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Review Article

A review of the formation and role of advanced glycated end products and their receptor in the progression of diabetic complications

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Abstract

In diabetic type 2, a persistent hyperglycemic state leads to the formation of covalent adducts via a non-enzymatic reaction between glucose and proteins. The reaction is called glycation reaction, results in the formation of a heterogeneous group of compounds called Advanced Glycated End Products (AGEs), which play a crucial role in the initiation and progression of diabetic complications. The glycation reaction disrupts the normal functions of molecular conformation and changes the activities of various enzymes by altering receptor functioning. The AGEs accumulate in different tissues and the circulating blood of a person. AGEs play a significant role in accelerating the receptor expression for AGEs that cause various diabetic complications via different mechanisms by disrupting molecular conformation, interfering with the functioning of receptors, and intra- and extracellular crosslinking. AGEs for crosslinking with other endogenous molecules, such as lipids and proteins, contribute to the development of diabetic complications. The chief receptor for the AGEs is the Receptor for Advanced Glycated End Products (RAGE). The RAGE/AGE signaling activates different pathways such as NF-Kb, MAPK/ERK, and TGF-β. This review aims to recapitulate the formation of AGEs and the role of AGE/RAGE receptors in the progression of diabetic complications. The pathophysiological cascade activated by AGEs has a dominant role in the onset of complications associated with diabetes. This review may help in offering therapeutic interventions to lower the formation of AGEs and slow down the progression of complications related to Diabetes Mellitus.

Keywords: AGEs; Diabetes; Diabetic complications; RAGE

Introduction

Diabetes Mellitus is a group of metabolic diseases characterized by abnormal functioning of the pancreas that can either produce insufficient insulin or stop producing insulin. Diabetes Mellitus type 2 (T2DM) is one of the most frequent global diseases, with around 350 million cases reported in 2014. This number is expected to increase dramatically shortly, resulting in serious health, economic, and health challenges. Chronic diabetes results in hyperglycemia, one major factor leading to diabetic complications **[1]**. It is estimated that 90% of the cases of diabetes are type 2, and only 5-10% have type 1. Patients with diabetes have a greater risk for macroangiopathies like cerebrovascular, cardiovascular, and low extremity arterial diseases **[2]**. Persistent hyperglycemia is an essential factor in

leading to Diabetes type 2-related complications [3]. The exact mechanism involved in the role of hyperglycemia in the onset and progression of diabetes-related pathogenesis and complications is not understood clearly yet. Nevertheless, the glycation of proteins is an advanced hypothesis in this regard [4].

Insulin resistance and hyperglycemia affect different organs and tissues, resulting in complications in the organs and systems. These complications can be micro and macro, such as Diabetic macroangiopathies, which include issues in the coronary arteries, peripheral arteries, cerebral arteries, renal arteries, and diabetic microangiopathy, including diabetic nephropathy and diabetic retinopathy [5]. These micro and macrovascular complications adversely affect the quality of life of a person with diabetes. The death risk is higher in diabetic patients due to major adverse cardiovascular events than in non-diabetics [6]. Individuals with type 2 diabetes are more likely to develop cardiac failure than non-diabetic people [7]. Various factors and mechanisms play a role in the progression of complications such as AGES. These advanced glycated end products produce reactive oxygen species (ROS), which initiates oxidative stress intracellularly [8]. In turn, the elevated level of reactive oxygen species helps the production of AGEs, thereby forming a vicious cycle between AGEs and oxidative stress [9]. Individuals with diabetes are more prone to developing several severe health issues and to avoid or lower these complications preventing vascular complications is the crucial goal. Diabetes type 1 and type 2 have shown that hyperglycemia plays a significant role in the progression of nephropathy, neuropathy, and retinopathy [10]. The question here is what consequences are caused due to hyperglycemia? Multiple studies have shown a direct correlation between the development and progression of diabetic vascular disease and diabetes-associated complications [11]. The mechanisms through which the increased level of glucose in the body leads to tissue damage are complicated and involve more than one mechanisms. The formation of Reactive Oxygen Species (ROS) occurs due to various mechanism such as increased production of advanced glycation products, direct glycation of lipids, an enhanced expression of receptors for Advanced Glycated End Products AGEs, and higher activation of polyol, hexosamine, and protein kinase C pathways. The (Fig. 1) shows the five pathways involved in Reactive Oxygen Species (ROS) production [12].

This review focuses on the Advanced Glycated End Products (AGEs), the formation of AGEs and their role in metabolic dysfunction in diabetes Mellitus. The primary aim of this review is to summarize the molecular mechanism of AGEs and their role in the pathogenesis of complications associated with Diabetes Mellitus.

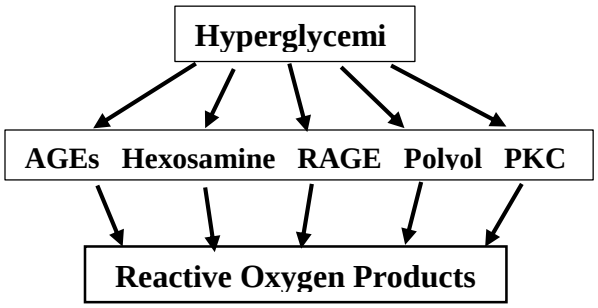

Figure 1. Five pathways involved in ROS production

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Advanced glycated end products (AGES)

Advanced Glycated End Products (AGEs) are a heterogeneous group of macromolecules produced by the Maillard reaction. It is a non-enzymatic reaction between the carbonyl groups of reducing sugars and the free amino groups of proteins. During the Maillard reaction, a Schiff base is produced that rearranges into Amadori compounds which later undergo irreversible condensation and dehydration reactions resulting in the production of AGEs that are yellowish-brown with odor **[13]**. The reactions involved in the formation of AGEs are produced from dicarbonyl compounds formed due to autoxidation and degradation of various products such as Methylglyoxal, α-hydroxy aldehydes, 3-deoxyglucosone, and others. The Maillard reaction comprises three stages, i.e., Initial, intermediate, and late. In the initial stage, different reducing sugars such as galactose, mannose, fructose, pentose, and xylulose react with the free amino groups of amines, forming a Schiff base after rearrangement forms the Amadori product. The degradation of this Amadori product occurs in an intermediate stage, resulting in the production of reactive dicarbonyl compounds such as deoxyglucose, glyoxal and Methyl Glyoxal. The last stage consists of irreversible glycation resulting in the formation of Advanced Glycated End Products (AGEs). These AGEs gather on long-lived proteins and impair the physiological function of these proteins **[14]**. The stages involved in Maillard's reaction are shown in (Fig 2).

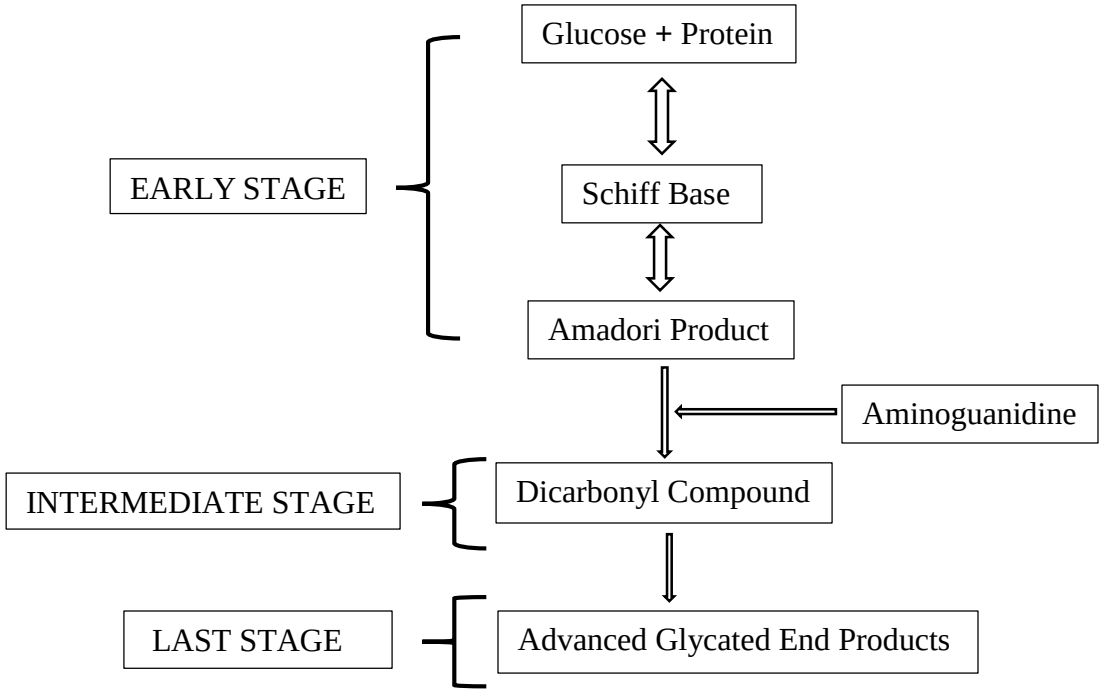

Figure 2. The three stages of Maillard Reactions

In the Maillard reaction, the critical phase is the formation of intermediate products during the rearrangement of Amadori. When Amadori breaks, it gives alpha dicarbonyl, Methylglyoxal, and 3-deoxyglucosone. The formation of Advanced Glycated End Products (AGEs) increases as a person ages, accumulating in the skin, pericardial fluid, and collagen of a person. AGEs are an essential factor that causes the pathogenesis

of diabetes and different complications associated with it [15]. In case of chronic hyperglycemia, Advanced Glycated End Products (AGEs) are produced actively and accumulated in various tissues along with the circulating system, which results in complications in various organs of the diabetic. Besides Endogenous, exogenous Advanced Glycated End Products (AGEs) such as smoke, diet, and tobacco, also enter the human body. The formation of AGEs is enhanced by prolonged heating and microwave cooking [16]. Food processing especially heating for extended periods, has an enhancing effect on the production of lipo-oxidation and glycol-oxidation products. Advanced Glycated End Products level is also reported through inflammatory markers to be higher in smokers and patients with a high diet that contains Advanced Glycated End Products [17].

The accumulation of AGEs in the body is either exogenous or endogenous [18]. Advanced Glycated End Products are present in various edible items and cigarette smoke. The use of dry heat technology in the thermal processing of food, such as baking, frying, barbecuing, and use of microwave heating results in the formation of these products. Glycotoxin is another food-derived AGE formed due to food processing to increase the safety, flavor, and conservation of food. Advanced Glycated End Products (AGEs) are heterogeneous, and their heterogeneity depends on the structure of protein-bound AGEs that states their modification to that particular protein. AGEs also accumulate in the body of diabetic patients through the excretion of AGEs via defective renal function because plasma levels of AGEs and renal clearance are inversely associated [19]. This slowly creates a cycle where the elevated pool of circulating AGEs in the plasma alters the structure and shape of different proteins and binds with specific receptors. Besides endogenous sources of AGEs, it is also accumulated in the body via an exogenous route where harmful products in different food lead to AGE accumulation. Different food processing methods, including microwaves, sterilization processes, and heating, lead to the generation of exogenous AGEs, which accelerate the Maillard reaction. It is well-established that dietary AGEs are linked with the plasma level of AGEs which, as a result, promotes the oxidative, degenerative and inflammatory processes involved in the progression of many chronic illnesses [20]. 10-30 per cent of these dietary AGEs are absorbed in the circulatory system, but the mechanism of this absorption is yet to be understood [21]. Exogenous AGEs contribute significantly to the pool of AGEs in the body through the Maillard reaction. The advanced glycated products are produced from glucose-derived dicarbonyl precursors, which is why these are often accumulated intracellularly [21]. The formation of AGEs through non-enzymatic reactions is accelerated by hyperglycemia in diabetes. In chronic hyperglycemic conditions, these AGEs are produced increasingly and gathered in tissues and blood, leading to vascular complications in diabetics. A study by [22] evaluated the AGE level spectrofluorometrically and found that AGEs were 23 times higher in people with diabetes than in healthy individuals. Tissue-bound and circulating AGEs can be measured by different techniques such as Fluorescence spectroscopy (which utilizes fluorescence properties of AGE), MS-based method, Enzyme-linked immunosorbent assay (ELISA), high-performance liquid chromatography, and Gas chromatography [23].

Pathophysiology of the age-rage mediated pathway in diabetes-related complications

Different receptors have been discovered for AGEs. One of which is RAGE which plays a significant role in initiating intracellular signaling and disrupting cellular function by

binding to AGEs. Receptor for Advanced Glycated End Products (RAGE) is a receptor responsible for AGEs related to diabetic vascular complications that lead to activation of stress response resulting in cellular dysfunction and inflammation [24]. RAGE is a transmembrane receptor belonging to the immunoglobin superfamily composed of 404 amino acids. Besides AGEs, RAGE is characterized by binding to multiple ligands such as S100 calcium-binding proteins, amyloid-beta proteins, and high mobility proteins B1 and amphotericin [25]. Two primary mechanisms are involved in the pathophysiology induced by AGEs in Diabetes Mellitus. Advanced Glycated End Products (AGEs) harm cells either by trapping and crosslinking proteins or by binding to receptors on the cell surface and affecting it indirectly [26]. AGEs can impact the functions of a cell through binding with Toll-like receptors, pattern recognition receptors, scavenger receptors, and protein-coupled receptors [27]. The most crucial receptor on the cell surface is the RAGE (Receptor for advanced glycated end products) receptor. It was identified and named due to its ability to bind to AGEs. The characteristic of RAGE is that instead of specific amino acids, it can recognize 3-D structures, which is why it is considered the pattern-recognition receptor [28].

RAGE is a multi-ligand receptor that also interacts with members of the calgranulin family, amyloid-β peptide, high mobility group box-1, and beta-sheet fibrils in certain diseases, neurodegeneration, amyloidosis, cancer, and inflammation [29]. It is expressed in more than one cell type, such as T lymphocytes, smooth muscle cells, endothelial cells, monocytes, podocytes, dendritic cells, neurons, cardiomyocytes, and transformed cells [29]. Depending on the stimulus and cell type, RAGE activates various signal transduction cascades. Signal transduction is necessary for RAGE action because RAGE ligand-dependent actions are blocked when the cytoplasmic domain of RAGE deletion occurs. The effect of RAGE on the proliferation of T lymphocytes was studied in a human donor-reactive T lymphocyte study. The peripheral blood mononuclear cell incubated with sRAGE to block antibodies to RAGE showed a significant decrease in lymphocyte proliferation [30].

Reduced proliferative responses were observed after RAGE null OT II infusion into the OVA-immunized host [31]. An intriguing link has been found between the pathogenesis of type 1 diabetes, diabetic complications, and RAGE [32]. Ovarian tissue from women with polycystic ovarian syndrome showed increased RAGE, AGE, and activated NF-kB p65 subunits. Polycystic ovarian syndrome is linked with an increased risk of type 2 diabetes. In the study of PCOS, the increased expression of RAGE in macrophages and elevated levels of advanced glycated End products suggest that AGE-RAGE-dependent inflammation may be linked with the pathogenesis of type 2 diabetes and its complications [33]. In diabetes type 1 and type 2, RAGE ligands damage the pancreatic function resulting in hyperglycemia. Autoimmune attack on the beta cells results in infiltration of inflammatory cells and elevated release and expression of HMGBA and S100. Hyperglycemia causes the rapid production of AGEs, leading to the recruitment of RAGE in the target organ. Various ligands and AGEs damage cells, including smooth muscle cells, podocytes, cardiomyocytes, peripheral and nervous neurons, Muller cells in the retina, and endothelial cells. In type 2 diabetes, the increased blood glucose level leads to the generation of AGEs that develop inflammation, particularly in organs prone to complications [34].

The general mechanism involved in diabetic complications with significant contribution

from AGEs includes the formation of crosslinks between key molecules in ECM, leading to a permanent change in structure, change of cell function, and the interaction of AGEs and RAGE on the cell surface. AGEs can potentially change the properties of the large matrix protein collagen, laminin, and vitronectin through an intermolecular covalent bond between AGE=AGE and crosslinking on type 1 collagen and elastin [35]. When bound together, the RAGE and AGEs result in cellular dysfunction, which is called metabolic memory. Metabolic memory is a long-term effect of AGEs gathered previously. It can maintain the over-expression of RAGE, persistent activation of NFkB, start and progression of oxidative stress, and induction of tissue-specific inflammation. These are sustained even if hyperglycemia is reduced [36]. In diabetics, the hyperglycemic memory instigated by RAGE/AGEs is linked with the pathogenesis of diabetic complications. The interaction of AGE and RAGE facilitates the generation of oxidative stress, and activation of platelets and macrophages induces vascular inflammation and fuels the migration of inflammatory cells into the AGE-laden foci in diabetes. This shows the role of AGE and RAGE interaction in developing and progressing diabetes-associated vascular complications [37]. The cross-talk between diabetogenic factors such as improper diet, inflammation, lifestyles, hyperglycemia, AGE/RAGE axis, oxidative stress, and environmental factors contribute to the etiology of metabolic memory. These molecular changes are translated to epigenetic aberration by metabolic memory, which causes the expression of pathological genes linked with diabetes-linked complications [38, 39]. RAGE is also a soluble circulating isoform such as esRAGE (endogenous soluble RAGE) and hRAGEsec (human RAGE secreted). Multiple mechanisms are reported that result in the production of soluble proteins, splicing of mRNA to remove the transmembrane domain, and cell surface proteolytic cleavage [40]. The AGE-RAGE interaction results in the activation of signals through NFkB, NADPH oxidases, TGF- β, and MAP kinase, which starts the expression of vascular adhesion molecule-1, E-selectin, and different inflammatory cytokines such as TNF- α, IL-1β, and IL-6 [41]. When ligated, RAGE can upregulate the excess production of reactive oxygen species by reducing NADPH oxidase and activating various signaling cascades via MAPK, P13K, and Ki-Ras pathways that lead to the activation of the nuclear factor. This nuclear factor enhances the production of reactive oxygen species and results in damaged cell function and mitochondrial dysfunction. The hyperreactive immune cells elevate ROS production and inflammation, leading to complications and damage to organs like the eyes, kidneys, and heart [42].

Therapeutic agents and interventions to prevent age formation

Different strategies can be used as a pharmaceutical intervention to lower diabetic vascular complications. Various experimental studies have shown that pharmacological interventions that potentially interfere directly or indirectly with AGEs have beneficial effects on diabetic complications. Different agents can inhibit AGE formation. One of the first inhibitors of AGE formation was Aminoguanidine, a hydrazine compound. It acts as a nucleophilic trap for the intermediates of carbonyl. The reaction occurs with initial products of glycation and its derivate that are not bound to proteins such as 3-deoxyglucosone [43]. Aminoguanidine is known to prevent different diabetic complications, and HbA1c has been reduced in a clinical trial. Aminoguanidine used for people with type two diabetes has shown a reduction in proteinuria and retinopathy

progression in people with diabetes through a Placebo-controlled clinical trial [44, 45]. This agent lowers the ECM accumulation of laminin and fibronectin in streptozotocin-induced diabetic rats with diabetes-related nephropathy. It also lowers the AGE vascular accumulation and acts as a NOS inhibitor [46]. Another therapeutic agent is a derivative of Vitamin B6 called Pyridoxamine. This agent stops the breakdown of protein-Amadori intermediate to protein AGE product. In diabetic rat models, Pyridoxamine inhibits AGE formation by lowering hyperlipidemia, and it scavenges the carbonyl byproducts of lipid and glucose breakdown [47]. Another pharmacologic intervention for the inhibition of AGE formation is utilizing carbonyl traps. The well-known metformin has long been used for type 2 diabetes due to its potential to react with Methylglyoxal. This agent interferes with AMP-activated protein kinase to reduce the blood glucose level [48]. Cleavage of the AGE crosslink also lowers the formation of AGEs. The drugs used through this mechanism are called AGE-crosslink-breaking drugs. ALT711 is one of the most promising drugs used in this category. Different human and animal subjects have been given ALT711 (Alagebrium), which has been shown to improve diabetes-related complications. It lowers the myocardium's and arteries' stiffness related to diabetes [49].

To prevent the formation of AGE, the interaction between AGE and RAGE can be inhibited by using Eendin-4. It attenuates the development and progression of nephropathy in diabetic subjects [50]. The enzyme glyceraldehyde-3-phosphate dehydrogenase is inhibited by Poly ADP ribose Polymerase (PARP), leading to elevated AGE production. The inhibitor of PARP has been used to improve endothelial function, neuropathy [51], and diastolic function [52]. A derivative of vitamin B1, Benfotiamine plays a significant role in preventing the formation of AGEs by inhibiting the activation of three major pathways of hyperglycemia damage (Intracellular AGE formation, diacylglycerol-protein kinase C pathway, and Hexosamine Pathway. The mechanism for this agent is enhancing the activity of a rate-limiting enzyme of the non-oxidative pentose phosphate pathway transketolase [53]. Another choice to lower the AGE formation is the choice of diet and nutrition. High fat intake is rich in protein and fat, increasing AGE formation. Food that is cooked at high temperatures also increases the number of AGEs. A diet rich in AGEs results in elevated serum AGE levels and thus increases AGE-cross linking in patients with diabetes. Diabetic subjects who take a diet rich in AGEs have higher expression of VCAM-1, MAPK, and NF-αB compared to the subject that takes a diet with low AGE [54]. Therefore, a diet low in AGEs may help lower the AGE accumulation in the serum, and drugs may inhibit the absorption of these dietary AGEs like AST-120 [55].

Conclusion

Advanced Glycated End Products (AGEs) represent a heterogeneous group of compounds formed by the non-enzymatic reaction between protein and glucose. The glycation reaction increases in case of a persistent hyperglycemic state in diabetic patients. Advanced Glycated End Products are known to be a significant cause of diabetes-related complications. They can be formed exogenously through nutrition or endogenously due to hyperglycemia, lipidemia, and oxidative stress. Advanced Glycated End Products (AGEs) and AGE-RAGE interaction play a significant role in diabetes-related diseases; therefore, Modulating and preventing the formation of AGEs is a promising tool for reducing diabetic complications. Targeting the AGE-RAGE interaction and lowering the glycation of circulating advanced glycated end

products and proteins could be a preventive approach to delay or inhibit the onset of diabetic complications. Elucidated understanding of cellular receptors of AGE, biochemistry, and formation of AGE, and effects of AGE on intracellular and extracellular activities will pave the way for finding promising therapies to inhibit AGE formation, accumulation, and interaction with its receptor. Future research is needed to identify the therapeutic agent of promising pharmacological value that will inhibit AGE formation and help avoid diabetes-related complications.

Authors' contributions

Designed the study, did the literature review, and wrote and edited the manuscript: N Hassan.

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