

# World Journal of *Diabetes*

*World J Diabetes* 2023 August 15; 14(8): 1146-1329



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The primary aim of *World Journal of Diabetes* (*WJD*, *World J Diabetes*) is to provide scholars and readers from various fields of diabetes with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

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**INDEXING/ABSTRACTING**

The *WJD* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, PubMed Central, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2023 Edition of Journal Citation Reports® cites the 2022 impact factor (IF) for *WJD* as 4.2; IF without journal self cites: 4.1; 5-year IF: 4.5; Journal Citation Indicator: 0.69; Ranking: 51 among 145 journals in endocrinology and metabolism; and Quartile category: Q2.

**RESPONSIBLE EDITORS FOR THIS ISSUE**

Production Editor: *Yu-Xi Chen*; Production Department Director: *Xu Guo*; Editorial Office Director: *Jia-Ru Fan*.

**NAME OF JOURNAL**

*World Journal of Diabetes*

**ISSN**

ISSN 1948-9358 (online)

**LAUNCH DATE**

June 15, 2010

**FREQUENCY**

Monthly

**EDITORS-IN-CHIEF**

Lu Cai, Md. Shahidul Islam, Michael Horowitz

**EDITORIAL BOARD MEMBERS**

<https://www.wjgnet.com/1948-9358/editorialboard.htm>

**PUBLICATION DATE**

August 15, 2023

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**INSTRUCTIONS TO AUTHORS**

<https://www.wjgnet.com/bpg/gerinfo/204>

**GUIDELINES FOR ETHICS DOCUMENTS**

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<https://www.wjgnet.com/bpg/gerinfo/240>

**PUBLICATION ETHICS**

<https://www.wjgnet.com/bpg/GerInfo/288>

**PUBLICATION MISCONDUCT**

<https://www.wjgnet.com/bpg/gerinfo/208>

**ARTICLE PROCESSING CHARGE**

<https://www.wjgnet.com/bpg/gerinfo/242>

**STEPS FOR SUBMITTING MANUSCRIPTS**

<https://www.wjgnet.com/bpg/GerInfo/239>

**ONLINE SUBMISSION**

<https://www.f6publishing.com>

## Advanced glycation end products: Key mediator and therapeutic target of cardiovascular complications in diabetes

Savita Bansal, Archana Burman, Asok Kumar Tripathi

**Specialty type:** Endocrinology and metabolism

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0  
Grade B (Very good): B, B  
Grade C (Good): C  
Grade D (Fair): 0  
Grade E (Poor): 0

**P-Reviewer:** Ma JH, China; Rojas A, Chile

**Received:** January 29, 2023

**Peer-review started:** January 29, 2023

**First decision:** March 1, 2023

**Revised:** March 21, 2023

**Accepted:** May 22, 2023

**Article in press:** May 22, 2023

**Published online:** August 15, 2023



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### Abstract

The incidence of type 2 diabetes mellitus is growing in epidemic proportions and has become one of the most critical public health concerns. Cardiovascular complications associated with diabetes are the leading cause of morbidity and mortality. The cardiovascular diseases that accompany diabetes include angina, myocardial infarction, stroke, peripheral artery disease, and congestive heart failure. Among the various risk factors generated secondary to hyperglycemic situations, advanced glycation end products (AGEs) are one of the important targets for future diagnosis and prevention of diabetes. In the last decade, AGEs have drawn a lot of attention due to their involvement in diabetic pathophysiology. AGEs can be derived exogenously and endogenously through various pathways. These are a non-homogeneous, chemically diverse group of compounds formed non-enzymatically by condensation between carbonyl groups of reducing sugars and free amino groups of protein, lipids, and nucleic acid. AGEs mediate their pathological effects at the cellular and extracellular levels by multiple pathways. At the cellular level, they activate signaling cascades *via* the receptor for AGEs and initiate a complex series of intracellular signaling resulting in reactive oxygen species generation, inflammation, cellular proliferation, and fibrosis that may possibly exacerbate the damaging effects on cardiac functions in diabetics. AGEs also cause covalent modifications and cross-linking of serum and extracellular matrix proteins; altering their structure, stability, and functions. Early diagnosis of diabetes may prevent its progression to complications and decrease its associated comorbidities. In the present review, we recapitulate the role of AGEs as a crucial mediator of hyperglycemia-mediated detrimental effects in diabetes-associated complications. Furthermore, this review presents an

overview of future perspectives for new therapeutic interventions to ameliorate cardiovascular complications in diabetes.

**Key Words:** Type 2 diabetes mellitus; Cardiovascular complications; Hyperglycemia; Advanced glycation end products; Reactive oxygen species; Oxidative stress; Endothelial cells; Receptor of advanced glycation end products; Anti-advanced glycation end products strategies

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**Core tip:** Cardiovascular diseases (CVDs) in type 2 diabetes mellitus impose a clinical and an economic burden on the healthcare system. Early diagnosis of diabetes may prevent its progression to complications and decrease its associated comorbidities. The present manuscript reports the clinical relevance of estimating advanced glycation end products (AGEs) in diabetes. The deleterious effects of AGEs include many important biochemical reactions central to the development and progression of cardiovascular complications in diabetes. Therefore, AGEs are one of the important targets for future diagnosis and prevention of diabetes. The epidemiology of CVD in diabetes, AGEs as a crucial mediator of diabetic CVD, and an overview of different strategies for countering the accumulation of AGEs is discussed along with new therapeutic interventions to ameliorate their effects.

**Citation:** Bansal S, Burman A, Tripathi AK. Advanced glycation end products: Key mediator and therapeutic target of cardiovascular complications in diabetes. *World J Diabetes* 2023; 14(8): 1146-1162

**URL:** <https://www.wjgnet.com/1948-9358/full/v14/i8/1146.htm>

**DOI:** <https://dx.doi.org/10.4239/wjd.v14.i8.1146>

## INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a cluster of metabolic disturbances consequent to non-utilization of glucose due to insufficient production/secretion of insulin or its resistance. T2DM poses a major threat to global health. The number of people with T2DM is increasing at an alarming rate and has become one of the leading causes of death worldwide. The upsurge is corresponding with rising obesity, aging populations, increasing urbanization, calorie dense diets, economic development, and reduced physical activity. The global prevalence of diabetes as described by the International Diabetes Federation in 2021 was estimated to be 536.6 million (10.5%) and it is projected to reach 783.2 million (12.2%) by 2045[1]. Prevalence is expected to be higher in urban areas compared to rural ones. The estimated global cost of diabetes is slated to rise from 966 billion USD in 2021 to 1054 billion USD by 2045[1,2]. Consequently, T2DM imposes both a clinical and an economic burden on the health care system. DM is a complex pathophysiological process associated with several disabling and life-threatening health problems. Since DM basically affects blood vessels, it can affect almost any part of the body. People with diabetes are at risk of developing several complications affecting the heart, eyes, kidneys, and nerves. Vascular dysfunction is the single most serious consequence of long-standing DM[3,4] resulting in debilitating morbidity and mortality due to cardiovascular diseases (CVDs)[5,6]. The CVDs that accompany DM include stroke, myocardial infarction, peripheral artery disease, and coronary thrombosis[7].

Early diagnosis of DM may prevent its progression to CVD and decrease its associated comorbidities. Persistent hyperglycemia is considered to be an important factor in the development and the progression of diabetic complications and the exact mechanism of the deleterious effects of hyperglycemia on the onset of diabetic complications is still being explored[8]. Numerous hyperglycemia-induced mechanisms have been hypothesized to account for vascular complications in T2DM. These include the hexosamine pathway, polyADP-ribose polymerase activation, protein kinase C (PKC) activation, aldose reductase-mediated polyol pathway, and enhanced formation of advanced glycation end products (AGEs)[9-11]. Among these, the AGE-mediated pathways have been explored in the last decade because of mounting evidence that AGE accumulation is the crucial factor in the progression of diabetic complications[12,13]. AGEs are heterogeneous compounds resulting from nonenzymatic reactions of reducing sugars with other biomolecules such as lipids, proteins, and nucleic acid. This nonenzymatic glycation of proteins, lipids and nucleic acids is a slow and complicated process depending on the relative concentrations of the reactants. The moderate presence of AGEs has been noticed in healthy individuals whereas, its formation increased under hyperglycemic conditions[14]. The severity of the complications in T2DM through AGEs corresponds with the quantum of hyperglycemia and varies with the structural and functional changes generated in most macromolecules. Also, AGEs interact with their receptors namely the receptor of AGEs (RAGE), and trigger the activation of multiple signals that can affect cellular functions and metabolism through upregulation of inflammation and oxidative stress[15,16].

The importance of AGEs in diabetic CVD is corroborated by the fact that the serum level of AGEs in T2DM CVD patients is higher compared to DM patients without CVD[17,18]. Studies have shown the association of AGEs with the prevalence as well as pathophysiological mechanisms of CVD in T2DM[19-21]. Jia *et al*[22] found that the tissue level of AGEs was independently associated with cardiac systolic dysfunction in T2DM patients with heart failure compared to T2DM patients without heart failure[22]. *In vitro* studies have shown that treatment of cardiomyocytes with AGEs for 24

h significantly reduces calcium transient in cells due to increased reactive species (RS) production[23]. Elevated serum AGEs predicted increased mortality due to CVD in Finnish women with DM who were followed up for 18 years[24]. In a recent review article by Dozio *et al*[25], the involvement of glycation in cardiovascular remodeling causing molecular, cellular and interstitial changes in the heart and vessels through different mechanisms has been demonstrated[25]. In a cross-sectional study carried out by De la Cruz-Ares *et al*[26] in 540 subjects, AGE levels and intima-media thickness of carotid arteries was consistently observed to be higher in CVD patients with T2DM[26]. Ninomiya *et al*[27] highlighted the importance of AGEs as a screening marker of atherosclerosis[27]. The AGE-RAGE axis further activates the pathological inflammation in plaques and atheromas[28]. Ren *et al*[29] identified the inhibition of prostacyclin in endothelial cells by the AGE-RAGE system, which promotes the formation of plasminogen activator inhibitor (PAI)-1 contributing to the stabilization of thrombus formation by inhibiting the fibrinolytic activity[29].

This review focuses on summarizing the clinical relevance of AGEs in CVD development and progression in T2DM. Different anti-AGE strategies are also being discussed that may become potential candidates for future preventive and therapeutic strategies in diabetic CVD.

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## EPIDEMIOLOGY OF CVD IN T2DM

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Current trends in the epidemiology of CVD in T2DM present an underlying connection between chronic and uncontrolled T2DM and vascular complications[30]. T2DM poses a major risk for the development of CVD and T2DM-associated mortality[5]. Prevalence of coronary artery diseases, peripheral vascular diseases, and carotid artery disease has been observed in different macrovascular complications in T2DM[31]. Numerous epidemiological studies suggested that T2DM can accelerate atherosclerosis and increase the incidence of heart attacks and strokes[31,32]. Patients with T2DM have a two- to six-times higher risk of heart failure than non-T2DM patients and heart failure accounts for > 50% of deaths in T2DM patients[6,33,34]. CVD is a major comorbidity affecting about one-third of all people with T2DM. A cohort study carried out on 1.9 million people by Dinesh *et al*[35] identified T2DM as a significant risk factor for CVD, including stroke, heart failure, atherosclerosis, and myocardial infarction[35]. T2DM patients are also prone to various cardiovascular risk factors, such as hypertension, dyslipidemia, and obesity that can directly promote the occurrence of cardiovascular complications in T2DM[36,37].

A cohort study carried out by Shah *et al*[33] demonstrated that the occurrence of peripheral artery diseases and heart failure was higher in T2DM by 16.2% and 14.7%, respectively[33]. Another cohort study carried out by National Health and Nutrition Examination Survey demonstrated that T2DM increases the risk of stroke by 26.3%, hemorrhagic stroke by 50% and ischemic stroke by 50% [32,38]. An American heart report of 2014 revealed a risk of heart failure of 40% in T2DM patients compared to patients without T2DM[39]. A prospective study showed that angina, coronary angioplasty, myocardial infarction, and congestive heart failure were among the predictors of all-cause mortality in T2DM[40]. A systematic review by Vaidya *et al*[41] has shown that 15%–81% of T2DM patients have at least one cardiovascular complication[41]. Einarson *et al*[42] confirmed that CVD imposes a substantial burden on the treatment of T2DM at both patient and population levels[42]. On an average patients treated for both CVD and T2DM resulted in an additional cost ranging from \$3418 to \$9705 compared to T2DM alone. Given the substantial economic and health burden of CVD in T2DM patients, there is a need to understand the mechanism of T2DM-CVD relationship and early diagnosis of T2DM to prevent its devastating complications.

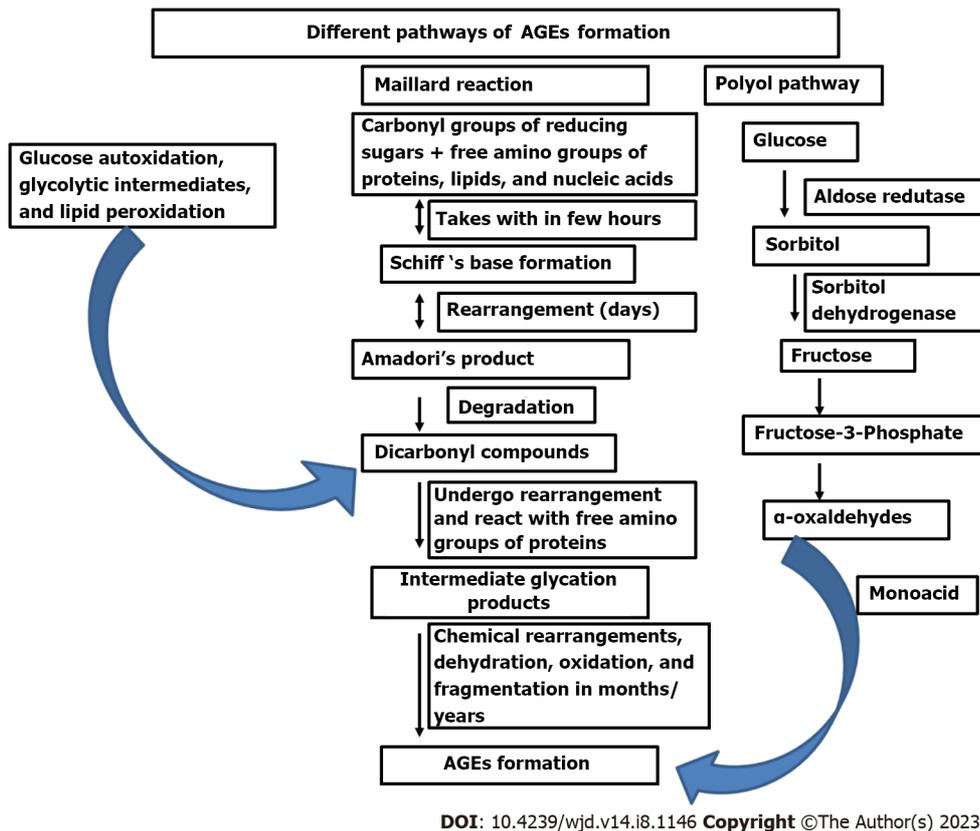
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## DIFFERENT PATHWAYS FOR AGEs FORMATION

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AGEs are chemically modified complex group of heterogeneous molecules formed either exogenously or endogenously by different pathways specifically, Maillard reaction, polyol pathway, and oxidation reactions (Figure 1). The Maillard reaction was first described in 1912 by French Scientist Louis Camille Maillard as “browning reaction” due to the associated yellow-brown color change when reducing sugar was heated with amino acid[43]. The AGEs formed through the Maillard reaction secondary to hyperglycemic condition is under intense investigation since a positive correlation is found with vascular complications like CVD, retinopathy, neurodegenerative diseases and other parameters of aging[44-46]. Maillard glycation reaction is different from enzymatic N-/O-linked glycosylation of proteins since they produce crosslinked products obtained from spontaneous and nonenzymatic action of reducing sugars or their derivatives on other molecules, altering the structure and function of important cellular and extracellular components[47,48]. In healthy individuals AGEs are formed minimally and are cleared efficiently from the system. Formation and accumulation of AGEs becomes more rapid and pronounced under hyperglycemic conditions, oxidative stress, inflammatory conditions, and obesity[9,16]. AGE levels are higher in aged individuals, due to either overproduction or slower clearance indicative of their pathophysiological implications[49,50].

Accrual of AGEs is a multistage process starting with covalent binding of functional groups of monosaccharides to free amino groups of proteins, lipids, and nucleic acids forming labile reversible Schiff base intermediates under a hyperglycemic environment. This reaction is reversed if the hyperglycemia abates timeously. The initial Schiff's base transforms over a period of days to a ketoamine, called Amadori's product. The Amadori products are more stable, but the reaction is still reversible. The most well-recognized Amadori product is glycated hemoglobin, which is widely used as a reliable marker of glycemic control. Amadori products can be degraded into a variety of dicarbonyl compounds like 3-deoxy-glucosone, glyoxal and methyl-glyoxal, which can further react with proteins to form intermediate glycation products. Yellow-brown irreversible AGEs are formed after a sequence of chemical modifications including dehydration,



**Figure 1 Pathways for endogenous advanced glycation end products formation.** Formation of AGEs occurs through different pathways. Maillard reaction which occurs at three stages: (1) Covalent binding of reducing sugars to free amino groups of proteins, lipids, and nucleic acid resulting in reversible Schiff base formation within hours; (2) it undergoes chemical rearrangement over a period of days to form a more stable Amadori product (the reaction is still reversible); and (3) Amadori's products can be degraded into many reactive dicarbonyl compounds undergoing chemical rearrangements leading to the formation of irreversible AGEs. These spontaneous rearrangements are slow and often taking months to years but enhanced in presence of oxidative stress, and metal ions. Autoxidation of glucose and the peroxidation of lipids into dicarbonyl derivatives also results in AGEs formation. Monosaccharides glycolytic intermediates and dicarbonyl compounds formed during glycolysis also play an important role in AGEs formation. Polyol pathway, where glucose is converted to sorbitol by the enzyme aldose reductase and then sorbitol is converted to fructose by the action of sorbitol dehydrogenase. Fructose metabolites are converted into  $\alpha$ -oxaldehydes and interact with monoacids to form AGEs. AGEs: Advanced glycation end products.

oxidation, and fragmentation reactions (Figure 1). These spontaneous rearrangements are normally slow, often taking months to years. Nevertheless, the presence of oxidative stress, metal ions, and other catalysts can substantially increase the post-Amadori formation of AGEs. They are stable and accumulate inside and outside the cells and some of them have fluorescent properties[9,12,16].

Besides the Maillard reaction, other pathways such as the Hodge pathway, Namiki pathway and Wolff pathway can also result in AGEs formation, through autoxidation interactions of Amadori products, monosaccharides (glucose, fructose, ribose and glyceraldehyde) with amino acids and lipids[16,51-53]. Besides monosaccharides, the reactive products formed during glycolysis can also form AGEs by attacking proteins and other components. Some of the important glycolytic intermediates identified in AGEs formation are glyoxal, methylglyoxal, glucose-6-phosphate, triose phosphates, glyceraldehydes-3-phosphate and dihydroxy-acetone phosphate and 3-deoxyglucosone[54,55]. Auto-oxidation of glucose, reaction between glycolipid and arginine/lysine also results in AGEs formation through glyoxal and methyl-glyoxal production[56,57]. The Polyol pathway where, enzymatically formed metabolites of glucose like sorbitol and fructose also contributes significantly to AGEs formation[58,59]. The free ribose formed during the degradation of nucleic acid also represents the main source of pentosidine formation[60].

Also, sugars vary in their susceptibility to the Maillard reaction, where D-glucose is less reactive and D-fructose is more reactive sugar as demonstrated in both thermally processed food and *in vivo* conditions[53,61,62]. Temperature also has a significant effect on early glycation product formation, where high temperature (120–180°C) accelerates the Maillard reaction in processed food, and the same reaction for Amadori's product formation *in vivo* conditions require much longer time[63].

Exogenous formation of AGEs through glyco-oxidation and lipo-oxidation reactions formed from heating food at high temperature and chemical processing, tobacco smoke components and other pollutants also contributes to the chemical load of AGEs. Blood and tissue AGE levels have been consistently observed to be higher in smokers and in patients on high AGEs diets compared to non-smokers and controls on low AGE diets[64-67]. Ingestion of exogenous AGEs has been shown to exacerbate diabetic complications like CVD in animal models, hence their role needs further exploration[68,69].

## TYPE OF AGEs

Due to variety of precursors and numerous pathways of nonenzymatic reactions, the AGEs are diverse in their chemical structure and properties. AGEs comprise a large number of chemical structures like N-carboxy-methyl-lysine (CML), pyrrolidine, pentosidine, cross-linked AGEs include GOLD [glyoxal-derived lysine dimer, 1,3-di(*N*-lysino imidazolium salt)], MOLD [methylglyoxal-derived lysine dimer, 1,3-di(*N*-lysino)-4-(methyl-imidazolium salt)], DOLD [3-deoxyglucosone-derived lysine dimer, 1,3-di(*N*-lysino)-4-(2,3,4-trihydroxybutyl)imidazolium salt], *etc.*[16,70-72]. The best biochemical and immunohistochemically characterized AGEs found in humans are pentosidine, carboxyl methyl lysine and methylglyoxal, which accumulate and can potentially be used as biomarkers[73,74]. CML is the most well-characterized AGE demonstrated in DM patients with CVD[75]. Structure and function of matrix proteins are modified with variable loss of function due to the aggregation of these adducts. Some of these AGEs have native fluorescence which can be used for their identification and quantification.

## AGEs AND DIABETIC-CARDIOVASCULAR COMPLICATIONS

AGEs formed secondary to hyperglycemic conditions are gaining prominence as the underlying mechanism of CVD complications in T2DM. DM patients are known to have 20%–30% more circulating AGEs compared to controls, whereas DM patients with CVD complications have up to 40%–100% higher levels of AGEs[17,76]. The AGEs remain significantly high even after correction of variables such as duration of diabetes, sex, and age in T2DM patients with complications compared to those without complications[77,78]. Statistical analyses have also shown the association of AGEs level with the development and severity of atherosclerosis in DM patients[79,80]. Clinical reports have indicated that serum AGE levels can act as important marker or predictor of heart failure and CVD mortality in T2DM since their deposition has been detected in atherosclerotic plaques and heart muscles[81,82].

The deleterious effects of AGE-mediated cardiovascular complications in T2DM involve various pathological changes such as plaque formation, arterial stiffening, and generalized endothelial dysfunction aided by prothrombotic gene expression[83-85]. These detrimental effects of AGEs can be explained at the cellular and extracellular level as shown in Figure 2.

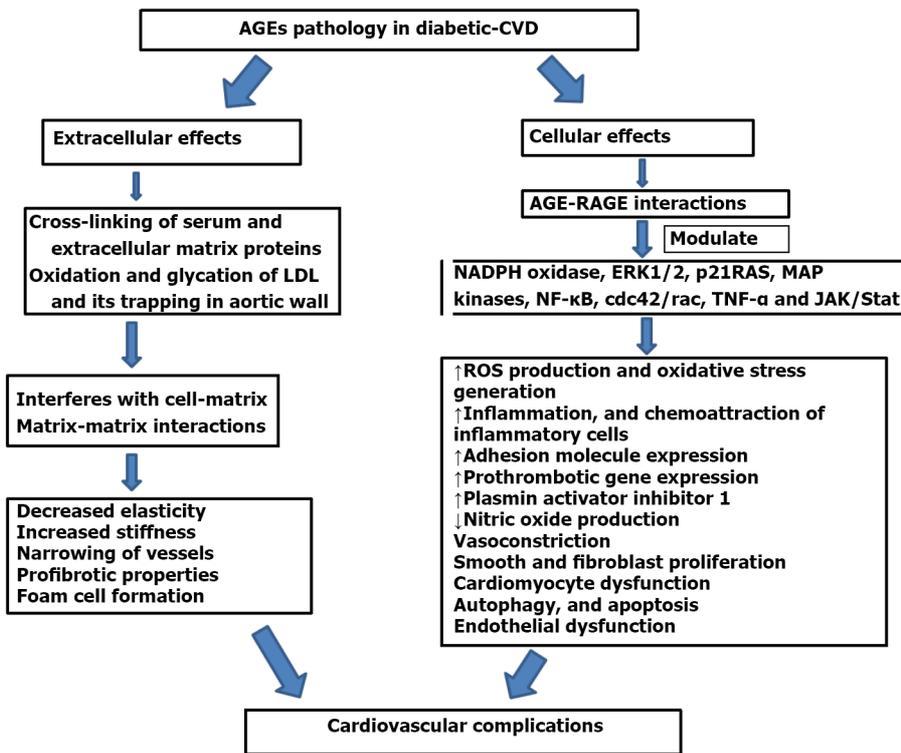
### AGE-RAGE axis in cardiovascular complications

At the cellular level, AGEs mediate their effects through interaction with their receptors, especially RAGE. RAGE is recognized by multiple ligands and has been localized on endothelial cells, vascular smooth muscle cells (VSMCs), immune cells and many others[86]. The presences of RAGE on multiple cells indicate its involvement in pathways affecting the vascular system in diabetes[87]. AGE-RAGE interaction activates signaling cascades leading to enhanced production of reactive oxygen species (ROS), oxidative stress, inflammation, adhesion molecule expression, endothelin-1, PAI-1, tumor necrosis factor (TNF)- $\alpha$ , chemoattraction of inflammatory cells, smooth muscle and fibroblast proliferation, autophagy, and apoptosis[88-90]. AGE-RAGE interaction modulates the cellular properties that possibly promote proinflammatory and procoagulant gene pathways through stimulation of signaling molecules such as extracellular signal-regulated kinase (ERK)1/2, p21RAS, mitogen-activated protein kinase (MAPK), nuclear factor (NF)- $\kappa$ B, cdc42/rac, and Janus kinase (JAK)/STAT and adversely affect the cardiovascular health in diabetes[91,92]. Cipollone *et al*[93] have studied the association of AGE-RAGE interaction and RAGE overexpression in human diabetic plaque macrophages by an increased inflammatory reaction, cyclooxygenase-2/prostaglandin E synthase-1 expression that may contribute to plaque destabilization through induction of metalloproteinase expression[93]. Also, the AGE-RAGE system activates inflammation in plaques and atheromas. Therefore, therapeutic approaches are now targeting the AGE-RAGE system to prevent the development of atherosclerosis[94].

### Glycation of cellular and extracellular components in diabetic CVD

AGEs are also involved in the covalent modifications and crosslinking of serum and extracellular matrix (ECM) proteins, lipids and nucleic acid leading to perturbation of their structure and functions. Proteins of ECM have slow turnover rate and longer half-life which make them more prone to glycation reaction and crosslinking under hyperglycemic conditions. Modification of ECM proteins and crosslinking interferes with cell-matrix and matrix-matrix interactions, leading to profibrotic action, decreased elasticity, increased stiffness and narrowing of vessels and other hallmarks of atherosclerosis [14,95]. Cellular proteins also undergo the nonenzymatic glycation reaction by glucose and its derivatives like glucose-6-phosphate, glyceraldehyde-3-phosphate, dihydroxyacetone-phosphate, GO, and MGO. Cellular AGEs have also been known to activate signaling pathways further impacting the diabetic vascular complications[96]. AGEs also induce crosslinking of intracellular proteins that participate in Ca<sup>2+</sup> homeostasis resulting in cardiomyocyte dysfunction[97]. AGE-RAGE interaction is also found to be associated with decreased Ca<sup>2+</sup> levels by upregulated ryanodine receptor which is involved in maintaining ionic balance during systolic and diastolic phases[98].

Development of cardiovascular complications in T2DM is also associated with increased incidence of low-density lipoprotein (LDL) oxidation, glycation of paraoxonase (PON)1, and high-density lipoprotein (HDL)[99]. Oxidation of LDL in arterial walls is the primary step in initiation and progression of atherosclerosis by foam cell formation. Recent studies have reported that glycated LDL can evade recognition by LDL receptors and can attach to arterial walls[100]. Non-enzymatic glycation of LDL is also responsible for impairment of hepatic receptor-mediated uptake and its removal. As a result, AGE-modified LDL is trapped in the subendothelium, causing its retention in the aortic wall where it is internalized by macrophages resulting in foam cell formation[101-103]. Glycation of LDL also makes it more vulnerable to



DOI: 10.4239/wjd.v14.i8.1146 Copyright ©The Author(s) 2023.

**Figure 2 Advanced glycation end product-mediated diabetic cardiovascular complications.** AGEs mediate their pathological effects at the cellular and extracellular level by multiple pathways. At the cellular level, they activate signaling cascades *via* RAGE and initiate a complex series of intracellular signaling leading to reactive oxygen species generation, oxidative stress development, inflammation, adhesion molecule expression, endothelin-1, plasmin activator inhibitor 1, tumor necrosis factor alpha, chemoattraction of inflammatory cells, smooth muscle and fibroblast proliferation, autophagy, and apoptosis. AGE-RAGE interaction modulate the cellular properties through stimulation of signaling molecules such as ERK 1/2, p21RAS, MAPK, NF-B, cdc42/rac, and Janus kinase/STAT and adversely affects the cardiovascular health in diabetes. AGEs also causes covalent modifications and crosslinking of serum and ECM proteins, altering their structure, stability, and functions. Modification of ECM proteins and cross-linking interferes with cell–matrix and matrix–matrix interactions, affecting the matrix–cell signaling and leading to profibrotic action, decreased elasticity, increased stiffness, narrowing of vessels, and other hallmarks of atherosclerosis. VCAM1: Vascular cell adhesion molecules; JAK: Janus kinase; RAGE: Receptor for advanced glycation end products; NADPH: Nicotinamide adenine dinucleotide phosphate oxidase; NF-κB: Nuclear factor-B; AGEs: Advanced glycation end products; MAPK: Mitogen-activated protein kinase; ROS: Reactive oxygen species; TNF-α: Tumor necrosis factor; ERK: Extracellular signal-regulated kinase; LDL: Low-density lipoprotein; ECM: Extracellular matrix.

crosslinking with collagen in the arterial wall. Elevated lipid-linked AGEs in LDL have also been noticed in T2DM patients[104]. Glycation of HDL also influences inflammation and affects the removal of cholesterol, leading to the development of atherosclerosis[105]. PON1 is an HDL-associated enzyme with antiatherogenic properties that protects LDL and cell membranes from oxidation. Glycation of PON1 is found to decrease its activity in DM, leading to the development of premature atherosclerosis[17,106,107].

### AGEs and oxidative stress in diabetic-CVD

T2DM patients are exposed to high oxidative stress, increased reactive species (RS) generation, and decreased antioxidant defense mechanism. Hyperglycemia-induced ROS generation unveils the pathophysiology of CVD in T2DM and increased production of ROS triggers the inflammatory cascades responsible for the pathogenesis of cardiovascular complications[108,109]. The level of transcription factors such as TNF-α and NF-κB is modulated by increased RS production mediated signal transduction pathways enhancing the proinflammatory events including inflammatory adhesion molecules, interleukin (IL)-6, IL-1, and cytokines[110-112]. The AGE-RAGE interaction is also involved in increased RS generation through stimulation of certain signaling mediators like ERK, phospholipase A2, phosphoinositide 3-kinase activation, activation of NADPH oxidase, inducible NO synthase (NOS), PKC and p38 MAPK[113-115]. Increased ROS production by mitochondria also triggers the inflammatory cascades in DM and prolonged exposure to high levels of ROS leads to oxidation, peroxidation and glyoxidation reactions resulting in increased oxidative stress markers such as protein carbonyl, oxidation of thiol group, lipid peroxidation, advanced oxidation protein products, and 8-OHdG[17,116]. Oxidative injury to biomolecules has also been observed in tissues and blood of diabetics with high AGEs concentration[117,118]. *In vitro* and *in vivo* studies have reported that increased ROS production by AGE-RAGE interaction causes DNA damage that induces endothelial cell death by triggering the apoptotic pathway[119,120].

### AGEs and endothelial cell dysfunction

Endothelial dysfunction is the hallmark for the development of cardiovascular complications in T2DM. The presence of RAGE on the endothelial cell surface suggests its relevance in endothelial dysfunction by interacting with AGEs in T2DM.

Lowered NO production, increased ROS generation, and enhanced expression of adhesion molecules, chemokines and cytokines are the hallmarks of endothelial dysfunction[121]. These conditions lead to inflammation, vasoconstriction, oxidative stress, myofibroblast migration, and proliferation inside the endothelial layer of vessels; all of which play a vital role in the development and progression of vascular complications in T2DM[122]. Under hyperglycemic condition endothelial cell proteins such as fibroblast growth factor and mitochondrial proteins undergo nonenzymatic glycation reactions affecting the vascular properties of cells by increased superoxide production, altering mitogenic and endothelial NOS (eNOS) activity[123,124].

Serum level of AGEs is negatively associated with the extent of endothelium-dependent vasodilation in T2DM patients [125]. NO acts as an antiatherogenic factor due to its effective vasodilatory, anti-inflammatory, and antiproliferative activities[110,126]. Increased ROS production by AGEs is one of the reasons for inactivation of NO as well their conversion to peroxynitrite form, thereby affecting the integrity of endothelial cells. Formation and accumulation of AGEs inside the endothelial cells is also found to be associated with reduced eNOS gene expression and increased eNOS mRNA degradation[126]. AGE-RAGE interaction on endothelial cells also results in enhanced production of asymmetric dimethylarginine, which is an endogenous inhibitor of eNOS and is one of the strongest marker of cardiovascular disease progression[127]. AGEs are also involved in NO quenching and inactivation of endothelium-derived NO[88]. Uhlmann *et al*[128] reported a significant reduction in NO production in AGE-treated cells *in vitro*. Their results implied that AGEs have a role in the modulation of NO activity in diabetic pathophysiology[128]. Ren *et al*[29] demonstrated the involvement of AGEs in reducing eNOS expression and NO bioavailability by increasing the oxidative stress development through activation of p38 and ERK1/2 in human coronary artery endothelial cells *in vitro*[29]. Therefore, accumulation of AGEs and AGE-RAGE interaction has an important impact on the pathogenesis of diabetic-CVD by affecting the vasodilating properties of endothelial cells. The AGE-RAGE axis also provokes the expression of p22hox and gp91hox, which are reduced form of NADPH oxidase in endothelial cells and causes its dysfunction[28].

Involvement of AGEs has also been noticed in the production of vascular endothelial growth factor (VEGF) by endothelial cells and thereby involved in atheroma formation. The activation of NF- $\kappa$ B by AGEs increases the secretion of VEGF (that prevent the repair of endothelial lesions resulting in atherogenesis), stimulates the differentiation of monocyte to macrophages and the accumulation of oxidized LDL in the vasculature leading to foam cell formation[29,129]. AGE-RAGE involvement has also been observed to inhibit the prostacyclin production and generation of PAI-1 in endothelial cells[130]. Formation and accumulation of AGEs have also been implicated in platelet activation and aggregation, stimulation of procoagulant activity, thrombus formation, and endothelial cell damage mediated by upregulation of protease-activated receptor-1 and -2 potentiates thrombin[131,132]. Decreased endothelial progenitor cell (EPC) function and mobilization poses a major risk for developing cardiovascular complications in T2DM[133]. AGE-RAGE interaction augments the apoptotic pathways and suppresses the migration and tube formation of late EPC by downregulation of Akt and cyclooxygenase-2[134]. Glycation of Arg-Gly-Asp motif of fibronectin by AGEs results in impairment of vascular repair by inhibiting EPC adhesion, migration, and spreading[134].

Vascular complications are also characterized by the adhesion and transmigration of monocyte into the subendothelial space. AGE-RAGE interactions enhance this process by activation of proinflammatory molecules such as NF- $\kappa$ B, which causes the overexpression of proinflammatory genes and adhesion proteins that aid monocyte adhesion to endothelial cells[103,135,136]. Foam cells and fatty streak formation take place in the vessel wall by monocyte and oxidized lipid at the adhesion site. These fatty streaks mature into advanced lesions with a fibrous cap that can dislodge resulting in an infarct or a stroke[137]. These observations suggest that AGEs have a definitive role in development and progression of vascular injuries observed in diabetes.

### AGEs and VSMC modifications

Recently researchers have identified the phenotype transformation of VSMCs into macrophages during cardiovascular pathology[138]. *In vitro* studies have shown the effects of AGEs on increased proliferative activity and production of fibronectin in cultured SMCs. Transforming growth factor- $\beta$  might act as a mediator in AGE-induced fibronectin production in SMC through AGE-RAGE interactions[139]. *In vivo*, the effect of AGEs on the growth of SMCs has also been noticed and is mediated by increased production of cytokines or growth factors[140]. Expansion of neointima is a unifying feature of atherosclerosis. Significant decreased in neointimal expansion, SMC proliferation, migration, and expression of ECM proteins have been demonstrated in homozygous RAGE-null mice. These data highlight the involvement of the AGE-RAGE axis in modulating the SMC properties and suggesting an important pharmaceutical target for suppression of neointima expansion[44,140]. VSMC phenotype transformation and calcification is one of the main pathological manifestations of atherosclerosis[141]. Recently Bao *et al*[142] showed the effect of AGEs on VSMC-derived foam cell formation and phenotype transformation. They identified the effect of CML on decreased expression of VSMC markers and increased expression of macrophage markers. They also noticed the involvement of AGEs in SMC migration and the secretion of proinflammatory factors[142]. Xing *et al*[143] explained the associated mechanism of phenotype transformation of VSMCs to macrophages by AGEs during atherosclerosis. They noticed that AGEs induced activation of RAGE/TLR4/FOXC2 signaling in macrophages with high expression of delta-like ligand (Dll)4 during M1 polarization. These altered macrophages promoted phenotype conversion of VSMC through Dll4/Notch pathway after cell-to-cell contact[143].

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## ANTI-AGEs THERAPIES

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The deleterious effects of AGEs in the development and progression of diabetic vascular complications have driven the

focus of pharmacological intervention towards attenuating the effects of AGEs. Although lifestyle modification, better glycemic control, regular physical activity, smoking cessation, restriction of AGE-rich diet have been reported to reduce the availability of precursors for glycation reactions and AGEs formation in T2DM[144-146]. A plethora of studies over the last few decades have been dedicated to in searching for pharmacological agents capable of interfering with glycation reactions and their sequelae. The underlying mechanism of action of these proposed drugs are based on AGEs inhibitors, AGEs crosslink breakers, detoxifying the dicarbonyls intermediates, and AGE-RAGE signaling blockers (Figure 3)[147, 148]. No AGE-modifiers have been approved as drugs as yet, although some AGE-associated medications are in clinical and preclinical testing. Phytochemicals having antioxidant and anti-inflammatory properties have the potential to arrest the detrimental effects of AGEs and downstream consequences of the AGE-RAGE pathway[149].

### **Inhibition of endogenous AGEs formation**

The first drug that was discovered to impede endogenous AGE formation was aminoguanidine with a guanidine group that is capable of trapping  $\alpha$ -dicarbonyl product of early glycation reactions and thereby preventing the subsequent reactions with proteins[150,151]. Bolton *et al*[152] demonstrated the role of aminoguanidine in reducing proteinuria and progression to retinopathy, however due to its side effects, it is unlikely to be used for therapeutic purposes[152]. Compounds structurally related to aminoguanidine such as ALT-946 and OPB-9195 have been developed and tested as potential drugs. ALT-946 therapy was found to reduce renal AGE accumulation, and reduce albumin excretion in animal models[153]. OPB-9195 is an antagonist of peroxisome proliferator-activated receptor- $\gamma$  and inhibits the glycooxidation and lipoxidation reactions. In animal models, OPB-9195 decreased the progression of nephropathy, lowered the blood pressure, and the serum level of AGEs[154,155]. LR-90 is another aromatic compound with anti-AGE properties due to its metal-chelating ability and its interaction with dicarbonyl compounds. It affords renoprotection such as improved renal albuminuria, reduction of connective tissue growth factors, fibronectin and collagen deposition in experimental model of type 1 and type 2 nephropathy[156]. TM2002 is a powerful AGE inhibitor that has transition metal-chelating properties and is nontoxic. It improves renal and cardiac lesions, and decreases infarct volume in different animal models[157,158]. Benfotiamine is a prodrug of thiamine monophosphate with AGE-lowering properties, mediated through preventing dicarbonyl formation[159,160]. In a pilot study, Brownlee *et al*[150] observed that treatment along with  $\alpha$ -lipoic acid improved complications in patients with type 1 or type 2 DM. Pyridoxamine also intervenes in the glycation process by blocking the transformation of Amadori products into AGEs[161]. They have the ability to trap ROS, thereby blocking the oxidative degradation of Amadori intermediates and preventing the formation of AGEs[162,163].

### **Preformed AGEs breakers**

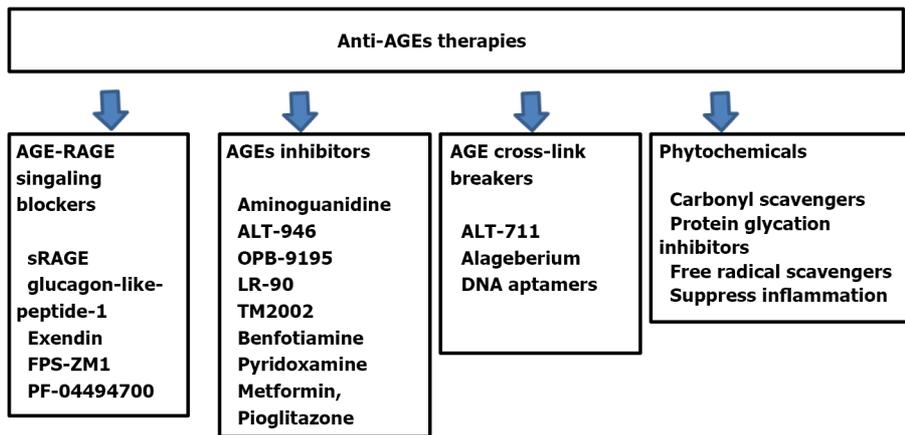
Among the deleterious effects of AGE accumulation, crosslinking of ECM is of prominence and results in cardiovascular stiffness. Phenylthiazolium bromide was the first reported AGE crosslink breaker that is not stable in aqueous solution [164]. Several of its derivatives have now been derived, such as ALT-711 or alageberium, and have the ability to break AGE crosslinks. The precise mechanism of their action relies on reaction with carbonyl groups present in AGE crosslinks and cleavage of carbon-carbon bonds. Application of alageberium in animal models has proved to be effective in reducing large artery stiffness and blood vessel fibrosis, attenuating atherosclerosis, diabetic nephropathy, and hypertension[165, 166]. The role of aptamers has been explored in biomedical and pharmaceutical industries[167]. Aptamers are a group of short and single-stranded DNA or RNA molecules with the ability to bind with high affinity/specificity to a variety of proteins. DNA aptamers raised against AGEs bind and ameliorate AGE-associated effects[168]. These specific DNA aptamers can become novel therapeutic agents for AGE-related pathologies.

### **AGE-RAGE signaling blockers/RAGE antagonists**

*In vitro* and *in vivo* studies have confirmed that AGE-RAGE axis is one of the major pathways for diabetic vascular complications. Therefore, it would be an ideal target to prevent the development and progression of complication in T2DM. Pharmacological agents that focus on the AGE-RAGE axis could function through different means such as inhibiting the RAGE expression, altering the AGE-RAGE signaling or by raising the blood level of soluble RAGE (sRAGE) to trap AGEs. sRAGEs are formed by alternative gene splicing of RAGE gene or proteolytic cleavage of membranous RAGE. Administration of sRAGE has shown to decrease albuminuria, glomerulosclerosis and diabetic CVD [169,170]. Statin and thiazolidinediones have been shown to ameliorate RAGE expression in conjugation with increased sRAGE[171,172]. The proposed underlying mechanisms of statin and thiazolidinediones have also been described. Activation of peroxisome proliferator-activated receptor- $\gamma$  can inhibit the phosphorylation of ERK1/2 and downregulate NF- $\kappa$ B, thereby lowering the expression of inflammatory cytokines and RAGE[173,174]. Other molecules such as glucagon-like peptide (GLP)-1 and its analog exendin also decrease RAGE expression through suppressing NF- $\kappa$ B and decreasing ROS production by inhibiting NADPH oxidase activity[175,176]. Studies have also reported the involvement of GLP-1 and exendin in reducing activation of the AGE-RAGE axis and its associated complications such as atherosclerosis and diabetic cardiomyopathy *etc*[177,178]. RAGE inhibitors FPS-ZM1 and PF-04494700 had neuroprotective effects against ischemic brain injury in a rat model and  $\beta$ -amyloid structures in clinical trials for Alzheimer's disease[179, 180]. The effect of FPS-ZM1 as a RAGE inhibitor is associated with decreased inflammation and oxidative stress by targeting other ligands of RAGE such as S100, high-mobility group protein 1, and amyloid  $\beta$ -protein[180-183]. The promising effect of RAGE blockers such as FPS-ZM1 and PF-04494700 in neurodegenerative diseases provides the rationale to study their effects in T2DM patients.

### **AGEs and hypoglycemic drugs**

The effects of many hypoglycemic drugs have also been studied in the context of decreasing AGE level and ameliorating



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**Figure 3 Anti-advanced glycation end product therapeutic strategies.** Anti-AGE therapies target multiple pathways based on AGE-mediated effects in type 2 diabetes mellitus and associated complications. These include inhibitors of AGE formation, AGE crosslink breakers, and AGE–RAGE for AGE signaling blockers. The uses of phytochemicals having antioxidant and anti-inflammatory properties are also providing options to arrest the detrimental effects of AGEs by reducing peroxidative inflammatory reactions through carbonyl scavengers, protein glycation inhibitors and free radical scavengers which can reduce oxidative stress. RAGE: Receptor for advanced glycation end products; AGEs: Advanced glycation end products; sRAGE: Soluble RAGE.

the effects of AGE–RAGE axis. Prasad and Tiwari[169] have reported the effects of rosiglitazone in inhibiting the AGE–RAGE interaction and found elevated sRAGE levels[169]. Similar results have been reported in a randomized placebo-controlled study of 111 patients with T2DM CVD, where increased sRAGE and decreased inflammatory markers were reported after 6 mo of rosiglitazone treatment[184]. Effects of glimepiride beyond glycemic control have been reported in reduction of toxic glyceraldehyde-derived AGE levels and increased colony-stimulating factors to potentially repair tissue damage in T2DM patients[185]. Metformin treatment inhibits development of adverse myocardial structural and functional changes by inhibiting the production and accumulation of AGEs[186,187]. Metformin also inhibits the AGE-induced VSMC proliferation[188]. Animal and *in vitro* models have shown the efficacy of dipeptidyl peptidase-4 inhibitors such as sitagliptin, cilizytin, vildagliptin and linalgliptin in inhibiting glycosylation, downregulating the levels of AGEs, RAGE and oxidative stress markers, and decreasing the expression of VCAM-1, PAI-1, and ICAM-1[189-192]. GLP analog liraglutide was also found to ameliorate atherogenesis by inhibiting AGE-induced expression of RAGE in a mouse model[193].

## CONCLUSION

T2DM imposes both clinical and economic burdens on the healthcare system. Recent reports have confirmed that CVD represents a substantial burden on the treatment of T2DM at both patient and population level. The pathophysiology of hyperglycemia in T2DM is closely associated with AGEs formation, accumulation, and their deleterious effects. The adverse effects of AGE accumulation include many important biochemical reactions that are central to the development and progression of cardiovascular complications in T2DM. AGE-mediated cardiovascular complications show many pathological changes such as plaque formation, arterial stiffening, neointimal proliferation, vasoconstriction, oxidation of LDL, and endothelial dysfunction. The probable mechanisms through which AGEs exert their detrimental effects include increased ROS generation, oxidative stress development, decreased NO production and its inactivation, inflammation, adhesion molecule expression, crosslinking of proteins, and prothrombotic gene expression. AGE–RAGE interactions also alter the cellular properties by promoting proinflammatory and procoagulant pathways acting through modulation of signaling molecules such as ERK1/2, cdc42/rac, p21RAS, TNF- $\alpha$ , MAPK, NF- $\kappa$ B, and JAK/STAT that adversely affect the cardiovascular health in T2DM. The AGE–RAGE axis is also involved in modulating SMC properties and neointima expansion, where it mediates SMC proliferation, phenotype transformation of VSMCs into macrophages during cardiovascular pathology. Therefore, clinical and experimental research is now focused on AGEs as new biomarkers or therapeutic target to prevent the development and progression of diabetic vascular complications. Based on AGE-mediated effects in pathogenesis of T2DM and its complications, pharmacological approaches are exploring combination therapies targeting multiple pathways based on inhibitors of AGE formation, AGE cross-link breakers, free radical scavengers, and anti-inflammatory therapies, detoxifying the dicarbonyl intermediates and AGE–RAGE signaling blockers that may attenuate AGE-mediated effects in diabetic cardiovascular. The use of phytochemicals with antioxidant and anti-inflammatory properties is promising for arresting the detrimental effects of AGEs. Also, there is a need to develop more specific and sensitive methods for the assay of circulatory AGEs. An epidemic of diabetes over the past half century has also been associated with increased consumption of modern heat-processed and highly palatable AGE-rich diet. Therefore, lifestyle modifications including dietary AGE restriction, regular exercise and cessation of smoking are some of the important interventions and practical ways to attenuate the effects of the AGE–RAGE axis and AGE-associated pathways.

## FOOTNOTES

**Author contributions:** Bansal S frames the review article; all authors have read and approved the final manuscript.

**Conflict-of-interest statement:** All the authors report no relevant conflicts of interest for this article.

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