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Review Article

Glycation End-Products and their Receptors: Pathophysiology and Therapeutic Targeting in Diabetes Mellitus

Hussain Saad Abdulrahman[1]*, Naza Mohammed Ali Mahmood[2]

[1] *Department of Pharmacy, Shaheed Salah Teaching Hospital, Sulaimani, Kurdistan Region, Iraq*

[2] *Department of Pharmacology and Toxicology, College of Pharmacy, University of Sulaimani, Kurdistan Region, Iraq*

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Abstract

Diabetes mellitus (DM) impairs cell metabolism and function in a variety of organs, increasing the risk of pathologies in organs such the kidney, neurological system, and eye, as well as fragility fractures. Advanced glycation end products (AGEs) are chemical moieties created by long-term hyperglycemia that interact with specific AGE receptors (RAGEs) to affect cellular metabolism and/or function. Some of the clinical effects of DM on cellular metabolism and organ function through the AGE-RAGE signaling pathway were detected through PubMed searches using the keywords "advanced glycation end product "RAGE", "sRAGE", "DM", and "complications." Tables were created for all published experimental and clinical research. Diabetic sequelae such as nephropathy, neuropathy, retinopathy, and osteopathy are all linked to AGE-RAGE signaling. Some clinical outcomes in diabetic individuals could be attributable to the effects of AGE-RAGE signaling. The AGE-RAGE signaling system, on the other hand, has some beneficial effects in a variety of tissues, including an increase in osteogenic function. As a ligand decoy, soluble RAGE (sRAGE) may increase in either RAGE production or destruction, and it cannot always reflect AGE-RAGE signaling. The AGE-RAGE axis can be targeted using a variety of drugs. They can also mitigate the negative outcomes. Although recombinant sRAGE can block the AGE-RAGE signaling pathway, it has numerous drawbacks, including AGE accessibility, an increase in other RAGE ligands, and a lengthy half-life (24 hours). It's linked to the loss of AGE/positive RAGE's effects. As a result, sRAGE is not a useful marker for assessing the RAGE signaling pathway's activation. Due to its limitations, recombinant sRAGE cannot be used in clinical practice.

Keywords: AGEs, Diabetes Mellitus, DM complications, RAGEs

النواتج النهائية لتفاعل الغلوزة ومستقبلاتها: الفيزيولوجيا المرضية والاستهداف العلاجي في علاج مرض السكري

الخلاصة

يضعف داء السكري استقلاب الخلايا والوظائف في مختلف أعضاء الجسم، مما يزيد من خطر اعتلال أعضاء مثل الكلى والجهاز العصبي والعين، فضلا عن هشاشة العظام. المنتجات النهائية المتقدمة للغليكة هي مركبات كيميائية تنتج عن فرط السكر في الدم على المدى الطويل والتي تتفاعل مع مستقبلات محددة للتأثير على وظائف الخلايا. تم الكشف عن بعض الآثار السريرية لداء السكري باستخدام الإشارات AGE-RAGE خلال عمليات البحث في PubMed وباستخدام الكلمات الرئيسية "المنتج النهائي لعملية التصلب الجانبي المتقدمة و "المضاعفات". و تم إنشاء جداول لجميع البحوث التجريبية والسريرية المنشورة حول الموضوع. من تبعات السكري اعتلال الكلى، والاعتلال العصبي، اعتلال الشبكية، واعتلال العظام، وكلها مرتبطة بأشارات AGE-RAGE. يمكن أن تعزى بعض النتائج السريرية في الأفراد المصابين بالسكري إلى تأثير ارتباط نواتج الغلوزة مع مستقبلاتها، من ناحية أخرى، لديه بعض الآثار المفيدة في مجموعة متنوعة من الأنسجة، بما في ذلك زيادة في وظيفة العظام. يمكن استهداف محور AGE-RAGE باستخدام مجموعة متنوعة من الأدوية. على الرغم من أن المستقبل الذائب يمكن أن يمنع مسار الإشارة AGE-RAGE ، إلا أنه يحتوي على العديد من العيوب. ونتيجة لذلك، فأنها ليست مفيدة لتقييم نشاط مسار هذا الأرتباط، وعليه لا يمكن استخدام المستقبل المؤتلف في التجارب السريرية.

* **Corresponding author**: Hussain S. Abdulrahman; Department of Pharmacy, Shaheed Salah Teaching Hospital, Sulaimani, Kurdistan Region, Iraq; Email: hussein.alzadi90@gmail.com

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INTRODUCTION

Fast food, which is high in carbohydrates and calories, and canned food, which has many additives such as colors, flavors, and taste, are both influenced by modern lifestyles. Elevated plasma glucose levels are caused by consuming such kind of diets [1]. As a result, metabolic illnesses including diabetes and obesity are more common in developed and industrialized countries. Diabetes Mellitus (DM) is a category of metabolic illnesses caused by insulin insufficiency (T1DM), insulin resistance (T2DM), or a combination of both. Its complications represent a global burden in terms of both health and economics [2]. Over the previous few decades, the rate of global propagation has increased rapidly. According to the International Diabetes Federation (IDF), there are approximately 400 million people worldwide aged 18 to 98, and the number of adult diabetic patients is expected to rise in the next decades. Adults diagnosed with diabetes are anticipated to number more than 650 million by 2045, due to a variety of factors including poor fast food consumption, lifestyle changes, lack of physical activity, and urbanization [3,4]. Diabetes Mellitus claimed the lives of around 1.6 million individuals worldwide in 2015 [5]. DM has a significant morbidity rate due to the vast spectrum of catastrophic consequences. Many organs and tissues are affected by chronic hyperglycemia, which is caused by a lack of insulin or insulin resistance. It causes major side effects such as nephropathy, neuropathy, retinopathy, and, most notably, cardiovascular events [6,7]. Increased protein glycation and gradual elevation of advanced glycated end products (AGES) in the tissues are caused by hyperglycemia. They were important in the development of DM Complications [8]. Diabetic people are four times more likely than non-diabetic persons to develop peripheral vascular diseases [9].

GLYCATION REACTION

The reaction between the carbonyl group of carbohydrates and an amino acid group of various substances such as protein, DNA, and lipids is known as glycation. The glycation process can take place in one of two ways: The first is enzymatic-dependent glycation, such as glycoprotein formation, while the second is non-enzymatic-dependent glycation (glycosylation), such as the chemical interaction between reducing sugar and proteins, as shown by the reaction of glucose with protein lysine residues to create ketoamine (Amadori adduct). The Maillard reaction is a non-enzyme-dependent reaction between the reducing sugar and amino acid terminus of proteins that occurs frequently during food processing. In the food, these complicated processes result in the creation of a brown products [10]. There are three stages of the non-enzymatic glycation process: initial, middle, and final [11]. The glycation process produces reversible unstable Schiff base through a covalent link between carbonyl and amino residue in the first stage, at a high temperature. The latter undergoes an Amadori reaction, which results in the formation of Amadori rearrangement products (ARPs), which are colorless and UV-insensitive [12]. ARPs reactions are pH-dependent reactions in the intermediate stage [11]. When ARPs are converted to furfural and hydroxymethyl furfural at pH 7, they mostly progress (HMF). Meanwhile, ARPs are converted to dehydroreductones and reductones at pH > 7 and low temperatures, resulting in the synthesis of aldehydes and aminoketones. After UV absorption, the color of the products changed to yellow at this stage. When the pH is greater than 7 and the temperature is high, additional compounds such as glyoxal (GO), methylglyoxal (MG), and diacetyl derivatives are generated. After UV absorption, the color of the products may turn yellow [13]. Many chemical reactions, such as condensation, dehydrogenation, isomerization, and rearrangement, create brownish low molecular weight (LMW) and high molecular weight (HMW) nitrogen polymers in the end stage. Melanoidins are the end products of browning without the need of enzymes. They are not to be confused with melanins, which are the end products of enzymatic activities [11]. The glycation process and the generation of glycation end-products happened at the same time [12]. Fournet *et al*. showed that the glycation process played a role in the pathophysiology of age-related non-communicable chronic illnesses affecting numerous organs [14].

ADVANCED GLYCATION END PRODUCTS (AGEs)

Advanced glycation end products (AGEs), also known as glycotoxins, is a broad word that refers to the molecules formed when a reducing sugar reacts with amino acid residues in proteins, lipids, and nucleic acids without the assistance of enzymes (Maillard reaction). Furthermore, excessive AGEs production might trigger and increase the process of oxidative stress within cells [15]. Furthermore, various processes, including the oxidation of carbohydrates, lipids, and amino acids, can produce reactive aldehydes that covalently bond to proteins, resulting in AGEs formation. On the other hand, a high amount of reactive oxygen species (ROS) encourages the synthesis and accumulation of AGEs. Many *in vivo* investigations have shown that oxidative stress caused by AGEs overproduction causes a variety of brain damages that can lead to illnesses [16]. AGEs can be

produced exogenously or endogenously. Exogenous AGEs can be produced by consuming roasted or broiled foods at high temperatures, as well as processed foods. The non-enzymatic glycation reaction is aided by the higher temperature (Maillard reaction). This reaction occurs when the carbonyl group of a reducing sugar and the amino group of a protein combine to generate an unstable reversible compound. The resulted Schiff's base is subsequently subjected to the Amadori rearrangement procedure, which produces Amadori rearrangement products (ARPs). The pH and temperature of the rearrangement stage are also important. Finally, ARPs undergo a series of complicated processes such as condensation and isomerization, which result in the formation of AGEs [17]. Many different types of AGEs have been identified, including 3DG-H1, 3-deoxyglucosone-derived hydroimidazolone 1, N-carboxyethyl-arginine (CEA), N-carboxyethyl-lysine (CEL), N-carboxymethyl-arginine (CMA), carboxymethyl cysteine (CMC), N-carboxymethyl-lysine (CML), 3-deoxyglucosone- -2-oxoethyl] -lysine, glyoxal-derived lysine dimer (GOLD), HbA1c, methylglyoxal-derived hydroimidazolone 1 (MG-H1), methylglyoxal-derived hydroimidazolone 3 (MG-H3), methylglyoxal-derived imidazolium crosslink (MODIC), and methylglyoxal-derived lysine dimer (MOLD). These chemicals are utilized in food processing because they have unique qualities (aroma, taste, and flavor). They will be absorbed from the intestine and reach circulation when high AGEs containing foods are consumed. They have a negative impact on a variety of organs [20]. Furthermore, AGEs are eliminated in the urine within 48 hours, and high serum levels of AGEs have been documented in renal failure patients [21]. Endogenous AGEs can also be formed by endogenous non-enzyme-dependent glycation of lipids and proteins [22], which is aided by chronic illnesses including hypertension and diabetes [23]. The accumulation of AGEs has been shown to be a biomarker of aging and has been linked to poor outcomes in both DM therapy and surgical interventions [24]. The production and actions of AGEs are governed by two processes. The first functions by using an internal glycosylase system (glyoxalase I and II) to prevent the synthesis of dicarbonyl molecules [25]. The interaction of AGEs with particular receptors is the second process (sRAGE, esRAGE). As a result of the lack of an intracellular signal, such interactions inhibit the effects of AGEs [26]. The action of cellular enzymes and the antiglycation mechanism are involved in the repair of damaged proteins protect cells and tissues in healthy persons against the formation of AGEs and other hazardous substances [27]. Our bodies, on the other hand, have no control over the formation and accumulation of AGEs during illnesses [28]. Furthermore, Eisermann *et al*. found that the ubiquitin-proteasome system (UPS) and autophagy are two other mechanisms that contribute to the detection and elimination of AGEs in human bodies [29].

AGEs RECEPTORS (RAGEs)

AGEs aren't just thought of as indicators for aging, hyperglycemia, inflammation, and oxidative stress. Many pathophysiological disorders are caused by the interaction of AGEs with their receptors (RAGEs). Not all AGEs have the same affinity for RAGEs; nonetheless, methylglyoxal has a significant (high affinity) interaction with RAGEs [30]. RAGE is a transmembrane receptor for advanced glycation end products. It has an intracellular tail and a highly hydrophobic transmembrane domain, and an extracellular region with three immunoglobulin-like domains, one V-type and two C-type (C1 and C2) domains [31]. The V-type domain is required for ligand binding. RAGEs are now identified as soluble forms (sRAGE) and can be found in a variety of biological fluids, including plasma, synovial fluid, CSF, and bronchoalveolar fluid [32,33]. sRAGE isoforms include sRAGE1/2/3, esRAGE (endogenous soluble RAGE), and hRAGEsec, among others (human RAGE secreted). The synthesis of distinct sRAGE isoforms is attributed to alternative splicing and proteolytic cleavage processes, according to numerous studies [34]. The majority of circulating sRAGEs were produced by splitting off the full-length receptor's cell surface. Matrix metalloproteinases (MMPs) and disintegrin are primarily responsible for this expression [35]. The synthesis of sRAGE is also linked to the G-protein coupled receptor [36]. Meanwhile, esRAGE is a less common variant of RAGEs [37] that results from alternative splicing of a variant RAGE form. Other than AGEs, RAGE binds to a variety of ligands, including high mobility group protein B1, S100 calcium-binding proteins (e.g., calgranulin), amyloid protein, and amphotericin [38]. Furthermore, AGEs can bind to a variety of receptors without triggering intracellular signaling, as evidenced by their binding to sRAGE and esRAGE. These receptors include macrophage scavenger receptor types I and II (SR-A) [39], oligosaccharyl transferase-4 (OST-48 or AGE-R1) [40], Lectin-like oxidized LDL receptor-1 (LOX-1) [41], and protein (AGE-R3) [43]. The transmembrane receptor AGE-R1 or OST has an extracellular N-terminal domain and an intracellular C-terminal domain. It's known as a (translocon receptor) and is involved in the translocation of polypeptides across the membrane of eukaryotes [44], with AGE-R2 containing a tyrosine-

phosphorylated section anchored in the cell's plasma membrane and playing a role in intracellular signaling similar to the fibroblast growth factor receptor [42]. Patients with low levels of the soluble form of RAGE are more inclined to DM and cardiovascular illnesses, according to a research of 1201 participants done over 18 years [45].

The AGEs Role in the Pathogenesis of Diabetic Complications

Excessive AGEs production has been linked to microvascular and macrovascular problems in diabetic and non-diabetic patients. As a result, two approaches can be used to explain the pathophysiology of DM-related problems caused by high AGEs [46]. To begin with, AGEs can tangle with proteins and cause conformational changes, altering their functions and characteristics. Second, AGEs can trigger intracellular signals through receptor- or non-receptor-mediated pathways. Finally, these interactions result in an overproduction of inflammatory mediators such as cytokines and ROS [47-49]. AGEs have also been linked to atherosclerosis, since they reduced low-density lipoprotein clearance and increased the expression of a number of atherosclerosis-related molecules, including VEGF [50,49]. Furthermore, AGEs have the ability to interact with particular receptors (RAGEs), which are involved in the pathophysiology of DM complications. The development of the AGE-RAGE complex during hyperglycemia triggers a cascade of signals including TGF, NFkB, MAP kinase, and NADPH oxidases. As a result, E-selectin, vascular adhesion molecule-1, VEGF, and different pro-inflammatory cytokines such as IL-1 and IL-6 can be induced. TNF-α is highly induced by all of these signaling molecules. Vascular fibrosis, calcification, inflammation, prothrombotic effects, and vascular injury are all caused by them. These symptoms are comparable to those seen in diabetic nephropathy, neuropathy, retinopathy, and heart disease. Furthermore, when AGEs interact with macromolecules such as proteins, DNA, and the extracellular matrix (ECM), the structural conformation changes that ensue can have an impact on their biological function. As a result of the glycation process of DNA [51], the DNA-AGEs complex forms in diabetics, causing multi-neurological damage [52] and cancer [53]. The binding of AGEs to ECM changes the structure and biological behavior of ECM in DM. Meanwhile, crosslinking collagen I with AGEs alters tropocollagen's molecular structure and impairs normal tendon function [54,55].

DM-Related Cardiovascular Diseases

Cardiovascular disease is the leading cause of death among diabetics, particularly those with T2DM [56]. When diabetic individuals maintain their plasma glucose levels within acceptable ranges for up to 6 years, the risk of cardiovascular events decreases [57,58]. Patients with T2DMD are four times more likely than non-diabetic patients to develop heart failure [59], and the mortality rate from diabetes cardiovascular complications is very high, reaching 75% of DM patients [60]. Nin *et al*. found that the occurrence of deadly and non-lethal cardiovascular events is associated with the blood level of AGEs during a 12-year period in a study of 339 diabetic patients [61]. Furthermore, Hassen and colleagues conducted a cohort study with a large number of T2DM patients and found that high levels of AGEs (e.g., CML, CEL, Pentosidine) are strongly associated with the prevalence of cardiovascular disease [62]. According to various studies conducted over the last seven years, a high AGEs/RAGEs ratio has a considerable impact on the development of aging-related disorders such as atherosclerosis [63], endothelial dysfunction [64], hyperthyroidism [65], and chronic renal failure [66].

AGEs in DM-induced Cardiovascular Disease: Mechanistic Issue

The accumulation of high AGEs in a chronic hyperglycemic state was linked to a higher incidence of cardiovascular diseases [67], most likely due to the initiation of oxidative stress [68], protein kinase (PKC) induction [69], chronic inflammatory reactions [70], mitochondrial dysfunction [71], and RAS activation [72] (Table 1).

Oxidative Stress

Oxidative stress is a condition in which the body's oxidation and antioxidation mechanisms are out of balance. Because of the stimulation of NADPH oxidase, xanthine oxidase (XO), and nitric oxide synthase (NOS), it may have a deleterious impact on several cellular functions [73]. The etiology of DM complications is complicated by oxidative stress [15]. Chronic hyperglycemia activates a NADPH-dependent oxidase, which catalyzes the production of ROS. It can lower anti-oxidant activity both enzymatically (superoxide dismutase) and non-enzymatically (ascorbic acid) [74]. As a result, oxidative stress causes inflammation, endothelial dysfunction, cardiomyocyte hypertrophy, and myocardial fibrosis, which leads to a decrease in left ventricular compliance, diastolic dysfunction, heart failure, arrhythmia, and/or sudden death.

Table 1. Summary of the clinical studies on the role of AGEs and RAGEs in diabetic cardiovascular complications

Author/year	Method	Participants	Result	Conclusion
Koska *et al*. (2018) [95]	Implication of AGEs and oxidative products in 1) a sub cohort Veterans Affairs Diabetes Trial (VADT), and 2) nested case-control subgroup from the ACCORD study.	VADT *n*=445 ACCORD *n*= 271	In low MetOs, 107 participants show high CVD events, and highest incidence of CVD in the VADT study.	Individuals with long-term T2DM with low MetOs and high AGEs (glyoxal hydroimidazolones, or carboxymethyl lysine, or 3-deoxyglucosone hydroimidazolones) are more prone to CVD.
Saku *et al*. (2020)[97]	The AGEs-RAGE role in calcified AS pathophysiology was evaluated	*n*=124; 54 subjects with calcified AS; 70 control subjects without heart disease	Calcified AS remarkably had a higher level of AGEs, RAGEs, and RAGE expression than controlled subjects	AGEs and RAGE play a role in the pathophysiology of calcified AS, which act as a marker for calcified AS after aortic valve surgery.
McNair *et al*. (2016) [98]	Investigate the correlation between AGEs-RAGE and atherosclerosis in two groups of Caucasian patients	*n*= 95; Divided into high cholesterol and normal cholesterol groups	sRAGE associates with HDL, whereas in hypercholesterolemia it has a passive role related to LDL, triglycerides, total cholesterol, and MDA.	A strong relationship observed between hypercholesterolemia and sRAGE, AGEs, MDA. Elevated sRAGEs increased HDL levels, conversely in the low level of sRAGEs.
Reichert *et al*. (2017) [99]	Longitudinal cohort study over 3 years, to determine the association of peripheral sRAGE with the CVD.	*n*= 1009 individuals with CVD	MI 3.4%, stroke/TIA 2.4%, cardiac death 9.5%, death due to stroke 0.8%. The CVD recurrence was high in patients with sRAGE level >838.19 pg/ml.	Serum sRAGE impacted negatively CVD patients, and the research result disagrees with the hypothesis that presumes sRAGE has a protective role in CVD.
Manganelli *et al*. (2019) [100]	A cohort study in APS Caucasian patients to detect the correlation between high mobility (HMGB1)/sRAGE and the clinical manifestation in APS patients.	*n*=90; 60 subjects with APS: 25 with primary APS and 35 with APS+ SLE	In recurrent abortion individuals with APS, the serum of sRAGE elevated when compared with APS individuals without (control subject).	Both HMGB1 and sRAGEs were elevated in response to the increase in pro-inflammatory mediators and may have a role in autoimmune diseases. HMGB1 is useful in monitoring particular treatments such as antiaggregants.
Al Rifai *et al*. (2015) [101]	Community-based prospective cohort study. Evaluate the role of AGEs-RAGE in AF.	*n* = 1068 participants	Patients with low sRAGE levels are more prone to develop AF.	There is an inverse relationship between sRAGE and inflammatory markers. No significant data support the role of sRAGE in the incidence of AF.

Role of AGEs in Atrial Stiffness

A 2018 study found a substantial link between AGEs and arterial wall stiffness, arrhythmias, systolic and diastolic dysfunction, congestive heart failure, coronary artery disorders, and the risk of in-stent restenosis [75]. The binding of the glycated forms of elastin and laminin with AGEs is responsible for all of these alterations. It has been linked to reducing nitric oxide (NO) generation through modifying cell-matrix interactions and weakening endothelial cell adhesion qualities [75]. Furthermore, the interaction of AGEs with cellular proteins that control intracellular Ca^{+2} levels (e.g., the sarcoendoplasmic reticulum Ca^{+2}-ATPase pump and the ryanoid receptor) alters Ca^{+2} concentration and disrupts cardiomyocyte contraction and relaxation, resulting in irregular diastolic tone [76].

Role of AGEs on Atherogenicity

AGEs can also crosslink with circulating biomolecules, changing their properties in recognizing and processing receptors, such as the glycation of apolipoprotein B100, which is linked to foam cell generation and atherosclerosis due to a reduction in LDL receptor capacity and an increase in circulating LDL-c [77,75]. Glycation of fibroblasts also causes the fibrinolytic process to be disrupted [75].

Role of AGEs in Endothelial Dysfunction and Inflammation

The accumulation of AGEs in endothelial cells has been linked to a decline in endothelial function. It may play a role in the onset of cardiovascular diseases. In this context, AGEs suppress NOS expression and reduce NO production, resulting in the accumulation of asymmetric dimethyl arginine (ADMA). It will exacerbate the thrombotic tendency and accelerate the evolution of arteriosclerosis [75,78]. AGE-RAGE signaling also activates many intracellular pathways, resulting in the production of pro-inflammatory cytokines (e.g., IL-6, TNF-α, TGF-β), vascular adhesion molecules (VCAM-1, ICAM-1, ET-1), and ROS, all of which are linked to the establishment of

vascular inflammation [79]. Other receptors that AGEs can interact with include lipoxygenase-1 (LOX-1) and galactin-3 [80,81], and they can also boost LOX-1 expression, which is involved in atherosclerosis and cardiovascular diseases. The interaction of methylglyoxal hydroimidazolones 1 (MG-H1) with RAGEs upregulates ROS and intracellular adhesion molecules (ICAM) expression in human umbilical vein endothelial cells (HUVECs), according to Ishibashi *et al*. (2017). THP-1 (macrophage) adherence to HUVECs was also engaged in the inflammatory process and was thought to be an indication of atherosclerosis [82]. According to this findings, AGEs may play a role in cell damage by stimulating vascular endothelial growth factor (VEGF), plasminogen activator inhibitor (PAI-1), and thrombosis development [83].

Role of AGEs in Vascular Smooth Muscle Cells Function

The development of the AGEs-RAGEs complex changes the physiologic function of the vascular smooth muscles and contributes to atherosclerosis [84]. The biological cell cycle was disrupted by the buildup of AGEs in blood vessels and activation of the ERK/MAPK and Akt/mTOR pathways, which altered cellular proliferation by inducing death and autophagy [84]. Furthermore, RAGE expression enhances the formation of ROS, which activates NADPH oxidase and activates P38 MAPK [85], upregulates matrix metalloproteinase (MMP2/MMP9), and increases migratory capacity and lipocalin-2 expression [86]. Increased ROS expression promotes the transcription of receptor activator of NFκ-B ligand (RANKL), which leads to bone formation differentiation [87]. As a result, diabetic people are more likely to develop osteoporosis and have a higher risk of fractures [88,89].

Role of AGEs in Platelets Activation and Aggregation

Overexpression of AGEs and their interaction with RAGEs on the platelet membrane can affect platelet function, modifying platelet function through a cascade of intracellular events [90]. In this regard, AGEs promote platelet aggregation by modifying the phospholipid content of the cell membrane [91], increasing glycoprotein GPIIb [92], overexpressing ROS, and enhancing COX action and thromboxane A formation, which are the primary factors in microthrombus formation [93]. Maugeri and colleagues have revealed another platelet aggregation route involving the interaction of HMGB1 with neutrophil RAGE, which leads to activation of autophagolysosomes via the MAPK pathway [94].

DIABETIC NEPHROPATHY

Because of end-stage renal disease, diabetic nephropathy has a significant mortality and morbidity rate (102,103). Through auto-oxidation, glycosylation, and polyol pathways, both endogenous and exogenous AGEs contributed to affecting nephron biological processes and altering their structure [104]. Hyperglycemia promotes the synthesis of AGEs, which causes tubular endothelial cells to produce plasminogen activator inhibitor 1 and transglutaminase mRNA, allowing fibrosis-exacerbating macrophages to thrive [105]. Furthermore, activation of the AGEs receptor results in the production and release of pro-inflammatory cytokines and free radicals, which worsens nephropathic consequences by changing the glomerulus function [106]. In addition, lipid metabolism, RAS, systemic, and glomerular hypertension all had a role in the onset and progression of diabetic nephropathy [107]. Many investigations have shown that AGE levels in the blood are significantly linked to diabetic nephropathy, glomerulopathy, and mesangial cell proliferation [108,109]. After degradation by macrophages or extracellular proteolytic enzymes, AGEs are excreted through the renal pathway, yielding low molecular weight (LMW) AGEs (Table 2). However, high molecular weight AGEs may resist these enzymes by covering the enzymes' target site, resulting in the formation of LMW AGEs that are completely different from natural LMW AGEs [110-112].

DIABETIC NEUROPATHY

Diabetic neuropathy (DN) is a progressive disorder induced by chronic hyperglycemia that affects 30 to 50 percent of diabetic people [116]. It's possible that severe DM is linked to a loss of sensation in peripheral tissues, as well as an increased risk of infections like diabetic foot, which can lead to amputation [117]. Uncontrolled hyperglycemia contributes to the development of DN via several pathways, including the polyol route, the AGEs-RAGEs axis, the PKC pathway, and the hexosamine pathway [118,119]. Hyperglycemia activates the polyol pathway, in which glucose is converted to sorbitol by an aldose-reductase enzyme. This reaction depletes cellular NADPH, which lowers cytoplasmic antioxidants like glutathione (GSH) [120], inhibits the role of glyceraldehyde-3-phosphate dehydrogenases (GAPDH) in glycolysis pathways, and is linked to the activation of the hexosamine pathway through increased aggregation of GAPDH metabolites [119]. Furthermore, AGE accumulation and binding with RAGEs in nerves cause oxidative stress and the production of ROS, which leads to NFκB-induced

apoptosis and neuronal injury [121]. Furthermore, AGE accumulation was linked to metabolic alterations in Schwan's cells, which led to cell death [122]. Diabetic neuropathy was strongly linked to PKC activation of PKC pathways by diacylglycerol after prolonged hyperglycemia [123]. Meanwhile, aggregation of hexosamine pathway proteins has been associated to diabetic neuropathic problems, with dyslipidemia perhaps playing a role [124]. Al-Sofiani *et al*. reported a substantial link between sRAGE and high-frequency hearing loss in 2019 [125].

Table 2. Clinical and animal studies on the role of AGEs and RAGEs in diabetic nephropathy

Type of Study	Method	Participants	Result	Conclusion
Human study Normand *et al* (2018) [113]	Prospective, randomized, cross-over trial; evaluate the role of AGEs in renal hemodynamic variations. Renal perfusion and oxidative metabolism were assessed by PET [^{15}O]H_2O and [^{11}C].	*n* = 10 healthy subjects	High-AGEs diet significantly increased renal perfusion, while low-AGEs diets do not show significant results. Oxygen consumption increased in high-AGEs diets.	Only high-AGEs contents are associated with renal hemodynamic changes with exacerbation of diabetic nephropathy.
Animal study Haraguchi *et al* (2020) [114]	Analyses of renal tubular lesions of early-stage diabetic kidney in (STZ)-induced DM animal model	*n* = 6 mice	STZ induces renal tubules apoptosis. AGEs accumulated in renal glomeruli and renal tubules, and RAGE expression increased compared with control kidneys.	The AGEs-RAGE axis is strongly associated with proximal renal tubules in the diabetic kidney.
Human study Perkins *et al*. (2020) [115].	Prospective case-control study	*n* = 85 subjects, 30 T1DM patients without albuminuria, and 22 patients with microalbuminuria and GFR decline, 33 subjects with microalbuminuria without GFR decline	Urinary excretion of pentosidine in MA subjects had a higher rate than NA subjects and higher in low GFR than normal GFR with or without MA. G-H1 and CMA increased and decreased respectively in MA with or without GFR decline.	The fraction excretion markedly higher in T1DM subjects with MA and decreased GFR compared with T1DM with or without MA. Elevated fraction excretion of AGEs may act as a clinical manifestation of depleted cation transport of the kidney.

DIABETIC RETINOPATHY

Diabetic retinopathy (DR) is a progressive condition that causes structural and functional loss of the retina and is the leading cause of blindness in adults and the elderly [126]. In the chronic condition, it is characterized by retinal vascular damage exhibited as blood-retina barrier breach and inducing the development of new vessels. Mild DR microaneurysms are the most common symptom; second, moderate DR with exudate, hemorrhage, and microvascular abnormalities; and third, severe DR microvascular damage with more than 20 hemorrhagic foci. Neovascularization was observed during the proliferative period, which results in neural and retinal vessel injury [128]. Retinal cells consume a lot of oxygen and are particularly vulnerable to oxidative stress and the generation of ROS, especially in hyperglycemic circumstances that change retinal structure and function. Inflammatory alterations, mitochondrial dysfunction, cell death by apoptosis, and gradual neurovascular injury of the retinal tissue are all triggered by these processes [129]. The polyol pathway was activated during hyperglycemia, resulting in increased expression of the Aldo-reductase enzyme, which is responsible for the synthesis and aggregation of sorbitol in the retina, causing edema and altering the blood-retinal-barrier function [130]. The expression of VEGF, which plays a key role in angiogenesis, increased permeability, and increases pro-inflammatory mediators, increased during the ischemia situation. All of these pathways have a role in DR pathogenesis [131]. Excessive production of AGEs, which are also involved in damaging retinal pericytes and bipolar cells [132], activates the hexosamine pathway, which negatively influences the connection between retinal pigmented endothelial cells, increases vascular permeability, and disrupts retinal vasculature [133,134]. Many studies have found that uncontrolled glycemic states are the primary cause of DR, and that managing hyperglycemia, blood pressure, and lipid profile has a good impact on reducing deterioration and the

occurrence of retinal complications [135]. By producing ROS through the stimulation of various processes such as polyol and hexosamine and PKC pathways, oxidative stress plays a significant role in the pathogenesis of DR [136]. The synthesis of sorbitol and the consumption of NADPH are facilitated in DM by activation of the polyol pathways. This has been linked to the activation of aldose reductase and sorbitol dehydrogenase [137], which causes NADPH levels to drop [138]. Obrosova *et al*. found low levels of NADPH and ATP in diabetic rats' lenses, while significant quantities of sorbitol and fructose were found [139]. New blood vessels proliferate and vascular permeability changes under hyperglycemic or hypoxic situations as a result of diacylglycerol (DAG), which is produced by the polyol pathway, stimulating the PKC pathway (PKC Ca^{+2} and DAG dependent kinase) [140,141]. Because the rate of glycation rises in hyperglycemia, the synthesis of AGE precursors was abnormally high. Meanwhile, AGEs increased VEGF and pericyte apoptosis, and AGEs-RAGEs binding increases ROS production, depletes superoxide dismutase (SOD) and catalase, and alters the antioxidant activity of both GSH and ascorbic acid [142]. Furthermore, hyperglycemia can cause inflammatory reactions that raise cytokine levels as well as the creation of hydrogen peroxide, which helps NFκB develop. VEGF, COX2, MCP1 (monocyte chemotactic proteins), VCAM, and ICAM expression was considerably increased at this stage [131,143]. Meanwhile, COX2 increases the synthesis of PGs, stabilize HIF-1, and supports the expression of VEGF, NF-KB, and COX2; this pathway has been implicated in the formation of retinal aneurysms [144]. Furthermore, Tao *et al*. found a link between the hypoxic state of retinal micro-capillaries and the formation of AGEs, which predisposes to angiogenic processes [145]. Meanwhile, Kanda *et al*. discovered AGE accumulation at the optic peripheral nerve [146-148]. AGEs were found to play a significant role in the pathogenesis of several ocular illnesses in the cornea [149-153], lens [154-157], vitreous humor [158,159], and optic nerve [160,161], according to several investigations.

BONE METABOLISM

Diabetics are more likely to fracture bones because persistent hyperglycemia changes bone metabolism, composition, and inhibits fracture healing [162]. Due to increased levels of glycated collagen and AGE aggregation in the bone, many variables contribute to altered bone metabolism and bone dysfunction (e.g., oxidative stress, depleted IGF-1, an elevated level of Sclerotin, and decreased bone density) [162,163]. The activation and potentiation of inflammatory and oxidative stress pathways by the AGE-RAGE axis played a key role in the impairment of bone metabolism [164]. Furthermore, the AGEs-RAGEs axis and RAGEs ligands disrupt bone remodeling [165], as well as cytokines (TGF-β and IGF-1) during osteoblast development [166]. AGEs (Pentosidine) have been discovered in the bone cells of diabetic patients [167]. Both osteoclasts and osteoblasts are affected by AGEs, with osteoclastogenesis induced by overexpression of RANKL mRNA and osteoblast downregulation impacting the mineralization process [168-170]. Furthermore, depending on the concentration of human fetal osteoblastic cells (hFOB), AGEs have a protective and destructive effect on hFOB cells. At low concentrations, it preserves hFOB cells by inducing osteoblastic cells to function and dropping osteoclastic function cells out, whereas at high concentrations, it has the opposite effect [171]. Glycated collagen has a lower ability to attach to osteoblasts via discoidin domain receptors (DDR2) and integrin receptors [172], resulting in lower lysyl oxidase synthesis. AGEs enhance collagen synthesis, while a decrease in collagen leads to rapid breakdown [173]. AGEs-modified proteins, on the other hand, interact with RAGEs to limit collagen synthesis in fibroblasts; moreover, increased pro-inflammatory cytokines affect collagenase production [174]. In diabetic individuals, resistance to glycated collagen degradation causes a decrease in the amount of C-telopeptides of type 1 collagen (CTX-1), as well as depletion of osteoblast, and a decrease in collagen synthesis causes a decrease in the level of N-terminal propeptide of type I collagen (P1NP) [175]. Table 3 summarizes various human studies on the effects of diabetes on bone metabolism.

Conclusion

AGEs are heterogeneous chemical compounds that are formed when sugar reacts with macromolecules, either enzymatically or non-enzymatically. RAGE develops as a result of intrinsic cellular signaling induced by AGEs. The formation of AGE/RAGE and diabetes complications share a number of risk factors. The inhibition of several pathogenic alterations in the setting of DM could be due to an AGE-RAGE interaction. sRAGE levels can be raised as a result of excessive RAGE production or degradation, and it doesn't always reflect AGE-RAGE signaling. Targeting the AGES-sRAGE axis (Table 4) could be a good strategy to reduce the consequences of the AGE-RAGE signaling pathway in many tissues and organs damaged by long-term hyperglycemia, however it can't be used in clinical practice due of the limitations.

Table 3. Clinical studies on the role of AGEs and RAGEs in DM-induced disturbance of bone metabolism

Author/year	Method	Number of participants	Result	Conclusion
Rabelo *et al*. (2018) [176]	Analysis of cortical fractal dimension and lacunarity, and collagen crosslinks content in cortical bone.	35 postmenopausal women femoral neck sample; 17 with fracture; 18 with OA and carcinoma.	Increase in the pentosidine femoral neck of osteoporotic fractures independent of age.	Bone quality and risk of hip fracture are associated with the level of Pentosidine. Increased pentosidine worsen the quality of bone and the incidence of hip fracture increased.
Tamaki *et al*. (2018) [177].	A prospective cohort study to evaluate the utility of serum pentosidine and esRAGE levels as predictors of fragility fractures.	1,285 Japanese men aged ≥65 years	The crude fragility fracture HRs (95% CI) PEN 1.56 (1.05–2.31) esRAGE 0.79 (0.54–1.15) esRAGE/PEN 0.65(0.44–0.95).	The high level of sRAGE/pentosidine was associated with a reduced risk of fractures.
Vaculik *et al*. (2016) [178] .	A cohort study to measure serum & bone pentosidine levels in femoral neck fracture and advanced hip osteoarthritis using HPLC.	111 patients undergoing hip surgery; 70 with a femoral neck fracture and 41 with advanced hip osteoarthritis.	Serum and bone pentosidine levels were elevated in both fractured and arthritis patients.	There is a significant relationship between pentosidine level and hip fracture and osteoarthritis. Pentosidine can be a biomarker for assessing the quality of bone.
Furst *et al*. (2016) [88]	A cross-sectional study to determine the impact of AGEs on bone materials strength in T2DM patients.	35 postmenopausal women; 16 with T2DM and 19 controls.	AGEs level was highly correlated with decreased bone material strength and lower bone formation marker.	T2DM alters bone materials strength.
Farley *et al*. 2016 [179]	A cross-sectional, case-control study to determine whether bone matrix from fracturing and non-fracturing T1DM contained more AGEs than bone from healthy patients.	15 subjects; 5 fractured with T1DM; 5 T1DM without fracture; 5 healthy subjects	The fractured with T1DM had a high level of AGEs (Pentosidine) than the other groups.	Bone structure and density in T1DM are affected by a high level of AGEs (Pentosidine).

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Conflicting interests

Nothing declared.

Data sharing statement

N/A

Table 4. Studies on pharmacological targeting of the AGEs-RAGEs axis to treat diabetes mellitus

Medication	Targets	Type of Study	Study Outcomes
Spironolactone [115]	AGEs-RAGEs axis inhibitors	An animal study using male Sprague-Dawley rats	Protect agaist diabetic-nephropathy by hindering the AGEs-RAGEs complex and increase SIRT-3 expression.
Catalpol (Iridous glucoside) [116]	Anti-inflammatory Anti-apoptotic Anti-oxidant	Review of 100 publications	Reduces nephropathy, cardiopathy, and neuropathy.
Resveratrol [117]	Anti-inflammatory Antioxidant	Review of 21 clinical trials	Attenuates production of IL-1β, iL-6, TNF-α, and inducible nitric oxide synthase, and COX2
Glucopyranoside [118]	AGEs formation inhibitor	Animal study, Zebrafish	Potent antiglycative
Irbesartan [119]	Angiotensin II receptor antagonist	An animal study using male rats	Decrease cardiopathy through decreasing AGEs and expression of RAGEs.
Fluorofenidone [120]	Inhibitor of p38 MAPK, TNF-α, and TGF-β.	Animal Study using four weeks old mice	Alleviates nephropathy reducing ROS and modulating the mitochondrial function.
Hesperetin [119]	Inhibits AGEs formation with anti-inflammatory activity	An animal study using male rats	Nephroprotection via inhibiting AGEs formation, and decrease RAGEs expression in endothelial cells.
Interleukin-10 [119]	Anti-inflammatory Immune-regulatory	Animal study using male rats	Preserves the Schwan's cells by inhibiting the phosphorylation of NF-$_K$B.
SGLT-2 inhibitor, phlorizin analogs [121]	Na^+-glucose cotransporter 2 inhibitor	A meta-Analysis of five large clinical trials	Cardio and renal protection via inhibition of the AGE-RAGE axis.
Zafirlukast [122]	Interleukin receptor antagonist	Human primary chondrocytes	Attenuates the development and progression of OA by decreasing AGEs
FPS-ZM1 and Valsartan [123]	Selective RAGE inhibitor and ARB	An animal study using male rats	Synergistic effect to prevent worsening of diabetic nephropathy.
Pyridoxamine (B6) [124]	Glycation process inhibitor	An animal study using male rats	Blocks RAGE-NF-$_K$B/ERK pathway and attenuates diabetic neuropathic pain.
Aminoguanidine [125]	AGEs and advanced oxidative protein product inhibitor	An animal study using male rats	Preserves against cardiac fibrosis through interrupting the AGEs-RAGE axis.
Glycine [180]	Antioxidant	An animal study using rats	Restrains production of AGEs and inhibits the RAGE.
Metformin [181]	Antihyperglycemic agent	Human study	Blocks AGEs formation; decreases inflammation, and elevates the esRAGE.
Dulaglutide GLP-1 analog [182]	Antidiabetic agent	In vitro study using hSW1353 cell line.	Regulates AGE-induced inflammation and damage in chondrocytes.
Vitamin D [183]	Supplement	A clinical trial	Attenuates the onset of cardiovascular complications after 3 months.

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