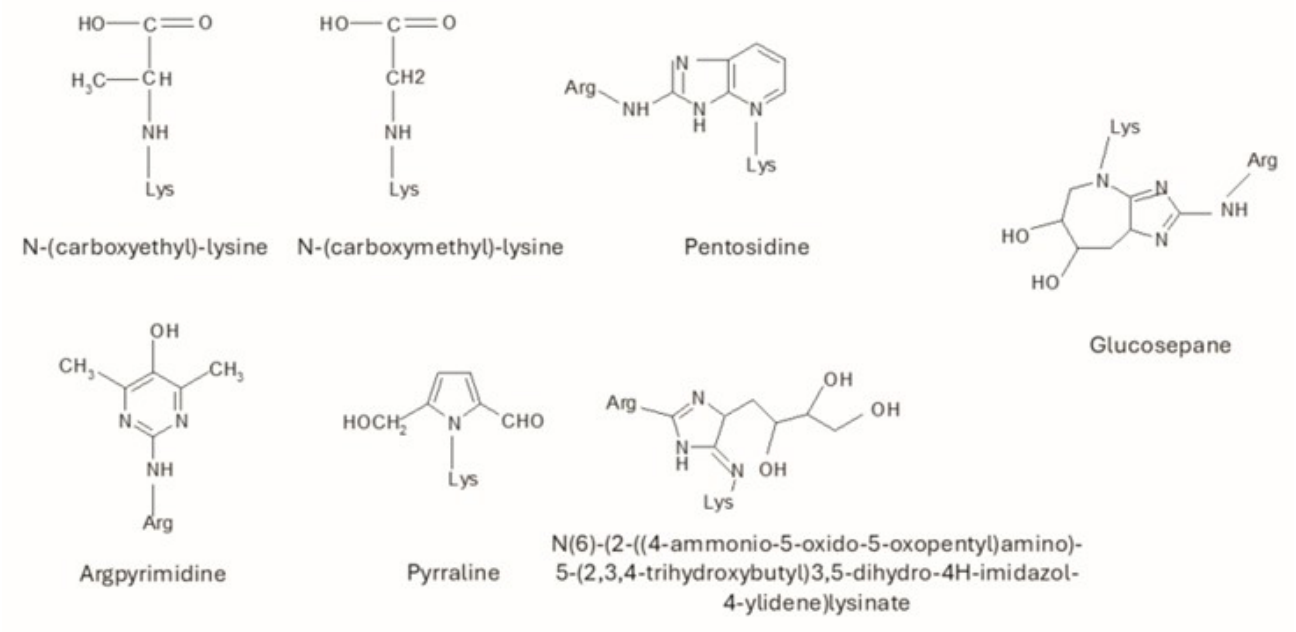

Figure 2. Representative biologically active advanced glycation end products

to forming cross-links between its subunits, can also bind other proteins, such as Igs and low-density lipoproteins.[22]

The phenomenon of cross-linking, in which free amino and carbonyl groups are involved, is not limited to glycation. It is postulated that cross-linking is a fundamental mechanism underlying the aging process.[23] Glycated fibrin demonstrates reduced susceptibility to plasmin-mediated digestion, similar to that of collagen.[24] The effects of glycation on collagen can be classified into two main categories. First, it forms intramolecular cross-links between two adjacent molecules by binding to lysine and arginine residues. These cross-links are likely located between the triple helix and adjacent molecules within the collagen fiber. The result of their formation includes alterations in physical properties, primarily increased fiber stiffness, elevated thermal denaturation temperature, and resistance to enzymatic degradation. Second, glycation induces modifications of collagen amino acid side chains, leading to changes in the charge characteristics of the molecule and affecting interactions between collagen fibers. If these modifications occur on specific regions of the molecule, they may also influence interactions between collagen fibers. Both types of modifications are unfavorable for maintaining the optimal properties of collagen as a structural scaffold and a regulator of interactions within the ECM. Therefore, glycation is a process responsible for structural and functional changes in different types of collagen across various tissues of the body.[25]

4. Interaction of advanced glycation end products with membrane receptors and their biological effects

Advanced glycation end products play a critical role in aging and disease-related pathology due to their ability to interact with specific membrane receptors on certain cell types. This property is unique to AGEs; unlike early glycation intermediates such as Schiff bases and Amadori products, AGEs are immunogenic and are selectively recognized by dedicated membrane receptors.[26,27]

The presence of receptors for AGEs on the cell surface has been demonstrated in multiple cell types, including smooth muscle cells, monocytes, macrophages, lymphocytes, cardiomyocytes, neurons, dendritic cells, and endothelial cells.[28] The first cell type in which receptors for AGE-modified proteins were identified was macrophages.[29] The molecular weight of this receptor was subsequently characterized, and it was shown to participate in AGE endocytosis and degradation. It was observed that the binding of AGEs to macrophage membrane receptors increases the synthesis and secretion of cytokines, including interleukin-1 and tumor necrosis factor-α (TNF-α; also known as cachectin).[30] These cytokines, acting on mesenchymal cells, stimulate the secretion of collagenase and other proteases.

It was also found that TNF-α, acting in an autocrine manner, increases the expression of AGE receptors on macrophages, resulting in enhanced binding, endocytosis, and degradation of AGEs. This effect contributes to the accelerated clearance of glycated erythrocytes under the influence of TNF-α.[31]

Another phenomenon associated with TNF-α is the stimulation of fibroblast proliferation. Based on these observations, a hypothesis has been proposed regarding the role of AGEs in ECM remodeling. According to this hypothesis, AGEs act as markers of proteins in aging cells, which are subsequently removed by tissue macrophages and proteolytic enzymes secreted by other mesenchymal cells. At the same time, fibroblasts synthesize new ECM components to replace degraded structures. The entire process is coordinated by cytokines, among which TNF-α plays a central role.[31-33]

The influence of AGEs on vascularization is characterized by the "angiogenic paradox," in which glycation products exert opposing effects depending on the tissue microenvironment.[34] In the retina, AGE–RAGE interactions activate the nuclear factor-κB pathway, directly stimulating the overexpression of vascular endothelial growth factor (VEGF), thereby promoting pathological neovascularization, as observed in proliferative retinopathy.[35]

Conversely, in cutaneous wound healing, AGEs act as inhibitors of angiogenesis. In this context, the accumulation of AGEs on basement membrane proteins such as collagen and laminin impairs endothelial cell adhesion and migration. Furthermore, AGE–RAGE signaling in the skin shifts the balance toward oxidative stress and sustained inflammation, leading to endothelial dysfunction and reduced expression of VEGF receptors (e.g., VEGF receptor-2). This context-specific response explains why diabetic pathology can simultaneously manifest as excessive vascularization in certain tissues and impaired healing in others.[36]

The biological fate of AGEs is dictated by the specific receptor they encounter. Macrophages express a suite of scavenger receptors—including SR-AI/II, CD36, and AGE-R1—which function as a systemic "clearance" mechanism.[37] These receptors bind AGE-modified proteins and initiate receptor-mediated endocytosis, trafficking them to lysosomes for proteolytic degradation into peptide fragments. Under healthy conditions, AGE-R1 functionally antagonizes RAGE by competing for shared

ligands, thereby reducing the systemic AGE burden.[38]

In contrast, RAGE (expressed on endothelial cells, smooth muscle cells, and neurons) does not typically internalize its ligands for degradation. Instead, RAGE acts as a potent signaling receptor. Upon ligand binding, the RAGE cytoplasmic tail activates the mammalian target of rapamycin/signal transducer and activator of transcription 3 and Ras/mitogen-activated protein kinase pathways, leading to the nuclear translocation of nuclear factor-κB. This triggers the transcription of pro-inflammatory cytokines (TNF-α, interleukin-6) and, crucially, the upregulation of RAGE itself. This positive feedback loop sustains a state of chronic cellular stress rather than a transient response. In diabetic environments, the "scavenger-to-signaler" balance shifts, as protective macrophage-mediated degradation becomes overwhelmed or downregulated, leaving more AGEs available to activate RAGE-dependent signaling pathways in the vasculature and nervous system.[39]

The balance between ECM degradation and the synthesis of new matrix proteins ensures the proper maintenance and remodeling of this structure. When this balance is disturbed—either through increased AGE formation, as occurs in diabetes, or through insufficient clearance, as observed during aging—conditions arise that promote histopathological changes.[40]

5. Clinical significance of non-enzymatic protein glycation

Tissue damage caused by the accumulation of harmful products of non-enzymatic glycation of proteins (Table 2) contributes to the development of multiple diseases, including diabetic and non-diabetic cardiovascular diseases, kidney damage, Alzheimer's disease, osteoarthritis, and premature aging.[41,42] Based on current understanding of AGE-mediated cellular processes, these compounds play a significant role in the development of atherosclerosis.[43]

The deposition of glycated proteins in the renal glomeruli promotes structural alterations that progressively lead to glomerulosclerosis and functional decline. AGEs are therefore key pathogenic factors in age-related renal disease.[44,45] Glycation of lens proteins is one of the mechanisms underlying cataract formation. With age, glycation of crystallins—the principal structural proteins of the lens—increases, leading to the formation of insoluble, high-molecular-weight protein aggregates.[47,48]

Non-enzymatic glycation also affects the central nervous system (CNS). In the pyramidal cells of the hippocampus, an increasing accumulation of CML with age has been demonstrated. This observation suggests that AGEs contribute to neuronal aging and the pathogenesis of Alzheimer's disease. In another degenerative disease of the CNS—Pick's disease—AGEs have been identified as probable pathogenic contributors. In the histopathological changes characteristic of this disease—Pick bodies and ballooned neurons—the presence of CML and pentosidine has been detected.[48]

Table 2. Tissue-specific accumulation of advanced glycation end products

AGEs	Tissue type	References
CML	Renal glomeruli	49
CML and pentosidine	Central nervous system	50
Pentosidine	Lung collagen	51
Argpyrimidine and pentosidine	Skin	52
CML	Heart	53
Pentosidine, CEL, and CML	Cartilage	54
Pentosidine	Oocytes	55
Pentosidine	Intervertebral disk	56
Pentosidine	Patellar tendon	57

Abbreviations: AGE: Advanced glycation end product; CEL: Carboxyethyllysine; CML: Carboxymethyllysine.

It was also found that serum levels of CML, a dominant

AGE, are independently associated with chronic kidney disease and estimated glomerular filtration rate. The presence of CML in renal glomeruli, particularly in the mesangial region, indicates its involvement in structural and functional alterations associated with diabetic nephropathy.[49,58] AGEs are involved in the pathogenesis of many diseases, including neurodegenerative diseases such as multiple sclerosis (MS). This disease is accompanied by a marked increase in protein glycation, particularly in pathways leading to CML formation. The duration of the disease and the degree of motor impairment are not consistently correlated with the progression of glycation processes. However, the disease process associated with MS may modulate the relationship between CML and pentosidine levels. Both AGEs—pentosidine and CML—have been identified in the neuronal cell bodies (perikarya) and extraneuronal deposits in both Alzheimer's disease and aged brains. Pentosidine has been found in the fibrillar structures of the neuropil and in the core of senile plaque. In young individuals without CNS disease, staining for pentosidine and CML is minimal.[50,59]

The mechanisms by which AGEs promote neurodegeneration include enhanced inflammation, increased oxidative stress, promotion of protein aggregation, disruption of the blood–brain barrier, and induction of cell death via activation of the AGE–RAGE signaling pathway.[60] The binding of AGEs to RAGE on neural cells activates signaling pathways that sustain chronic inflammation and oxidative stress, leading to neuronal damage. This is associated with the accumulation of misfolded proteins within the endoplasmic reticulum, exacerbating endoplasmic reticulum stress and impairing protein folding.[14] Protein misfolding is a key contributor to neurodegenerative processes, ultimately leading to synaptic loss and cognitive decline.[61,62]

The physical decline associated with aging is strongly influenced by glycation within the musculoskeletal system. In skeletal muscle, AGEs modify the myosin heavy chain, impairing myofibrillar ATPase activity and reducing muscle contractile force—a key mechanism underlying sarcopenia.[63] Simultaneously, in the ECM, AGE-induced cross-linking of type I and II collagen increases the mechanical stiffness of tendons and bone. This process, often referred to as "molecular tanning," renders connective tissues brittle and less resilient to mechanical stress, thereby contributing to progressive loss of mobility and increased fracture risk in the elderly.[64]

The discovery of non-enzymatic glycation as a mechanism leading to increased collagen cross-linking has drawn attention to its potential role in age-related deterioration of lung tissue quality. Studies in rats have shown that AGE accumulation and pentosidine-associated fluorescence in lung collagen increase with age. Therefore, glycation contributes to the decline in pulmonary mechanical properties observed in elderly individuals.[65]

The phenomenon of cross-linking also applies to the musculoskeletal system, where collagen is most abundant. For example, the amount of pentosidine bound to articular cartilage proteins increases with age.[56] At the same time, a decrease in proteoglycan content in the cartilage ECM has been observed, correlating with increased pentosidine levels.[56] This suggests a potential role for AGEs in the development of degenerative joint disease.

Collagen is a major structural protein of the dermis, tendons, and basement membranes. The integrity of these membranes determines selective permeability across capillary walls, including those involved in renal filtration. These structures are frequently compromised in patients with diabetes-related complications and in aging populations.[66]

Collagen, a key structural component of capillary basement membranes, forms a three-dimensional network with large pores that support other matrix components.[67] It has been found that glycation impairs the formation of this three-dimensional network. Therefore, this mechanism may represent a critical form of glycation-induced damage, as it contributes to increased stiffness of vascular walls, including veins and the aorta, thereby impairing blood flow.[68]

In the skin, non-enzymatic glycation reactions also promote the formation of cross-links through the action of AGEs in the ECM. The formation of these intermolecular cross-links within skin tissue is associated with the reduction in elasticity observed during aging. Therefore, glycation plays an important role in chronological skin aging.

As a result of collagen glycation, the following changes have been observed: (i) alterations in the morphology and organization of fibroblasts; (ii) an increase in CML levels; (iii) induction of fibroblast apoptosis; (iv) altered organization of ECM components (e.g., procollagen I, III, and collagen IV); (v) increased expression of β and **α**6 integrins in the epidermis; and (vi) elevated collagenase activity.

To verify the biological effects of glycation, a well-known inhibitor of this process—aminoguanidine—was used. After exposure to this agent, reduced CML levels were observed, indicating decreased AGE formation and attenuation of advanced glycation-related markers.[69,70]

6. Prevention of non-enzymatic glycation

of proteins

Research is underway to develop drugs that protect free amino groups on proteins during the early stages of glycation or inhibit cross-link formation at later stages.[71] Aspirin (acetylsalicylic acid) has been shown to exert protective effects against glycation. The aspirin molecule transfers its acetyl group to protein chains, thereby partially inhibiting glycation. However, the precise mechanism remains incompletely understood. This effect does not appear to result from direct occupation of glycation-prone sites. Notably, aspirin can protect proteins even when glycation occurs at sites distinct from those undergoing acetylation. Regardless of the exact mechanism, acetylated proteins exhibit reduced cross-link formation, which is functionally significant.[72]

However, aspirin itself may induce structural alterations in proteins and potentially initiate degradative processes. Importantly, it does not promote polypeptide chain unfolding or protein denaturation, nor does it cause lens opacification. Instead, it has been reported to protect against lens clouding induced by cyanides and certain sugars.[73]

Recent literature increasingly attributes the protective effects of aspirin to its role in post-translational modifications. While earlier studies proposed that aspirin weakly binds to and passively occupies glycation sites, more recent evidence supports an active chemical modification mechanism.[74,75] Specifically, aspirin's antiglycative activity is primarily mediated through non-enzymatic acetylation of N-lysine residues, which competitively blocks nucleophilic attack by reducing sugars. This effect is further supported by its ability to chelate pro-oxidant metal ions, which otherwise catalyze the conversion of Amadori products into irreversible AGEs.[76]

In addition, aspirin and its metabolites can sequester transition metal ions, thereby attenuating glycoxidation reactions that accelerate AGE formation.[77] Emerging evidence also suggests that aspirin may stabilize proteins against reactive dicarbonyl species, such as methylglyoxal, although acetylation remains the dominant direct protective mechanism.[10]

Ibuprofen has also been reported to exhibit antiglycative properties. Compounds that inhibit the formation of AGE complexes are thought to act by targeting reactive carbonyl groups of Amadori intermediates, thereby preventing cross-link formation through reduced interaction with protein amino groups.[10] Antiglycative activity has also been attributed to anti-rheumatic drugs such as penicillamine and aminoguanidine. In addition, flavonoids have demonstrated efficacy in inhibiting pentosidine formation in collagen, remaining active even at micromolar concentrations, and thus represent promising candidates, particularly in the context of diabetes management.[20,78]

The development of agents that inhibit protein glycation is of considerable clinical importance, as such interventions may mitigate secondary complications of diabetes and other AGE-related pathologies.[69] Evidence also indicates the presence of enzymes capable of reversing glycation, a process termed deglycation, which have been identified in vertebrates, bacteria, and fungi.[79] However, only vertebrate enzymes have been shown to mediate deglycation of large intracellular proteins via ATP-dependent mechanisms. Nonetheless, there is currently no conclusive evidence supporting the use of these compounds to prevent the formation of AGEs in humans.[80] In vertebrates, deglycation occurs via ATP-dependent phosphorylation of fructosamines, catalyzed by fructosamine-3 kinase (FN3K). However, its therapeutic applicability remains limited due to the predominantly extracellular localization of pathogenic AGE cross-links, as well as the potential systemic accumulation of reactive by-products, such as 3-deoxyglucosone.

The deglycation process in vertebrates is not a simple cleavage reaction. It is a complex process driven by phosphorylation. FN3K recognizes fructosamines (Amadori products) in proteins and destabilizes them. This enzyme uses ATP to phosphorylate the third carbon of the deoxyfructose molecule, resulting in the formation of an unstable intermediate, fructosamine-3-phosphate. Because fructosamine-3-phosphate is highly unstable, it spontaneously dissociates from the protein, regenerating the free amino group and releasing 3-deoxyglucosone. The reason these enzymes have not been successfully used as therapeutics against AGEs in humans is attributed to several metabolic paradoxes.[81] First, while FN3K removes Amadori products, the resulting by-product, 3-deoxyglucosone, is itself a highly reactive dicarbonyl. If the body's detoxification systems become overwhelmed, this can contribute to increased glycation stress.[82]

Another factor is its predominantly intracellular localization. FN3K is primarily an intracellular enzyme, whereas the most severe AGE-related damage, particularly that leading to vascular stiffening and collagen cross-linking, occurs in the ECM.[83] Developing a way for these enzymes to act effectively outside the cell remains a significant pharmacological challenge.

Finally, substrate specificity is a major factor. Human FN3K is highly evolved to target specific ketoamines. Expanding its domain of action to prevent a diverse range of AGE precursors without disrupting essential glycoconjugates requires careful maintenance of metabolic

balance.[84] Substances that mitigate glycation-related damage in the body are currently in clinical trials.[85] It should be noted that, in recent years, a simpler strategy for reducing glycation has been emphasized: lowering dietary sugar intake. The main argument against excessive sugar consumption is linked to the mechanism of protein glycation. Only the first glycation reaction requires the presence of free glucose molecules. The second stage of glycation is irreversible; its product, known as the Amadori product, persists in the body until it is removed through protein turnover within specific tissues.[86]

In the case of long-lived proteins, such as collagen found in basement membranes, the product of the Amadori reaction remains long enough to form cross-links and AGE adducts. The risk is further increased by sucrose, which, as a disaccharide, is converted in the body into simple sugars: glucose and fructose. Both of these sugars contain reactive carbonyl groups that facilitate glycation. Fructose has recently gained attention as a potent contributor to protein glycation in humans. It has been shown that fructose induces glycation at a faster rate than glucose.[87] Some cells in the body can convert glucose into fructose, which further promotes AGE formation. This occurs via the polyol (sorbitol) pathway, a recognized biochemical process that is activated under hyperglycemic conditions.[88]

In conditions of hyperglycemia, certain cells that do not require insulin for glucose uptake (such as those in the retina, kidneys, nerves, and seminal vesicles) experience an overload of glucose. To handle this, they activate the two-step polyol (sorbitol) pathway. In the first step, aldose reductase reduces glucose to sorbitol, consuming nicotinamide adenine dinucleotide phosphate in the process. In the next step, sorbitol dehydrogenase oxidizes sorbitol to fructose, which is a much more potent glycating agent for AGE formation.[89] High sugar consumption can rapidly contribute to obesity, which is a component of metabolic syndrome and is associated with increased formation of non-enzymatic glycation products derived from the Maillard reaction, and, consequently, with the development of multiple diseases, including diabetes.[90,91]

7. Conclusion

Empirical work on the process of protein glycation encounters many methodological difficulties, particularly in the quantitative assessment of the rate of formation of reaction products and cross-links. Accurate measurement of cross-link formation in non-enzymatic protein glycation is challenging due to the complexity of reaction products, the slow and heterogeneous nature of the process in biological tissues, and limitations in current analytical techniques. This structural heterogeneity arises from the diversity of glycation products, a wide array of chemical modifications, multiple potential amino acid residues for cross-link formation with differing reactivities, and their typically low abundance.[92]

Additional challenges in assessing the rate of cross-link formation in protein glycation include analytical limitations in detection, such as poor ionization efficiency of glycation-derived peptides, and the fact that specific modifications, such as β-O-GlcNAc, are labile and prone to dissociation during mass spectrometry analysis, necessitating specialized detection methods.[93]

Non-enzymatic glycation occurs slowly *in vivo*, making it difficult to measure real-time kinetics under physiological conditions. Experimental acceleration (e.g., elevated temperature) may alter reaction pathways and reduce biological relevance. Furthermore, early-stage glycation products are often reversible, and intermediate species may degrade, complicating the accurate determination of the net rate of stable cross-link formation.

Cross-link formation is in constant competition with the formation of mono-adducts (single glycation sites).[94,95] *In vivo*, the presence of various proteins, lipids, and sugars complicates the specific identification of glycation-induced cross-linking. It is also difficult to distinguish glycation-induced cross-linking from other age-related modifications, such as oxidation or enzymatically driven cross-linking. These challenges necessitate the use of advanced analytical approaches, such as high-resolution mass spectrometry combined with specialized bioinformatics tools, to accurately map and quantify the kinetics of glycation-induced cross-links.

A more detailed understanding of these phenomena may provide valuable insights into the molecular mechanisms of aging. There are significant potential practical applications of knowledge in this field. Precise determination of AGE concentrations in body fluids and tissues may help clarify the dynamics of diabetic complications and estimate biological aging rates. There is also potential for the development of therapeutic agents targeting these processes in the future. This would have substantial implications for the prevention and treatment of age-related and metabolic diseases.

Acknowledgments

None.

Funding

This work was funded by the Ministry of Education and Science, Poland, under the research project number WZ/WB-IIŚ/7/2025.

Conflict of interest

The authors declare they have no competing interests.

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Writing–review & editing: Agata Jabłońska-Trypuć, Adam Cudowski

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Not applicable.

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