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Review Article

Advanced Glycation End Products—Physiology and Pathological Activity: A Literature Review

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Abstract

Advanced glycation end-products (AGEs) are chemically complex and varied substances that are made inside or outside the body during different biological processes. Condensation between the carbonyl groups of reducing sugars and the free amine groups of proteins, lipids, or nucleic acids produces them non-enzymatically. The accumulation of AGEs in vivo triggers a number of signaling pathways by binding with receptors for AGEs (RAGE) that are intimately linked to the development of chronic metabolic disorders. Because of their capacity to stimulate oxidative stress, inflammation, and apoptosis, AGEs are thought to have pathogenic implications. AGEs play a role in the onset and progression of a number of aging-related pathological conditions, including cancer, diabetes, cardiovascular diseases, liver or neurodegenerative diseases, and intestinal diseases. AGEs have an impact on health and aging, particularly in hyperglycemic people. Lowering the risk of AGE-related issues and maintaining overall health can be achieved by monitoring AGE levels and adopting nutritional interventions. This review aims to show the role of AGE in the health and pathologies of various diseases.

***Keywords*:** AGE; Hyperglycemia; Inflammation; Oxidative stress; RAGE.

منتجات نهائية للجليكيشن المتقدم— الفسيولوجيا والنشاط المرضي: مراجعة الأدبيات

الخلاصة

(AGEs) هي مركبات غير متجانسة ومعقدة كيميائيًا، تُنتج إما داخليًا أو خارجيًا خلال عمليات بيولوجية مختلفة. تتكون هذه المركبات بشكل غير إنزيمي نتيجة لتفاعل التكثيف بين مجموعات الكربونيل في السكريات المختزلة ومجموعات الأمين الحرة في البروتينات أو الدهون أو الأحماض النووية. يؤدي تراكم AGE في الجسم إلى تحفيز عدد من مسارات الإشارات الخلوية من خلال الارتباط بمستقبلات هذه المركبات(RAGE) ، والتي ترتبط ارتباطًا وثيقًا بتطور الاضطرابات الأيضية المزمنة. ونظرًا لقدرتها على تحفيز الإجهاد التأكسدي والالتهاب وموت الخلايا المبرمج، يُعتقد أن AGEs لها آثارًا مرضية. تلعب هذه المركبات دورًا في بدء وتطور عدد من الحالات المرضية المرتبطة بالشيخوخة، بما في ذلك السرطان والسكري وأمراض القلب والأوعية الدموية وأمراض الكبد أو الأمراض التنكسية العصبية وأمراض الأمعاء. تؤثر AGE على الصحة والشيخوخة، لا سيما لدى الأشخاص الذين يعانون من ارتفاع سكر الدم. يمكن خفض خطر المشاكل المرتبطة بـ AGEوالحفاظ على الصحة العامة من خلال مراقبة مستوياتها واتباع تدخلات غذائية مناسبة. تهدف هذه المراجعة إلى تحديد دور AGEs في الصحة وألأمراض مختلفة.

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INTRODUCTION

Advanced glycation end products (AGEs) are heterogeneous molecules that are generated from nonenzymatic products during the Maillard reaction, a spontaneous reaction that occurs by a nucleophilic addition between the carbonyl group of a reducing sugar and the free amino group of a protein, aminophospholipid, or nucleic acid (Figure 1) [1].

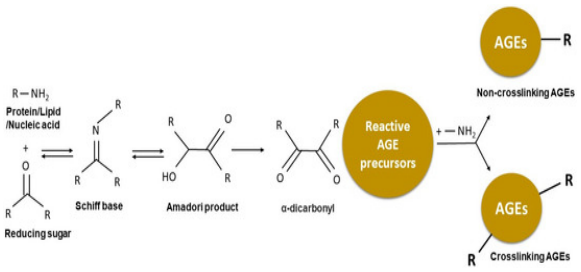

Figure 1: Scheme of the Malliard Reaction [1].

Advanced glycation end products are harmful substances that change the structural features and function of tissues by crosslinking intracellular and extracellular matrix proteins. They can also modify other cellular functions by connecting to their cell surface receptor, known as the receptor for AGEs (RAGE). Cigarette smoke, high-carbohydrate diets, foods cooked at high temperatures, and sedentary lifestyles are some of the environmental variables that cause AGE formation, which in turn damages cell lipids and proteins. The pathophysiology of diabetes, atherosclerosis, and renal disorders has been linked to AGEs [2]. This review aims to establish the role of AGE in health and pathologies of various diseases.

Formation and Types of AGE Products

Advanced glycation end products (AGEs) are created via the Maillard reaction, which occurs when the carbonyl group of a reducing sugar condenses with the amino acid carbonyl amine to produce a Schiff base. After that, an Amadori reaction rearranges the Schiff base to create a stable Amadori product (Figure 2), which is subsequently degraded to produce extremely

reactive dicarbonyl molecules, including MGO, GO, and 3-deoxyglucosone [3].

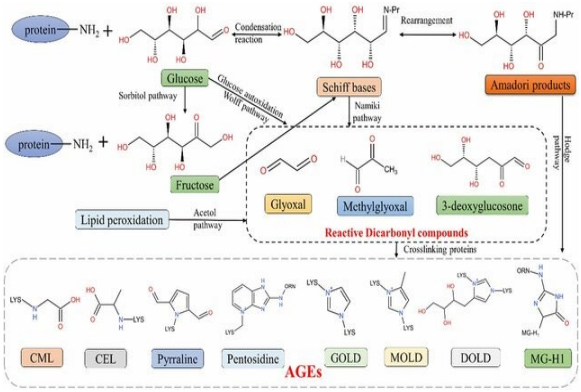

Figure 2: Main Pathways for The Formation of Advanced Glycation End Products [8]. Note: Cel: carboxyethyl lysine; CMl: carboxymethyl-lysine; Gold: glyoxal-derived lysine dimer; MG-Hi: methylglyoxal-derived hydroimidazolone 1; Mold : methylglyoxal derived lysine dimer.

These carbonyl intermediates directly interact with protein-free amino groups, causing significant biological damage. These carbonyl intermediates are also produced via the Wolff route, which metal-catalyzes glucose auto-oxidation and dehydration. The Namiki route—reverse aldol condensation and oxidative breakdown—creates GO, MGO, and 3-DG from unstable Schiff bases (Figure 2) [4]. Dicarbonyl compounds are produced in mammals by physiological metabolic systems like the polyol pathway, which converts glucose to MGO and 3-DG from tricarbon phosphate and fructose-3-phosphate [5]. Conversely, lipid peroxidation produces MGO, GO, and other compounds. Fructose 6-phosphate, glucose 6-phosphate, and other glycolytic steps create dicarbonyl molecules [5]. Two routes play a major role in the final production of AGEs. In the first process, Amadori products—primarily [N-(carboxymethyl)lysine] (CML), pentosidine, and glucosepane—directly produce AGEs via the Hodge pathway, namely by oxidative degradation or oxidative rearrangement [6]. The second method involves the direct reaction of dicarbonyl chemicals with protein arginine and lysine residues to produce AGEs. Interestingly, under high oxidative stress conditions, MGO synthesis also promotes AGE-derived cross-linking [6]. 3-deoxyglucosone and lysine react to produce pyraline. In the body, carboxymethyl lysine (CML) is the most significant AGE. Numerous studies have examined it and connected it to neurodegenerative illnesses. Either a metal-catalyzed oxidation reaction between polyunsaturated fatty acids and protein or an oxidative breakdown of Amadori products results in CML. Glyoxal lysine dimer (GOLD) and methylglyoxal lysine dimer (MOULD) are examples of non-fluorescent crosslink AGEs that are created when two glyoxal derivative molecules engage with two lysine residues [7]. Aldose reductase mediates the polyol pathway, which is another method of AGE production. Through 3-deoxyglucosone AGE intermediates, glucose entering the polyol pathway can directly produce AGEs; however, this reaction depletes NADPH and glutathione, and the oxidative stress that results indirectly encourage the development of AGEs. Long-lived proteins were primarily harmed by the reaction because the glycation processes were sluggish. Nevertheless, it was shown that even short-lived compounds, such as intracellular growth hormones, lipids, and nucleic acids, are glycosylated. The N-terminal amino groups of proteins, the thiol groups of cysteine residues, and the side chains of arginine and lysine residues are the main targets of protein glycation [8].

Receptors for AGE Products

When AGEs form, a variety of signaling pathways controlled by cell surface receptors are activated. The multi-ligand receptor for advanced glycation end products (RAGE) is the AGE-receptor that has been studied the most. Furthermore, the AGE-receptor complex was discovered, which includes AGE-R1/OST-48, AGE-R2/80K-H, and AGE-R3/galectin-3. These AGE receptors are expressed differently by cell or tissue type and are regulated by acute metabolic alterations, including aging, diabetes, and hyperlipidemia [9]. A gene on chromosome 6 encodes the 394-amino-acid multi-ligand transmembrane protein known as receptor advanced glycation end-products (RAGEs), a signal transduction receptor that belongs to the immunoglobulin superfamily. The most well-researched isoform of RAGE is its entire length, which consists of three domains: extracellular, transmembrane, and cytoplasmic (Figure 3) [10].

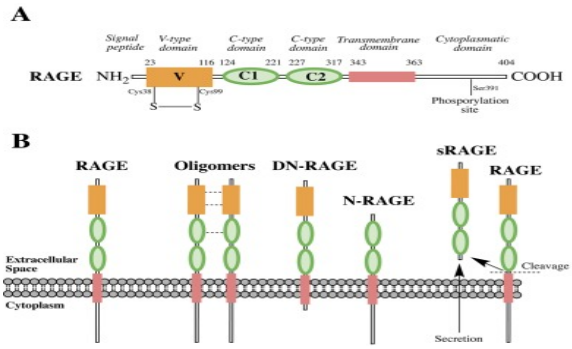

Figure 3: **A**) Structure of full-length RAGE, and **B**) RAGE isoforms [9]. Note: DN-RAGE: dominant negative RAGE, N-RAGE: N-truncated RAGE, and sRAGE: soluble (secretory) RAGE.

The RAGE's alternative splicing A freely circulating version of RAGE without a transmembrane domain that is unrelated to the pathogenic action of AGEs, soluble or secretory RAGE (sRAGE), is also produced by mRNA. Instead, they attach to AGEs and regulate endocytosis and degradation to eliminate them [11]. The pathophysiology of many diseases, including complications from diabetes, depends critically on the interaction between AGE and RAGE. AGEs trigger RAGEs, which in turn trigger inflammatory, angiogenic, proliferative, and apoptotic reactions by transducing signals from Janus kinases, extracellular signal-regulated kinases (ERKs), and mitogen-activated protein kinases (MAPKs) [10]. Vascular endothelial cells have the most well-researched AGE receptor isoform, full-length RAGE. When RAGE identifies AGE in endothelial cells, it activates NF-κB, which speeds up the production of growth factors, cytokines, and oxidative stress, leading to

inflammation [12]. The AGE/RAGE signaling cascade activates signaling pathways, including TGF-α and NADPH-oxidase 1 (Nox-1), leading to increased ROS production. ROS can affect numerous intracellular components, including DNA, lipids, and proteins in cellular membranes [13]. Furthermore, by triggering NF-κB, which migrates to the nucleus and triggers the release of inflammatory mediators, as well as upregulating RAGE, ROS intensify the inflammatory response and create a positive feedback loop [14]. RAGE expression is typically low in organs and tissues under physiological conditions. However, higher amounts are observed in chronic inflammatory diseases such as diabetes mellitus (DM), cardiovascular disease, Alzheimer's disease, cancer, and natural aging, or in pathological circumstances like atheromatous plaques where AGEs have accumulated [15]. RAGE has been discovered to be expressed by a wide variety of cells, including neurons of the central and peripheral nervous systems, endothelial cells, smooth muscle cells, monocytes/macrophages, T lymphocytes, cardiomyocytes, glomerular podocytes, dendritic cells, and transformed cells [16]. In tissues, RAGE is frequently under expressed. On the other hand, it becomes up-regulated under conditions where its ligands are plentiful, such as diabetes or aging. Smooth muscles, monocytes, and endothelial cells all expressed increased RAGE in diabetic vascular tissue [16].

AGE Physiology

The receptor for advanced glycation end products (RAGE) has a major effect on AGE-mediated signalling, ROS-related NF-κB activation, and the inflammatory response. Three main signalling pathways are stimulated by RAGE receptor activation: JAK/STAT, Rac1/Cdc42, and Ras/MAPK/NF-κB. Through NADPH oxidase, these signal transduction pathways generate reactive oxygen species (ROS), which in turn raise the production of pro-angiogenic factors (VEGF-A, VCAM1), pro-inflammatory modulators (IL-6, TNF-α), and RAGE itself. The downregulation of Glyoxalase 1 causes feed-forward amplification (Figure 4) [17].

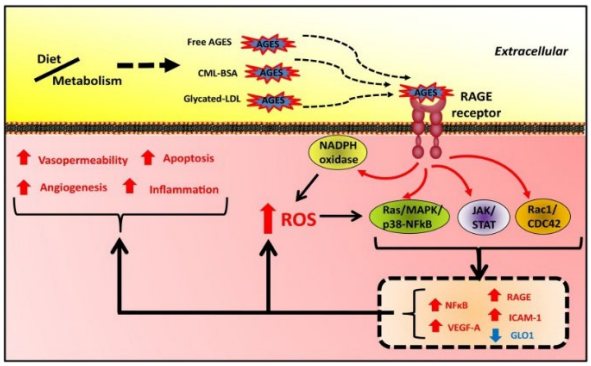

Figure 4: Activation of RAGE Signaling Pathways by AGE [17]. Note: ROS: reactive oxygen species, GLO1: Glyoxalase, ICAM-1: Intercellular Adhesion Molecule 1, VEGF-A: Vascular endothelial growth factor A.

RAGE expression was observed by Reynolds *et al*. in the endothelial cells of rat alveolar capillaries and embryonic arteries [18]. The bulk of research on RAGE during embryogenesis, however, suggests that it is crucial for lung organogenesis. Western blot analysis demonstrated a consistent increase in RAGE expression from fetal to adult lungs in rats, with adult lungs exhibiting a two-fold increase in mRAGE expression relative to neonatal lungs [19]. As type I epithelial cells proliferate during the alveolarization process, RAGE gradually rises from fetal development through birth and adulthood. Lung development is correlated with RAGE expression in the embryonic lung. RAGE is continuously overexpressed in the lungs as people age [20]. The accumulation of RAGE ligands, which in turn increases receptor expression via a positive feedback process, may be the cause of the rise in RAGE with aging. Simm et al. also discovered that while mRNA levels stayed constant with age, RAGE protein expression rose in human cardiac tissue, indicating that the turnover of the receptor declines with age [21]. RAGE is histologically present in the visceral pleural surface, pulmonary endothelium, alveolar macrophages, and bronchial and vascular smooth muscle in bovine tissues [22]. RAGE is significantly upregulated in inflammatory lesions associated with diseases like rheumatoid arthritis, inflammatory kidney disease, arteriosclerosis, and inflammatory bowel disease. Its ability to bind multiple proinflammatory ligands underscores its essential role in the propagation of immune and inflammatory responses. Major histocompatibility class III, encompassing a significant portion of the innate immune system, includes the gene responsible for coding RAGE (Ager) [32]. In neural cells, RAGE exhibits a dual nature: on the one hand, it can promote neuronal differentiation and improve cell survival; on the other hand, when it is activated, it causes neuronal death. Importantly, these conflicting effects appear to be dependent on certain characteristics of RAGE-bearing cells as well as the degree and duration of RAGE activation. In fact, it is well established that RAGE causes neuronal death when high concentrations of ligands are present, whereas modest levels of RAGE activation brought on by low ligand concentrations have pro-survival differentiation effects [24]. The pathophysiology of several neurological disorders, such as Alzheimer's disease, is influenced by the interaction between RAGE and AGEs or amyloid-β fibrils, which mainly causes oxidative stress and inflammation [25]. RAGE influences several processes, such as axonal growth and nerve regeneration, by activating inflammatory pathways that mostly involve macrophages [26]. RAGE inhibition inhibits peripheral nerve regeneration, inhibits phagocyte infiltration into neurons, and prevents the nerve's functional recovery [27].

AGE Product-Related Diseases

Pathological Mechanisms Related to AGE-AGER

Ages can cause diseases in many ways. They interact with their receptors, especially along the AGE–RAGE axis, which starts a lot of different biochemical reactions and signaling pathways, like apoptosis (cell death), autophagy (cell recycling), and proliferation (cell growth). Also, serum and extracellular matrix

(ECM) proteins, lipids, and DNA can covalently crosslink, which causes biochemical and cellular problems. For example, when AGEs cross-link to collagen or elastin in the extracellular matrix (ECM), they make proteins less flexible and delay their hydrolytic breakdown. This process causes thickening of the basement membrane, which jeopardizes blood vessel integrity and increases the hazards associated with bleeding disorders [29]. This is in addition to directly trapping or cross-linking the proteins. NF-κB transcription factor activation is the first of several inflammatory reactions brought on by RAGE activation. It then activates a number of downstream effectors, such as the stress-activated protein kinase/c-Jun N-terminal kinase (SAPK/JNK) pathway, mitogen-activated protein kinase (MAPK), Janus kinase signal transducer, and activator of transcription (JAK/STAT), p38, and Ras-mediated extracellular signal-regulated kinase (ERK1/2). These will further activate NF-B, HIF-1, STAT3, and AP-1 among other transcription factors [30]. These signaling pathways control a number of physiological processes and ultimately lead to AGE-induced illness in various tissues by causing apoptotic, fibrotic, thrombogenic, angiogenic, and proliferative reactions [31]. Chen and Guo have also found four more ways: (i) AGEs as antigens that cause immune responses, (ii) the failure of how mitochondria work, (iii) allergies caused by AGEs, and (iv) the creation of ROS, which causes oxidative stress [32]. The AGE–RAGE interaction may raise ROS levels by increasing the production of AGE. This could create a "catch-22" situation in which cells are constantly damaged because the mitochondrial and NADPH pathways are activated. When glucose is converted to fructose via NADPH, extra ROS are produced. Glyoxal (GLO) and MGO concentrations rise due to diminished endogenous antioxidant mechanisms, including GSH depletion, which accelerates glycation [15]. The AGE-RAGE complex can then either activate or inhibit the signaling pathways that lead to several clinical disorders, including cancer, aging, neurodegenerative illnesses, diabetes mellitus (DM), chronic kidney disease (CKD), and skin diseases. The detrimental effects of AGEs can be reversed by adopting healthy eating, cooking, and living practices [33].

Diabetes Mellitus Complications

In diabetes, AGEs accumulate in the several organs that are harmed, and hyperglycemia speeds up this accumulation rate. Systolic hypertension and diastolic dysfunction in diabetic patients are believed to be on the rise because of the increased vascular stiffness and decreased arterial and myocardial compliance brought about by AGE-induced intermolecular collagen cross-linking. Most diabetes-related problems, such as kidney, retina, and atherosclerotic plaques, are affected by AGE accumulation [34].

Diabetic retinopathy

People with diabetes mellitus are most often blinded by diabetic retinopathy (DR), which is marked by lesions in the retinal blood vessels that result from changes in vascular permeability, capillary micro-aneurysms, pericyte loss, and aberrant blood vessel development. Retinal AGEs develop after prolonged hyperglycemia [35]. Retinal endothelial microcirculation AGE buildup leads to premature capillary closure (occlusion). Additionally, they increase the production of intracellular cell adhesion molecules (ICAM), which harm the retina by mediating leukocyte adherence in retinal capillaries and the disintegration of the inner blood-retinal barrier [36]. Evidence suggests that diabetic retinal cells have increased RAGE mRNA levels due to high AGEs. Type 2 diabetics' AGE levels are favorably associated with oxidative indicators and RAGE mRNA expression. RAGE expressions may be greater in ligand- and inflammatory mediator-rich situations [37]. Research suggests that ligand-enriched environments may boost RAGE expression and aggravate proinflammatory processes [38]. When AGE connects to RAGE, important signaling pathways are turned on, such as NF-κB oxidative stress, the activation of PKC, and JAK/STAT phosphorylation [39]. Finally, it increases cytokine synthesis, including VEGF and TNF-α, and adhesion molecule expression. VEGF promotes angiogenesis in the retinal endothelium, causing proliferative retinopathy, whereas cytokines, including IL-α, IL-β, and IL-6, cause inflammation [40]. In contrast, AGEs independently induce retinal cells to release IL-6, which enhances VEGF expression and neovascularization. It has been shown that in human endothelial cells, AGEs may lower eNOS mRNA expression and raise TNF-α mRNA expression. This may cause vascular dysfunction in DM [41]. Hashim and Zarina (2017) also link AGEs to cataracts, which reduce lens transparency. Cataracts are a common cause of diabetic vision loss [42]. Glycation of lens proteins, called crystallins, causes diabetic cataracts. Permanent alterations in structural proteins caused by AGEs cause lens proteins to congregate and form high-molecular-weight aggregates, which disperse light and impair vision [37]. In vitro investigations indicated that AGEs in pericytes boost caspase-3 activity, which decreases the Bcl/Bax ratio and promotes apoptosis. Lack of pericytes, which maintain microvascular homeostasis, can cause retinal blood vessel endothelial cell damage and angiogenesis, causing diabetic retinopathy [43].

Diabetic nephropathy

The primary cause of end-stage renal failure in diabetics is diabetic nephropathy (DN). In clinical terms, it is characterized by the onset of proteinuria and the progressive decline in glomerular filtration rate over time. Additionally, it is a significant risk factor for macrovascular issues. There is a correlation between DN and AGE levels in renal tissue. AGEs throw off the equilibrium between the production and breakdown of collagen and other extracellular matrix (ECM) components found in the glomerular basement membrane. The basement membrane's AGE and collagen cross-linking will cause the membrane to thicken, hindering filtration, and ultimately result in glomerular function loss [44]. The AGE-RAGE axis is also important in DN. TGF-β is stimulated by AGE-RAGE signaling in mesangial cells, tubular cells, and

podocytes. By promoting the synthesis of type IV collagen, laminin, and fibronectin, TGF-β, a pro-fibrotic factor, thickens the basement membrane. Through the JAK/STATA signaling pathway, it is expressed. The other mechanism of DN is cross-talk between AGEs and the renin-angiotensin-aldosterone system (RAAS) [45]. The main function of the RAS's renin, angiotensin I, angiotensin-converting enzyme (ACE), and angiotensin II is to regulate fluid balance. Angiotensin II operates through the angiotensin II type 1 receptor (AT1R) to promote hypertrophy of mesangial and tubular epithelial cells. Conversely, AGEs stimulate the expression of AT1R, which raises the activity of angiotensin II [45]. Moreover, AGE causes kidney fibrosis and inflammation. RAGE activation also causes different cytokines to be expressed in kidney cells. In turn, these cytokines stimulate the creation of monocyte chemoattractant protein-1 (MCP-1) in renal cells, which is linked to the infiltration of monocytes and macrophages into the cell [46]. Furthermore, AGEs cause podocytopathy. Specialized cells called glomerular podocytes serve as a size-selective filtration barrier, controlling the flow of plasma proteins from the bloodstream into the urine. When RAGE is activated in podocytes, NF-κB signaling is triggered, which leads to the creation of zinc finger proteins called homeobox-2 E-box binding (ZEB2). A decrease in the number of podocytes per glomerulus and proteinuria may arise from podocytes detaching from the basement membrane due to epithelial-mesenchymal transition [47]. In DM patients, there was also a noteworthy correlation between AGEs, especially CML, podocyte damage, and proteinuria, which led to compromised kidney function [48].

Diabetic neuropathy

Diabetic neuropathic complications are prevalent and include polyneuropathy (damage of peripheral nerves) or mononeuropathy (destruction of a nerve owing to injury). Diabetic neuropathy is caused by structural or functional alterations in nerve fibers and glycation of cytoskeletal proteins. Due to accumulating glycated proteins, diabetic rats' experimental tests revealed reduced sensory motor conduction velocity, decreased nerve potential, and also impaired sciatic nerve functions. The loss of the myelin sheath around a neuron due to AGE accumulation may result in further vascular problems [49].

Cardiovascular Diseases

Advanced glycation end products' ability to cross-link with the matrix proteins in the vessel wall makes it stiffer, traps lipoproteins inside the artery wall, and interferes with their removal. AGE deposition in the radial artery and on atherosclerotic plaques in patients with and without diabetes who have chronic renal failure (CRF) [50]. Cardiovascular diseases (CVDs), such as coronary heart disease (CHD), are often regarded as resulting from diabetes mellitus. The primary methods that AGEs function are as follows: (i) collagen and elastin crosslinking, which results in cardiac fibrosis and myocardial stiffening of the blood vessels; (ii) AGEs and RAGEs interacting, which starts the NF-κB pathway, activates NADPH oxidase, and releases ROS; (iii) endothelial nitric oxide synthase activity and nitric oxide activity inhibition; and (iv) increased vascular permeability [51]. Advanced glycation makes the circulatory system's lipoprotein components susceptible, and receptors may have trouble detecting glycated LDLs. Glycated particles reaching the artery wall and being absorbed by macrophage receptors may cause lipid buildup. T-lymphocyte and macrophage adherence is improved by AGE-RAGE, which activates adhesion proteins via the NF-κB pathway. This adhesion mechanism of inflammatory reactions increased plaque growth [52]. The AGE-RAGE axis also regulates the expression of ATP-binding cassette transporter G1 (ABCG1) and cluster of differentiation 36 (CD36), both of which promote macrophage conversion to foam cells [53]. AGE-RAGE activated TGF-β, leading to increased migration and proliferation of smooth arterial muscle cells. This impairs the endothelial cell barrier and promotes inflammation-related plaque development. AGE-RAGE activation may diminish endothelial nitric oxide synthase, lowering NO synthesis, release, and bioactivity. This inhibition caused endothelial dysfunction and impeded vascular dilation and contraction [54]. The AGE–RAGE axis is connected to cardiac dysfunction. Long-term blood glucose elevation promoted non-enzymatic glycation of calcium (Ca^{2+}) homeostasis proteins such as SERCA and RyR. AGE-induced SERCA and RyR cross-linking hinders Ca^{2+} handling, affecting heart contraction and relaxation and causing diastolic dysfunction [55].

Neurodegenerative Diseases

Amyotrophic lateral sclerosis, Parkinson's disease (PD), Alzheimer's disease (AD), and prion disorders are among the most frequent neurodegenerative diseases. Their defining features include the progressive loss of neurons or neural tissue, as well as aggregated protein buildup in the brain. Extracellular amyloid β-peptide plaques and neurofibrillary tangles (NFTs) inside the cell made up of α-synuclein, τ-protein, and a broken form of cellular prion protein are signs of AD, PD, and prion diseases [56]. AGEs aggregate adducts and causes oxidative stress, causing mitochondrial malfunction and cognitive impairment. Oxidative stress contributes to neurodegenerative illnesses because the brain uses a lot of glucose and oxygen to function [57]. Advanced glycation end products in AD promote glycated protein aggregation, which strengthens crosslinks throughout the brain. In senile plaques, this raises the degree of β-amyloid aggregation. It has also been shown that AGEs help with the processing of amyloid precursor protein (APP). This strengthens the cell death pathway and raises the expression of SIRT1, which makes SIRT1 less protective in neuronal cells. Also, RAGE is one of two proteins that let β-amyloid that hasn't been broken down yet cross the blood-brain barrier and connect with the bloodstream. The other protein is called "receptor-related LDL protein" LRP [58]. The presence of several readily glycated Lys residues in the protein's sequence facilitates the α-synuclein's aggregation,

which contributes to the development of Parkinson's disease. AGEs increase the quantity of aggregated α-synuclein and, as a result, the development of Parkinson's disease by forming crosslinks [59].

Cancer

According to studies, AGEs have pro-inflammatory and pro-oxidant properties and may stimulate the receptor for advanced glycation end products (RAGEs), which may aid in the development of cancer [60,61]. Some potential pathways can account for the detrimental effect of AGEs and their involvement as a significant contributor to the beginning and progression of cancer. As previously stated, glycation and oxidation of proteins and lipids lead to the generation of AGEs. When advanced glycation end-products (AGEs) bind to their receptors (RAGE), they activate two signaling pathways: phosphoinositide 3-kinase (PI3K)/Akt and nuclear factor (NF)-kB. This can lead to the development of chronic illnesses, including cancer. Additionally, AGEs can take part in auto-oxidation processes, generate free radicals, and produce ROS. This can cause an imbalance between ROS and antioxidant defense at the cellular level, which leads to the buildup of free radicals and oxidative stress [62]. By affecting DNA, proteins, and lipids, the free radicals change cellular processes and trigger the development of tumors. By inducing oxidative stress, ROS produced by AGEs through mitochondrial activation weaken the antioxidant defenses. Glycation stress is therefore also a major contributor to the development of cancer [63]. Deng et al. found that in patients with colorectal cancer, glucose-derived AGEs caused invasion and metastasis [64]. AGE levels have been found to be higher in the serum of breast cancer patients than in healthy women [65]. Also, high intake of dietary AGE may contribute to increased breast cancer [66]. When prostate cancer cells were treated with exogenous AGE in vivo, it induced RAGE dimerization in stimulated fibroblasts and stromal cells, which allowed the cancer cells to survive and increase their ability to migrate. However, the proliferation of AGE-driven cancer cells was stopped by RAGE reduction in stromal cells. This suggests that AGEs-RAGE play a part in the interaction between tumor cells and tumor-associated fibroblasts/stroma, which leads to the development and spread of cancer [67]. In normal cells, AGE/RAGE-driven oxidative stress mediates biomolecular damage and induces apoptosis. In cancer cells, it inhibits apoptosis (anti-apoptotic) through autophagy induction, which induces resistance and metastasis [68]. AGEs contribute to cancer development by upregulating genes such as NOX-2, NF-κB, SP-1, MMP2, MMP9, and Bcl-xL, while downregulating NRF-2, Bcl-2, and p53. Most RAGE downstream factors produced by AGE-RAGE binding affect cancer genesis, progression, and metastasis. The combination of AGE and RAGE enhances glycolysis, glucose metabolism, invasion, metastasis, and angiogenesis by increasing HIF-1α expression, allowing cancer cells to adapt to their environment [69]. A prostate cancer mouse fed an AGE-rich diet had increased cancer cell migration and RAGE-mediated sustenance. RAGE inhibition in tumor stroma inhibited AGE-driven cancer development. Thus, AGE-exposed cancer cells activated RAGE in tumor-associated stroma, promoting cancer progression [67].

Methods of Measuring AGE Products

Instrumental and immunochemical techniques are two ways to identify and measure AGEs in biological materials. High-performance liquid chromatography coupled with mass spectrometry (HPLC/MS), gas chromatography coupled with mass spectrometry (GC-MS), liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS), spectrofluorometry, HPLC with fluorescent detection, and a method based on ultra-high-pressure liquid chromatography (UHPLC) are among the instrumental methods. Western blotting and the enzyme-linked immunosorbent assay (ELISA), which use antibodies specific to particular AGE structures, are the two primary immunochemical techniques [70].

Therapeutic Targeting of AGE Products

Medications that target AGEs fall into two primary categories: those that can break down the AGEs that have already formed and those that would prevent AGEs formation.

AGE product formation inhibitors

By scavenging AGE precursors, the experimental medication aminoguanidine (also known as pimagedine) prevents the production of AGE. Its two essential functional groups—a guanidino group and a nucleophilic hydrazine group—allow it to engage irreversibly with dicarbonyls, particularly glyoxal, methylglyoxal, and 3-deoxyglucosone. In diabetic animal models, it has been shown that aminoguanidine's scavenging action can reverse diabetic nephropathy by lowering albuminuria and renal vascular damage [71]. Autoantibody production, anemia, flu-like symptoms, and, in rare cases, crescentic glomerulonephritis are among the adverse effects linked to the usage of aminoguanidine. These might be connected to further biological roles of aminoguanidine. In essence, aminoguanidine is a strong scavenger of several metabolites, such as pyridoxal phosphate, pyruvate, and glucose, in addition to being a dicarbonyl scavenger and a strong inhibitor of inducible nitric oxide synthase and diamine oxidase [72]. By chelating copper and other transition metals that can contribute to the generation of ROS, aspirin has also been demonstrated to scavenge free carbonyl groups and lower AGE levels by targeting preformed intermediates [73]. Metformin, a biguanide that is widely used to treat DM2 patients as an antihyperglycemic medication, has been associated with significant anti-inflammatory and antioxidant qualities. Because of its structural resemblance to AG and its demonstrated ability to react with α-dicarbonyl compounds, metformin can be used as an inhibitor of AGEs, limiting the posterior formation of AGEs [74]. The late stage of the glycation process is inhibited by vitamins such as pyridoxamine, thiamine pyrophosphate, and its lipophilic derivative

benfotiamine, which prevent the conversion of Amadori products into AGEs. Their effects are, however, distributed across multiple levels. Thiamine pyrophosphate and benfotiamine enhance transketolase enzyme activity, facilitating the pentose phosphate pathway and inhibiting the buildup of glycolytic metabolites such as fructose-6-phosphate and glyceraldehyde-3-phosphate, which contribute to the formation of intracellular advanced glycation end products (AGEs) [75]. Chelation of transition metals, including Mg^{2+}, Cu^{2+}, and Zn^{2+}, serves as an additional approach to inhibit the formation of AGEs, since these metals favor the development of AGEs by acting as catalysts of oxidation processes under hyperglycemic conditions. In this regard, it has been found that the inhibitory effects on the production of AGEs are caused by the antioxidant and metal-chelating properties of certain antihypertensive drugs, such as losartan and valsartan. These traits have also been connected to decreased AGE plasma levels [76].

AGE product breakers

Chemicals that break down AGE protein crosslinks return proteins to their natural state and reverse their damaging effects. N-phenacylthiazolium bromide (PTB) and its derivative ALT-711, or alagebrium, can cleave AGE-AGE crosslinks, which keep AGEs bound to tissue proteins like collagen and elastin. Their specific mechanisms depend on how they react with the carbonyl groups in AGE crosslinks, which encourages spontaneous carbon–carbon bond breakage at physiological pH [75]. MnmC, an enzyme involved in bacterial tRNA modification, can catalytically restore the natural structure of lysine to the AGEs CEL and CML, according to an experiment. These drugs, especially alagebrium, have reduced arterial stiffness, blood vessel fibrosis, atherosclerosis development, cardiovascular disease, hypertension, and kidney damage in animal models [77]. TRC4186, another AGE cross-link breaker, demonstrated safety and tolerability in human subjects during a phase I clinical trial. TRC-4149 demonstrates promising efficacy in rectifying diabetes-related issues in both in vitro and in vivo studies. In phase I clinical trials, it had an excellent safety profile when administered orally as a single dose or in multiple doses. However, so far, no viable AGE breaker candidate suitable for medicinal use has been identified, despite ongoing efforts to develop innovative therapeutic alternatives [78].

Antagonism via RAGE-binding

The negative impacts of AGEs can potentially be mitigated by agents that inhibit their binding to RAGE. This antagonism may operate by inhibiting RAGE expression, disrupting RAGE-mediated intracellular signaling, or elevating plasma levels of circulating sRAGE, which can function as a decoy receptor to sequester AGEs. Among the most prominent examples of contemporary drugs that have been demonstrated to accomplish these objectives are statins and thiazolidinediones [75]. Both have demonstrated a reduction in RAGE expression in vivo as well as increased serum levels of sRAGE, in addition to their potential as lipid-lowering and oral hypoglycemic medicines. Some hypotheses suggest that increasing PPAR-γ can reduce proinflammatory cytokines and RAGE production by inhibiting ERK1/2 phosphorylation and suppressing NF-KB activation [75]. Furthermore, azeliragon, an oral RAGE antagonist, has demonstrated potential in the treatment of chronic complications of diabetes mellitus, such as diabetic retinopathy, in animal models of the disease. It has been demonstrated to be safe and efficacious at low doses in a variety of clinical trials (NCT02080364) [79]. GLP-1 and its homolog, exendin-4, are also being studied. A number of experiments have shown that they can lower the production of ROS and the expression of RAGE by blocking NF-KB and NADPH oxidase. As a result, these discoveries have been linked to minimizing the damage caused by AGE-RAGE axis activation in conditions such as diabetic retinopathy, atherosclerosis, and diabetic cardiomyopathy [80].

Conclusions

Progressive accumulation of AGEs in organs and tissues can damage cells, disrupt physiological processes, and lead to diabetes, cardiovascular disease, neurodegenerative diseases, chronic kidney disease, and metabolic disorders. AGEs are a class of compounds that are created by non-enzymatic glycation, known as the Maillard reaction. Multiple chemical mechanisms are involved in the development of AGEs. By trapping and crosslinking protein or interacting with their receptor RAGE, AGEs cause tissue and organ damage, oxidative stress, inflammatory reactions, and death. A novel approach to minimizing harm to target organs and enhancing patient quality of life may result from the development of drugs that either block the activity of these molecules, reduce their concentration, or oppose the AGE–RAGE axis. Because AGEs are believed to be better indicators than HbA1c, measuring them has also become more significant.

Conflict of interests

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