REVIEW ARTICLE

Molecular Mechanisms of Methylglyoxal in Diabetes-related Macrovascular Complications

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Abstract

Diabetes mellitus (DM) is a chronic endocrine and metabolic disease indicated by the presence of hyperglycemia. It has been known that hyperglycemia and oxidative stress are the main culprit of all DM complications, including macrovascular complications. As a byproduct of lipid, protein, and carbohydrate metabolism, methylglyoxal (MGO) is a highly reactive substance which plays a positive signaling role in helping cells regain redox balance under oxidative stress circumstances. DM-related problems lead to an excess of mitochondrial superoxide in the heart and big and small vascular endothelial cells. Elevated intracellular reactive oxygen species induce impaired angiogenesis in reaction to ischemia, trigger several proinflammatory pathways, and result in enduring epigenetic modifications that propel the continuous expression of proinflammatory genes even after glucose levels return to normal. Over time, the significance of the extremely quick advanced glycation end-products (AGE) production caused by the extremely reactive MGO has been clarified. It is now evident that MGO causes vascular tissue to react maladaptively. Glyoxalase 1 (GLO1) is the primary enzyme in an organism's enzymatic glyoxalase defense mechanism, which converts MGO to D-lactate in order to counteract the harmful effects of MGO. Understanding the role of the MGO–GLO1 pathway in the etiology of vascular disease in diabetes has advanced significantly. Therefore, it can be summarized that vascular damage are linked to diabetes. The AGE precursor MGO are important in determining the connection between diabetes and vascular damage. MGO and AGEs play a role in several phases of the development of diabetes complications. MGO and AGEs may be useful therapeutic targets for diabetes's macrovascular problems.

KEYWORDS: hyperglycemia, AGE, methylglyoxal, glyoxalase, D-lactate, gluthatione, oxidative stress.

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Introduction

Diabetes mellitus (DM) is a chronic endocrine and metabolic disease indicated by the presence hyperglycemia and vascular consequences (micro and macro). It is primarily defined by insulin insufficiency, insulin insensitivity, or both.(1) Numerous investigations have demonstrated the critical role that oxidative stress plays in the onset, course, and consequences of diabetes.(2–5) Oxidative stress was is a key player in the pathophysiology of diabetes and its sequelae.(6)

When there is a cell's redox imbalance, oxidative stress sets in, damaging membranes as well as essential macromolecules including DNA, proteins, and lipids. (7,8) It has been demonstrated that oxidative stress impairs insulin production and insulin action, the two main processes in diabetes.(9–15) There are two opposite

sides of oxidative stress role in the progression of DM. In addition to encouraging diabetes to develop, the process makes the disease and all of its side effects worse. Experimental data suggests that reactive oxygen species (ROS) contribute to type 1 diabetes (T1DM) via impairing beta-cell activity brought on by cytokines, inflammatory proteins, and autoimmune reactions.(4) Furthermore, it has been observed that hyperglycemia increases the risk of oxidative stress by suppressing antioxidant defense systems and generating free radicals from scratch.(9) The generation of ROS is prolonged under chronic hyperglycemia, leading to a significant suppression of antioxidant enzymes and non-enzymatic antioxidants in different tissues. This, in turn, aggravates oxidative stress.(16,17) This explains why oxidative cell and organism environments are more common in diabetics than in healthy people.(18,19)

Gluthatione (GSH) is a thiol buffer found in cells that is used by numerous antioxidant enzymes as a cofactor and as an antioxidant.(20) A GSH molecule is used by the glyoxalase system to detoxify methylgloxal (MGO). MGO is a reactive byproduct of lipid, protein, and carbohydrate metabolism that is produced in all cells, both in healthy and sick states.(21) The synthesis of MGO is achieved by a variety of non-enzymatic or enzyme-catalyzed processes. Conversely, the primary mechanism of MGO detoxification is the MGO pathway, whereby MGO is converted into the safe end product D-lactate (D-LAC), a reduced substrate that can power mitochondrial respiration, by the ubiquitous glyoxalase system, which consists of glyoxalase I (GLO1) and glyoxalase II (GLO2).(22)

Along with the potential involvement of D-LAC, the compartment-dependent significance of the MGO pathway in connection to oxidative pressure and adaptive metabolic alterations has been highlighted. Furthermore, there has been the presence of S-glutathionylation (SLG) within the intramitochondrial region and its connection to pathogenic occurrences. Lastly, it is suggested that SLG has a tactical function in cell survival during redox imbalance and that MGO plays a positive signaling role in helping cells regain redox balance under oxidative stress circumstances. (23) This review will discuss about the mechanism of diabetic macrovascular complication was induced by MGO especially due to fructose intake.

Biogenesis of MGO

As a result of the metabolism of glucose, fructose, proteins, and lipids, MGO is a highly reactive substance. Because it is a potent advanced glycation end-products (AGE) precursor, this metabolite has been linked to issues related to diabetes. Endogenous defenses against the reducing power of sugars were established by organisms. To keep fructose and MGO levels low, cells store the majority of glucose in non-reactive forms such glycogen.(24,25)

Glyceraldehyde-3-P (G3P) and dihydroxyacetone-phosphate (DHAP) are the starting materials for glycolysis. There are two ways that this can happen: either through non-enzymatic breakdown of G3P and DHAP, which results in the loss of the α-carbonyl group and phosphate, or through enzymatic conversion of G3P and DHAP into MGO, which is mediated by enzymes like MGO synthase and triose phosphate isomerase (TPI). This process uses anaerobic energy formation to produce lactate, or it can use the breakdown of G3P and DHAP to create MGO. Moreover, MGO synthase is generated by the metabolism of proteins, fructose (by aldolase B catalysis), lipids (by acetol mono-oxygenase), and ketone bodies (by cytochrome P450, acetol mono-oxygenase, and myeloperoxidase). Ultimately, threonine dehydrogenase (TDH) converts the metabolism of glycine and threonine to aminoacetone, forming MGO. Next, MGO is produced by semi-carbazide-sensitive amine oxidase from aminoacetone.(26) Furthermore, Amadori production deterioration may be the source of MGO.(24,25)

It is likely that MGO's endogenous production during hyperglycemia is primarily responsible for its contribution to problems similar to diabetes. Dietary peptides changed by MGO and AGEs are poorly absorbed, and a significant portion of those that enter the bloodstream are eliminated in the urine. Lower amounts of MGO can also be generated from processed food items, particularly those that include high-fructose corn syrup, which is one of the main exogenous sources of MGO. The production of dicarbonyls from fructose during the heating process has a significant impact on the amount of MGO.(24,25) Intracellular MGO levels are thought to vary between 1 and 4 μM. It has been hypothesized that MGO has a short biological half-life because of its reactive nature, and as a result, it is likely that the actual amount produced exceeds existing estimates.(26)

During the course of normal metabolism, cells established the GLO system, a whole enzymatic system that has been well-preserved throughout evolution that is devoted to the destruction of MGO. It consists of two enzymes: GLO1 and GLO2. MGO is catalyzed to become SLG by GLO1, and SLG is catalyzed to become D-LAC by GLO2. GLO1 activity is dependent on GSH and has been demonstrated to rise in rats after exercise. The breakdown of MG is also facilitated by other enzymes, including aldo-

keto reductases and alpha-dicarbonyl/L-xylulose reductase. N-Acetyl-Cysteine (NAC), isoflavones, and terpenes are some of the treatment approaches that have been established as alternate detoxification pathways for the detoxification of MGO, especially when the glyoxalase system is weak or malfunctioning.(25)

Hyperglycemia and Oxidative Stress in Diabetic Complication

Hyperglycemia is the main characteristic of DM, together with a partial or total lack of insulin action, insulin resistance that is specific to a certain pathway, and the emergence of diabetes-specific pathology in accelerated atherosclerotic disease, which affects the arteries supplying the heart, brain, and lower extremities. Among nontraumatic amputations, diabetic accelerated lower extremity vascular disease combined with neuropathy accounts for sixty percent of cases.(27) The risk of cardiovascular disease (CVD) is increased three to eight times by DM and poor glucose tolerance. Therefore, DM affects over 30% of patients hospitalized for acute myocardial infarction (AMI), and poor glucose tolerance affects 35% of patients.(28)

There are five main ways currently understood that hyperglycemia damages tissue: 1) increased glucose and other sugar flux via the polyol pathway; 2) increased AGE formation within cells; 3) increased expression of the AGE receptor and its activating ligands; 4) activation of protein kinase C (PKC) isoforms; and 5) overactivity of the hexosamine pathway (Figure 1). Nevertheless, clinical investigations that have solely blocked one of these routes have yielded poor outcomes, led to the ideas that the overproduction of ROS in the mitochondria due to hyperglycemia is the sole upstream event that activates all 5 pathways.(29,30)

Furthermore, the oxidative stress triggered by hyperglycemia activates a number of stress-sensitive

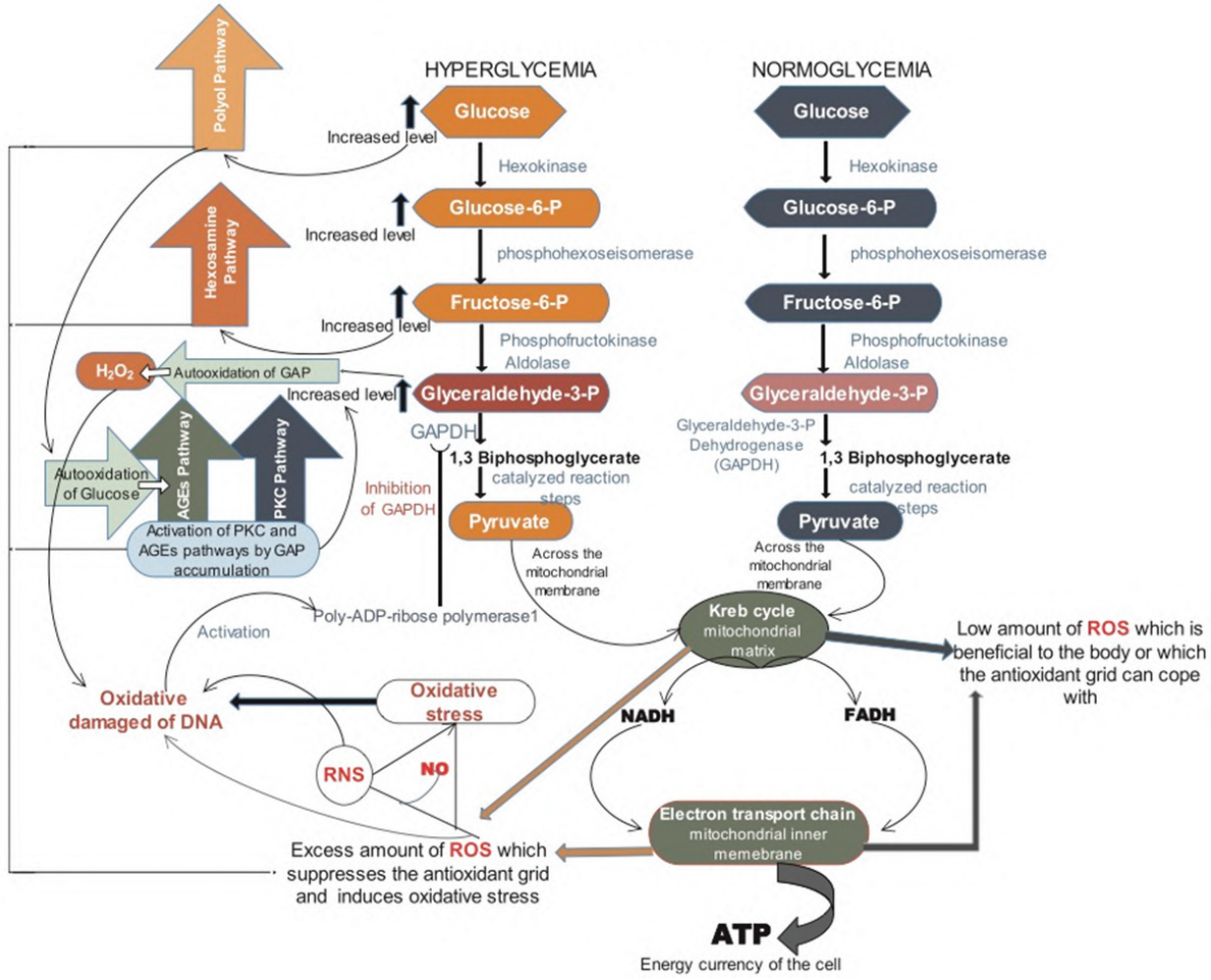

Figure 1. Glucose oxidation pathway and the induced-oxidative stress to hyperglycemic conditions.(1) (Adapted with permission from Elsevier Masson).

signaling pathways. These pathways include signaling components such as nuclear factor-κB (NF-κB), which functions as a transcription factor (31), as well as inflammation molecules like histocompatibility complex class II (32) and inducible nitric oxide synthase (iNOS) (33). All together, these activities play a major role in the inadequate secretion and action of insulin. Oxidative stress also affects the Jun N-terminal kinase (JNK) pathway's activation, which has been connected to the inhibition of insulin gene expression through pancreatic and duodenal homeobox 1 (PDX-1) DNA decrease and the hyperactivity of the hexosamine pathway (34), in the end lead to the micro and macrovascular complication of DM.

AGE can form in the body due to glycation, glycosylation, lipid peroxidation, and glucose autoxidation. Glycation is a non-enzymatic reaction that occurs between a carbohydrate and a molecule with a free amino group, such as a protein. Glucose, the body's most common reducing sugar, and the activities of free amino groups, particularly those found in proteins like arginine and lysine, are both involved in endogenous physiological glycation. This results in high blood sugar levels coming into contact with the body's proteins (chronic hyperglycemia). Glycation is increased as a result, which adds to the different difficulties related to diabetes. Subjects with diabetes or renal failure likely to have higher concentrations of the resultant carbonyl compounds in their systems.(35–37)

The identical glycation mediators are produced via the polyol, glycolysis, glucose autoxidation, and lipid peroxidation processes. Once created, these intermediaries react with amino acids in proteins, including lysine, much as they would during the glycation process, producing AGEs without going through glycation first. Because of this, the term 'AGE' refers exclusively to AGEs generated by glycation as well as the advanced end products created by the previously stated routes. This explains also why there is variation in the pathological expression of AGEs in DM, renal failure, and aging tissues. *In vivo*, phosphatidyl-ethanolamines, serines, and aminophospholipids are all present in glycated form and are present in membranes of cells and mitochondria. The phase transitions are impacted by the ensuing structural alterations, which modify membrane conductance, membrane potential, and membrane flexibility. The glycated forms' pro-oxidative function is also linked to cellular reactions including NF-κB transcription factor activation. Because they interfere with the control of autophagy and the cellular synthesis of bioenergy, they also likely to have a major effect on mitochondria.(38–42)

The nonenzymatic glycation crosslinking results in chronic diseases for example atherosclerosis as described. Glycation causes post-translational crosslinking of elastin and collagen which results in skin and vascular stiffening due to decreased viscoelasticity. This continues with the interaction between AGEs and its cell surface receptor (RAGE) and activate NF-κB, activator protein-1 (AP-1), and activator of transcription (STAT), induce the inflammation process and attrack the immune cells including T-cells, neutrophils, monocytes, B lymphocytes, macrophages with consequences of atherosclerosis.(43)

Glycolysis is necessary for the endothelium to produce ATP and absorb glucose through glucose transporters (GLUT)1. Glucose enter the polyol pathway and be converted to fructose by sorbitol. The reduced GSH is used during this process, which lowers the antioxidative capacity. This reaction results in the detection of both AGE formation and ROS generation. Dephosphorylation of the AGE precursor MGO may occur at the level of the glycolysis intermediates, G3P and DHAP.(44) Under normoglycemic circumstances, the most crucial route for MGO detoxification is the glyoxalase system, which protects cells from MGO toxicity.(45) The main cellular defense against dicarbonyl stress is GLO1, which neutralizes >99% of MGO to lessen MGO overload and prevent the development of AGE.(46) In addition to increased MGO synthesis and accumulation in hyperglycemia-induced carbonyl stress, activated inflammatory cells and hypoxia, which are two states marked by enhanced aerobic glycolysis and decreased mitochondrial respiration, and also showed excess glucose transit along the glycolytic pathway.(47)

It has been determined that AGE and MGO are important factors in determining the connection between diabetes and vascular damage. Endothelial dysfunction, intraplaque inflammation, macrophage polarization, and angiogenesis are all impeded by AGEs and MGO. AGE also aid in the production of foam cells and the calcification of vascular smooth muscle cells (VSMC), which ultimately aid in the promotion of atherosclerosis, the primary cause of all macrovascular complications associated with diabetes (24), as described in Figure 2.

Pathways of The Maillard Reaction

Age-related illnesses and chronic hyperglycemia have been linked to AGEs. AGEs have drawn a lot of interest in the last few decades as one of the various theories explaining aging, which is defined as the cumulative accumulation of damage

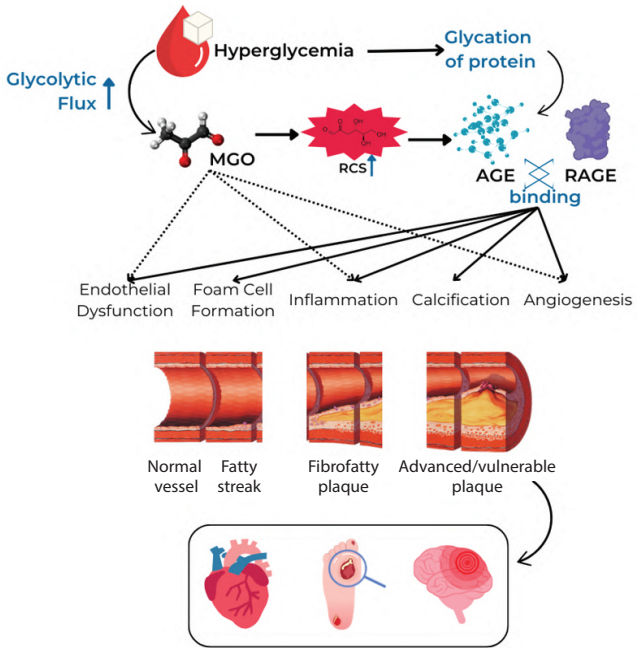

Figure 2. Hyperglycemia-induced MGO and AGE promote atherosclerosis and manifest into diabetic macrovascular complication. RCS: Reactive carbonyl species.

to an organism over time that results in illness and death by inducing oxidative stress and activate inflammatory signaling pathways.(48) A diverse family of compounds known as AGEs was first identified in the early 1900s using the traditional Maillard reaction. Glycation, a nonenzymatic interaction between reducing sugars like glucose and proteins, lipids, or nucleic acids, was found to occur in both healthy and pathological settings after glycated hemoglobin which was identified in diabetic patients.(49)

The majority of AGEs are harmful to human health because they interfere with hormone processes in the body (50) and cause age-related, noncommunicable, chronic inflammatory illnesses (51). For instance, through downregulating renal GLO1 and increasing the formation of MGO-derived hydroimidazolone (MG-H1), accumulation of MGO, a highly reactive glucose metabolite and a major precursor to AGEs, may induce hemodynamic, inflammatory, metabolic, and structural changes in the kidneys that might lead to the manifestation of diabetic chronic kidney disease. (52) However, the question of whether AGEs cause age-related disorders or are only a byproduct of them is still up for contention.(53)

The combinations of amino acids and sugars led to intensely brown colored structures and decarboxylation upon heating, researchers have focused on the non-enzymatic chemistry occurring during thermal food processing.(54) It soon became clear that the intricate chemical pathways of the so-called Maillard reaction are intimately related to the creation of color, scent, and taste. There is also a recent summary of the research timeline in this field. It was found that, under physiological settings, non-enzymatic browning processes also result in free and protein-bound Maillard products as analytical equipment performance improved. These posttranslational modification-causing activities are now recognized as significant pathogenic events in several age- and chronically-related illnesses, including Alzheimer's disease, diabetes (55,56), atherosclerosis (57), and uremia (58).

It is imperative to consider α-dicarbonyl compounds (α-DCs) as the primary key intermediates during the modification of amino acids and proteins. Thus, to comprehend the molecular basis of AGE generation and profile, one must be aware of the *in vivo* concentrations in various matrices. Nonetheless, it is quite difficult to analyze the entire α-DC spectrum analytically. Their high reactivity and derivatization to more stable chemicals prevents it to be direct analytical assessed. A variety of trapping agents, including aminoguanidines, hydrazines, cysteamines, o-diaminobenzene derivatives, and o-alkyl hydroxylamines was discussed as its trapping reagents.(59–63) Nonetheless, the most widely recognized method has developed into derivatization of α-DCs with o-phenylenediamine (OPD) to produce the matching quinoxalines.(64) Additionally, it was discovered that sample preparation and collection had a significant influence on the outcomes and needed to be closely monitored.(62,65–67)

Although carbonyl changes occur over the entire carbohydrate backbone, the initial state retains the C6-carbon structure. The 3-DG is produced non-oxidatively by dehydrating the Amadori product and 1,2-enolizing it.(68) The 1-DG is the result of 2,3-enolization (69), while the Lederer's glucosone (N6-(3,6-dideoxyhexos-2-ulos-6-yl)-L-lysine) is the result of 5,6-enediol.(70,71) Glucosone is produced when the Amadori product is oxidized.(72,73) Enzymatic processes can recycle ascorbic acid from dehydroascorbic acid.(74–76) However, some of the dehydroascorbic acid hydrolyzes irreversibly to 2,3-diketogulonic acid (2,3-DKG) in physiological solutions. These dicarbonyl molecules either directly precede some AGEs, such as glucosepane and pyrraline, or proceed through fragmentation processes to produce further reactive α-DCs with a carbon backbone shorter than C6.

The current understanding of the Maillard reaction *in vivo* takes into account many different physiological sources of α-DCs, such as fat autoxidation and metabolism, independent of Maillard chemistry. On the one hand, the

breakdown of triose phosphates, such as glyceraldehyde-3-phosphate and dihydroxyacetone phosphate, and the metabolism of ketone bodies, are responsible for the majority of MGO formed *in vivo*, while lipid peroxidation forms significant amounts of glyoxal.(77) Conversely, the glyoxalase system detoxifies both molecules.(78)

It is well known that the systemic rise in oxidative stress stimulates the development of AGEs *in vivo* and lead to chronic diseases. Oxygen is the key for Maillard chemistry degradation processes such the oxidative α-DC cleavage and the production of dehydroascorbic acid. Thus, measuring some advanced protein oxidation products is a viable method to assess the stress level *in vivo*. Furthermore, AGEs like carboxymethyl-lysine (CML), which are products of oxidative reaction pathways, can also use as analytical probes. But the majority of AGEs and their precursors can come from a variety of sources. Thus, side chains of proteins as the direct oxidation products, which are not dependent on Maillard chemistry, are frequently considered as indicators of oxidative stress. The oxidation product of methionine residues is methionine sulfoxide.(79,80) Hydroxyl radicals attack phenylalanine to create o-tyrosine, the isomer of p-tyrosine found naturally. The oxidation products of tyrosine residues include o,o'-dityrosine and 3-nitrotyrosine. Based on the redox-equilibrium created by protein-bound glycolaldehyde and glyoxal, a novel marker was developed in this concept. Glyoxal is glycolaldehyde in its oxidized state.(81)

Protein function is altered in a variety of ways by the posttranslational acylation of amino acids in the polypeptide chain, which neutralizes the positive charge. Because it affects the same targets as enzymatic regulation mechanisms, non-enzymatic acylation works similarly. The Maillard-derived protein changes, however, may be irreversible, cause accumulation, and have a negative impact on the properties of proteins.(49)

Advance Glycation End-products in Diabetes-related Macrovascular Complications

Glycation in cells or in long-lived extracellular proteins results in the production of AGEs. All tissues and fluids include protein glycation, a complicated chain of successive reactions known as the Maillard reaction that occurs when proteins react with substantial concentrations of glucose, fructose, or more reactive dicarbonyls.(82) Fructosyl-lysine is first generated as the Amadori adduct when glucose facilitates the process. This increase in hemoglobin is known as HbA1c, currently use as a better marker for diabetes patients diagnose and monitoring.(83) HbA1c somehow evaluates only products resulting from glucose. The development of AGE markers based on downstream products of glucose metabolism, such as α-DCs, which are markedly more reactive than glucose, is urgently needed. Additionally, their relationship to a number of age-related diseases has to be investigated.(84)

A non-enzymatic process called glycosation takes place when a carbohydrate and a molecule like a protein that has a free amino group interact. The body undergoes this cumulative, irreversible reaction on its own. At that point, every metabolic intermediate produced is reactive. Glycosylation, which is an enzyme-controlled physiological process that takes place during the production of glycoproteins, is completely different from glycocation, which is a physiological and pathological process that results in so-called glycated proteins. Glycation is the process that gives food its browning color during cooking when it takes place outside of the body.(85)

Exogenous glycation releases a water molecule, which is followed by the formation of a Schiff base through a reversible process. Heyns-Carson products are created from ketoses while Amadori products are formed from aldoses following the irreversible isomerization of the Schiff base. These products break down into a number of aldehydes and carbonyl compounds, such as glyceraldehyde, formaldehyde, and glyoxal, through a process called the retro-aldol reaction. These molecules can then react with another amino group. Glycation intermediaries are significant intermediary molecules that are also produced during endogenous glycation and are among the chemicals made by splitting these products. AGEs are produced when glycation intermediaries carry on reacting. The final products of endogenous glycation are known as AGEs. Food items may also contain an AGE, such as N-ε-CML or carboxyethyllysine (CEL), which can arise via exogenous glycation.(86)

High systemic glucose and fructose levels accelerate the glycation rate of long-lived proteins, which leads to the accumulation of AGEs. Two key processes link AGEs to diabetes and age-related human disorders: external consumption and endogenous generation. The first entails the biochemical modification of their biological roles through covalent crosslinking of serum proteins, enzymes, lipids, DNA, and extracellular matrix (ECM) proteins. Immunogenic DNA-AGEs are created when DNA is glycosated in conditions like diabetes, cancer

and neurological disorders. In diabetes and aging, long-lived ECM proteins lose some of their biomechanical and physical characteristics due to crosslinking by AGEs. Type I collagen glycation disrupts the process of normal collagen crosslinking (87) and modifies the tropocollagen molecular structure, which inhibits intrafibrillar molecular sliding in tendons that have stiffened (88). Skin and vascular systems stiffen as a result of glycation's post-translational crosslinking of elastin (Figure 3), which reduces viscoelasticity.(89) In diabetes and age-related cataracts, glycation of lens acrystallin causes the water-soluble protein to crosslink, which explains why there is a decrease in lens transparency and an increase in light scattering.(90)

The second process focuses on how AGEs interact with the receptors on their cell surfaces. The most well-researched AGE–receptor interaction is the receptor for AGE (RAGE), also known as the AGE–RAGE axis.(91) RAGE is a multiligand, pattern-recognizing receptor with distinct isoforms that are expressed in various organs such as the kidney, lung, brain, skeletal muscles, and endothelium. (84) Not all AGEs have the same affinity for RAGE due to the structural uniqueness of the RAGE V domain (92), For instance, AGEs generated from methyl-glyoxal exhibit a high affinity for RAGE (93). On the other hand, glycated amino acids that are free and not bound by peptides do not trigger the RAGE response, and proteins that have been changed with CML cannot bind to RAGE and trigger inflammatory signaling pathways.(94) Because of harsh processing conditions, studies on the AGE–RAGE axis have frequently been conducted with highly crosslinked proteins, which may resemble nutrition proteins. However, the impact of transport and digestion within the body was frequently

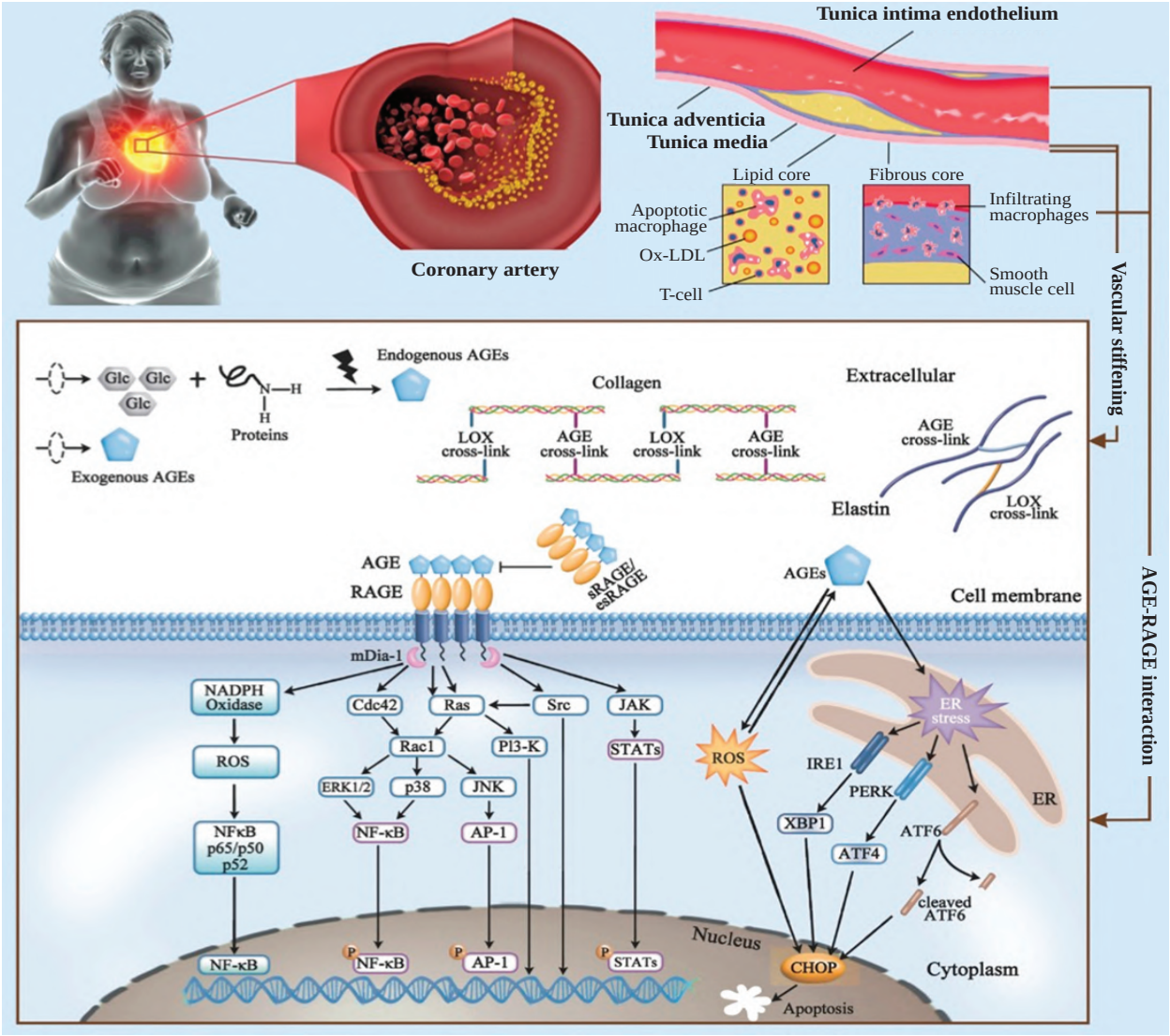

Figure 3. Molecular mechanisms linking AGEs to human disorders.(43) (Adapted with permission from Elsevier).

left out of those investigations. Crosslinked dietary proteins are unlikely to be able to enter the bloodstream intact from meals and reach RAGE due to their high molecular weight. The variety of RAGE ligands and their actions in various cell types make the signaling processes involved in the AGE–RAGE axis complex. Oxidative stress is a significant outcome of AGE–RAGE signaling. Through activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidases, malfunction of the mitochondria, or redox interaction between these two ROS-producing pathways, AGEs cause intracellular ROS generation.(95) The process by which the AGEs are generated frequently affects the consequences that are seen. ROS generation triggers the unfolded protein response, which in turn triggers endoplasmic reticulum stress and apoptosis induced by CCAAT/enhancer binding proteins homologous protein (CHOP).(96)

Fructose-mediated Ages Formation, Their Metabolic and Inflammatory Diseases

Western diet, combined with a sedentary lifestyle often be blamed as one factor to increase the risk of T2DM, non-alcoholic fatty liver disease (NAFLD), and metabolic syndrome (MetS), especially due to its high refined carbohydrate and sugar intake particularly in beverages. (97) Fructose, is a leading contender to significantly increase the incidence of MetS associated with an excessive inflammatory response and oxidative stress. Over 90% of fructose consumed is metabolized by the liver during first pass, where it stimulates *de novo* lipogenesis to drive hepatic triglycerides (TG) synthesis more potent than glucose, through the conversion of excess carbons into lipids; and this leads to dyslipidemia, endothelial dysfunction, hepatic insulin resistance, NAFLD, and cardiomyocyte lipid accumulation.(97–99)

Because of its increased stability in the open chain form and its keto group, fructose metabolism bypasses the rate-limiting glycolytic enzyme, phosphofructokinase, and proceeds through glycolysis in an unregulated manner. This makes fructose 8–10 times more reactive than glucose in the production of Maillard reaction products.(100–104) Hepatocytes utilise GLUT2 and GLUT8 to absorb fructose (Figure 4, reaction 1). Fructose is typically consumed with glucose in human meals. High-fructose corn syrup (HFCS) is 60% glucose, and apple juice is 66% glucose. Trioses (Figure 4, reaction 4) are produced quickly and directly as a result of fructokinase phosphorylation (Figure 4, reaction 2) and aldolase B splitting (Figure 4, reaction 3). A large portion of the triose pool forms the foundation of TGs in *de novo* lipogenesis when there is a concomitant glucose flux (Figure 4, reaction 5). These TGs may be released along with apoB100 as very low density lipoprotein (VLDL) (Figure 4, reaction 6). The fact that excess MGO generation results from an uncontrolled triose flux (Figure 4, reaction 7) has not received enough attention.(41,105,106)

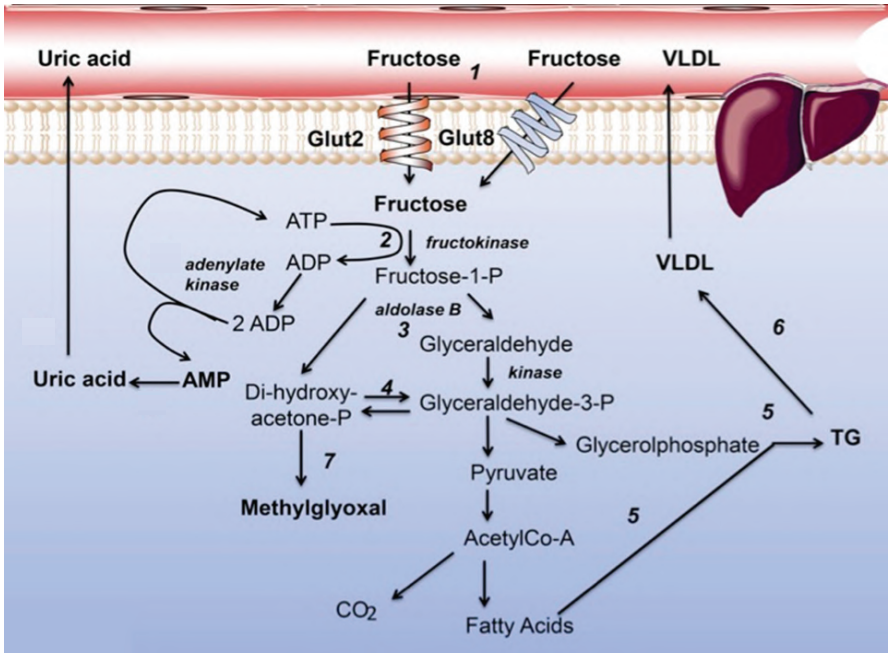

Figure 4. Fructose metabolism in hepatocytes.(106) (Adapted with permission from American Society for Nutrition).

DM have been linked to the Maillard reaction, as the adduct formation of reactive carbonyls in glucose, fructose, and their metabolites, such as deoxyglucosone or MGO, with amino groups in protein, DNA, and lipids.(6,107–113) Fructose forms the Heyns product instead of the Amadori product. The Heyns product and other fructose-mediated adducts are not detected by the widely used clinical techniques for glucose glycation.(114) This has hampered studies on fructose glycation's possible involvement in the etiology of chronic pain in humans. It was first suggested that endogenous fructose, which is produced via the sorbitol pathway, could be the source of AGEs especially CML content in tissues related to diabetes macrovascular complication.(115,116)

The original hypothesis that fructose served as an intracellular glycating agent was derived from the polyol pathway. The kidney, cornea, and peripheral nerves exhibit elevated intracellular fructose concentrations in diabetics with active polyol pathway.(115–117) Acceleration of the polyol pathway is associated with the pathophysiology of diabetic vascular issues.(115,116,118–120) Fructose can cause damage to endothelial cells because of following conditions: fructose reacts with proteins 10 times faster than glucose to form AGEs; fructose-AGEs can cause cellular senescence in Human umbilical vein endothelial cells (HUVECs); fructose-rich diets increase AGE formation, RAGE expression, and oxidative stress generation in rat adipose tissues, which leads to metabolic disturbances that are all mitigated by the use of DNA-aptamer raised against AGEs.(121,122)

According to certain research, pyruvate, a well-known substrate of the tricarboxylic acid cycle (TCA) in the mitochondria, is produced via fructose-derived glycolytic metabolism. Therefore, there's a good chance that problems with fructose metabolism will eventually affect oxidative metabolism. One typical characteristic of diabetic cardiomyopathy is impaired heart mitochondrial activity. This implies that even the low fructose levels may be harmful to cardiomyocyte mitochondrial function, metabolic disruption, lipid accumulation, inflammation, apoptosis, and also the pathological growth in an environment where the fructose metabolism is elevated. In light of this matter, prolonged fructose exposure may cause endothelial cell damage in part by activating fructose-derived AGEs and their receptor RAGE axis. It may also aggravate contractile dysfunction, oxidative stress, and increased inflammation in CVD such as peripheral arterial disease, stroke, coronary heart failure, hypertension, and other vascular and/or cardiac conditions.(122)

MGO, A Highly Reactive Dicarbonyl Compound in Diabetes and Its Vascular Complications

Recent studies showed that hyperglycemia-induced increased production of the reactive agent MGO and promotes the development of vascular problems. MGO is primarily generated as a byproduct of glycolysis. The correlation between MGO to vascular problems in diabetes including increasing the risk of hypertension, dyslipidemia, and obesity in addition to hyperglycemia suggest that MGO has a significant role in the emergence of vascular complications in people with diabetes.(123)

The strongest glycating agent in humans is the extremely reactive metabolite MGO.(124–126) At first, it was believed that high glucose levels are primarily responsible for the nonenzymatic glycation of DNA, lipids, and proteins, which results in the formation of AGEs, a diverse set of compounds.(127) These macromolecules suffer permanent damage from AGE production, which modifies their structural and functional integrity.(128) This damage also plays a role in aging-related illnesses, including diabetes and its sequelae, as well as neurodegenerative diseases. Among the sugars in biological systems with the least amount of reactivity is glucose.(55) In fact, other than glucose, a variety of reactive metabolites also play a substantial role in the development of AGEs, with MGO serving as the primary precursor.(125) Despite having a concentration in plasma that is approximately 25,000 times lower than glucose, MGO exhibits up to 50,000 times more glycation reactivity than glucose.(129) As a result, MGO rapidly produces glycation adducts on DNA (130), lipids (131), and proteins (132,133), which may alter their functionalities.

Apart from hyperglycemia, MGO production could also be significantly influenced by inflammation and hypoxia, since these circumstances also lead to an increase in glycolysis.(134) The glyoxalase system detoxifies MGO under physiological conditions. The enzymatic glyoxalase defence system converts MGO to D-lactate and relies mostly on GLO1, reduces the deleterious effects of MGO.(135) Every mammalian cell contains the glyoxalase machinery in its cytoplasm. MGO levels are impacted by a reduction in GLO1 expression or a decrease in GLO1 activity, which in turn affects MGO stress. Increased levels of MGO may also result from the impairment of GLO1, the rate-liming enzyme in the glyoxalase pathway, in terms of expression and/or activity. These results may help to explain the association

between MGO and a number of other age-related chronic inflammatory diseases, including cancer, hypertension, atherosclerosis, and disorders of the central nervous system, in addition to diabetes and its consequences.(136)

The nonenzymatic process involved in the production of MGO is present in all cells and organisms (137), both in healthy and unhealthy settings. MGO synthesis under healthy conditions occurs at a rate of around 125 mol/kg cell mass per day, or 0.1% of the glucotriose flux. (138) MGO formation is correlated with enhanced glucose metabolism, as seen in diabetes, as well as other metabolic pathways including gluconeogenesis and glyceroneogenesis that are linked to elevated triose levels. The breakdown of glycated proteins, acetone oxidation in the breakdown of ketone bodies during diabetic ketoacidosis, threonine catabolism, and lipid peroxidation are minor causes of MGO production.(139) MGO is also found in a number of everyday items, however because MGO in food products is metabolized or interacts with proteins prior to absorption in the gastrointestinal system, exogenous sources of MGO are unlikely to have a major impact on plasma MGO levels.(140)

The primary features of diabetes-related vascular endothelial dysfunction include decreased endothelium barrier function, elevated oxidative stress, inflammation, and abnormalities in vasoregulation as a result of hyperglycemia.(141) An intracellular excess of glucose flux causes four distinct biochemical pathways to overactivate endothelial cells. These pathways are then connected by a single upstream event, which is the overproduction of ROS in the mitochondria. Endothelial cells mostly produce ATP by glycolysis, as opposed to smooth muscle cells.(9,142) Facilitated diffusion is the mechanism by which glucose is transported into endothelial cells, and GLUT1 is the primary insulin-independent pathway for glucose absorption.(143) Consequently, a surge in intracellular storage of glucose and its metabolites, such as MGO, will result from increased blood glucose concentrations.(144)

Ultra-performance liquid chromatography tandem mass spectrometry (UPLC-MS/MS), is now the state-of-the-art method for measuring MGO. The usual plasma levels of MGO in healthy individuals have been estimated to be ~60–250 nM, and the levels of MGO in cells have been calculated to be ~1–5 M MGO, utilizing UPLC-MS/MS and controlling sample processing to avoid artificial synthesis of MGO The increased intracellular levels of MGO compared to extracellular levels are difficult to explain because there is a dynamic interchange of free MGO between cellular and extracellular compartments.(145) Higher amounts of MGO that has been reversibly and unstably bound to cellular proteins may be the cause; in this case, the MGO assay conditions will measure free MGO rather than a dynamic exchange. T1DM and T2DM patients had greater fasting plasma MGO concentrations, which momentarily rise in both normoglycemic and diabetic patients throughout the postprandial period.(146) There have been reports of plasma levels of MGO in individuals with renal illness that are up to six times greater; these levels rise with the stage of the disease.(41)

Cell redox homeostasis, oxidative stress that could result in permanent oxidative damage must be prevented by maintaining a balance between the generation and removal of ROS. Reduced GSH is a key component in this delicate balance since it is necessary for both the scavenging of reactive 2-oxoaldehydes MGO and ROS. MGO is a cytotoxic substance that is constitutively produced as a consequence of glycolysis and other forms of nutritional catabolism. It is detoxified in a GSH-dependent way by the glyoxalase pathway, which is made up of the GLO1 and GLO2 II processes. The cellular GSH/GSSG ratio can rapidly decline in response to a natural increase in ROS generation (oxidative eustress), which can trigger the reversible SLG of important proteins in an effort to restore the redox balance. Under oxidative stress conditions, there is also a rise in MGO levels, which are most likely driven by a number of factors, including a drop in GSH levels and/or a bottleneck in glycolysis brought on by reversible SLG and inhibition of G3P dehydrogenase.(23) Alternative MGO detoxification has beed described under defective glyoxalase system. The cytosolic glyoxalase system in MGO converts it almost exactly to D-LAC *in vitro*, indicating that MGO in the extracellular compartment enters the cells for detoxification. (138) The minor fraction of MGO that is not metabolized will react with protein and DNA to form AGEs.(147)

Since CML has been demonstrated to trigger foam cell apoptosis, AGEs resulting from elevated MGO synthesis may facilitate apoptosis and concurrent atherosclerosis progression.(148) More MGO and AGEs may accumulate in the atheroma as a result of inflammation, which both upregulates GLO1 and enhances metabolic activity (149), making the plaque more unstable and susceptible (150).

Clinically speaking, lowering MGO accumulation and raising GLO1 activity may open up new treatment avenues for minimizing the pathophysiological changes brought on by elevated MGO levels (Figure 5).(151) GLO1 inducers can be another therapy method for lowering MGO. Activators of this nuclear factor erythroid 2-related factor 2 (Nrf2) transcription pathway are crucial for continuing

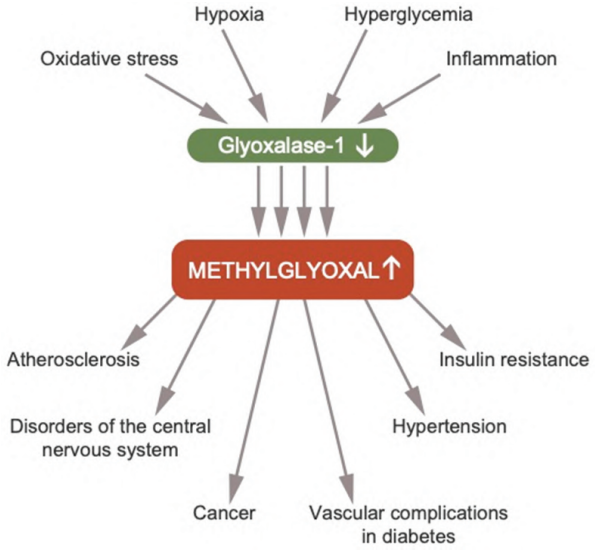

Figure 5. Decreased expression of GLO1 occurs in the context of hyperglycemia, inflammation, hypoxia, and oxidative stress. (123) (Adapted with permission from the American Physiological Society).

research because GLO1 expression is regulated by Nrf2 binding to the antioxidant response element (ARE) in the GLO1 promoter. In this sense, isothiocyanates, such as sulforaphane, are intriguing. It is known that these substances, which are present in cruciferous vegetables, activate Nrf2. Nrf2 has been known as therapeutical target in T2DM.(152,153) Nrf2 activators have been shown to lower cellular and extracellular quantities of MGO and MGO-derived protein adducts, boost GLO1 expression, and decrease mutagenesis and cell detachment.(154) These results emphasize the significance of the Nrf2-ARE-GLO1 pathway-mediated regulation enhancement of cell defenses against MGO. Therefore, patients with age-related illnesses where MGO plays a critical role may benefit from dietary bioactive inducers of GLO1.

Therapeutic Options to Reduce AGEs in Patients with Diabetes

While there are now no clinically viable interventions to treat issues linked to MGO, over time, a number of methods to reduce MGO have been developed. Treatments that target MGO, such as MGO scavengers and GLO1 inducers, are effective in treating disorders where MGO is essential.(123) Apelin-13 is a cytoprotective polypeptide ligand that protects against MGO-induced aortic endothelial dysfunction. According to research, apelin-13 inhibits MGO-induced endothelium apoptosis and UPR by activating the AMPK pathway. Apeline-13 has the potential to treat diabetic cardiovascular issues since it controls the AMPK activation pathway to reduce MGO-induced UPR and endothelial dysfunction.(155)

The often-prescribed insulin sensitizer, metformin, are known to decrease excessive ROS generation and cell apoptosis by reducing oxidative stress, mitochondrial damage, and inflammatory reactions, as well as elevating antioxidant levels, which is associated with PI3K/Akt and Nrf2/HO-1 signaling pathways activation. Metformin prevented MGO-induced apoptosis, inhibited the increment of the Bax/Bcl-2 ratio, and attenuated the activation of cleaved caspase-3 in a dose-dependent manner, confirming the cytoprotective effects of metformin against MGO-induced apoptosis. Metformin prevented MGO-induced apoptosis by inhibiting the activation of cleaved caspase-3. Metformin markedly inhibited MGO-induced ROS generation and caused a clear decrease in superoxide dismutase (SOD), catalase (CAT), and phospholipid hydroperoxide glutathione peroxidase (GSH-Px) activities *in vitro*. Metformin inhibited MGO-induced depolarization of matrix metalloproteinase (MMP) and protected against mitochondrial morphological changes in a dose-dependent manner.(156,157) Torvastatin 20 mg/day for 3 months can significantly improve the level of GLO1 activity ($p<0.001$) and thereby prevent diabetic complications.(158)

By directly binding to excess MGO, NAC lowers blood pressure by reestablishing cytosolic Ca^{2+}, nitric oxide, and Ca^{2+} channel activity. Increased tissue glutathione levels are another effect of NAC. In rats with streptozotocin (STZ)-induced diabetes, treatment with the antioxidant NAC regulated the overexpression of connective tissue growth factor and myocardial PKCβ2, and it also reduced the development of cardiac hypertrophy.(157)

Polyphenols which can be found from various sources (159), such as from citrus and pomegranates have been shown in experiments to be able to scavenge α-DCs. Consuming citrus and pomegranate complex (CPC) capsules for four weeks can lower the plasma level of MGO in elderly people by 9.8%. The main flavonoid glycoside in sweet orange extract, hesperidin, is known to stimulate GLO1 and forms adducts with MGO, which may lower the quantities of both molecules in the system. Punealogan and ellagic acid, the two main polyphenolic chemicals found in pomegranate fruit extract, have strong antioxidant properties. According to certain *in vitro* experimental research, ellagic acid and urolithin A, a metabolite of ellagitannins and ellagic acid produced by the gut microbiota, scavenge MGO to prevent non-enzymatic glycation.(160)

By limiting the generation of ROS, genistein can prevent the MGO-induced apoptosis by blocking the activation of caspase-3 and the MAPK signaling pathways. These results point to genistein's advantageous effect and offer fresh information on its possible therapeutic uses in maintaining endothelial function in diabetic vascular problems.(161)

A flavonoid called fisetin, a dicarbonyl scavenger, loaded with collagen type I hydrogel (Fisetin-HG) has been found to reduce MGO-AGE accumulation, increase GLO1, the primary enzyme that metabolizes MGO, and lower oxidative stress in the myocardial infarct heart. These results have been linked to improved cardiac function and a smaller scar size. In addition, this treatment decreases pro-inflammatory macrophages in the infarct location while increasing pro-healing macrophages and neovascularization.(162)

Conclusion

Vascular damage are linked to diabetes. The AGE precursor MGO are important in determining the connection between diabetes and vascular damage. MGO known to directly correlated with hyperglycemia and abnormal angiogenesis, increasing oxidative stress and endothelial dysfunction, thus linked to atherosclerosis which lead to diabetes macrovascular and microvascular complication. Fructose is 8–10 times more reactive than glucose in the production of Maillard reaction products thus accelerated the pathophysiology of diabetic vascular issues. Different treatment approaches that target MGO scavengers and GLO inducers have been developed throughout the past ten years. Inducers of this enzyme that are bioactive offer novel therapeutic approaches for age-related conditions associated with MGO and may be useful therapeutic targets for diabetes's macrovascular problems.

Authors Contribution

AM drafted the original manuscript, critically revised the manuscript manuscript, and designed the figures. NMD edited and revised the manuscript. AW proposed and concepted the manuscript topic, and gave critical suggestions to the final draft. All authors have agreed with the final revisions of the manuscript.

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