Toxicology International
DOI: 10.18311/ti/2026/v33i1/47232
INFORMATICS JOURNALS
eISSN: 0976-5131 | Vol 33(1), 2026 | pp. 10-23

AGE-RAGE Signaling in Diabetes and Its Vascular Complications: Molecular Mechanisms and Therapeutic Perspectives: A Review of Current Literature

M. Nalini[1*], M. Teja Sri[2], G. Gowri[1], Nagaraju Bandaru[3], S. Madhavi Latha[4]

[1]*Department of Pharmacology, Raghu College of Pharmacy, Visakhapatnam - 531162, Andhra Pradesh, India; nalinimathala8@gmail.com*

[2]*Andhra University, College of Pharmaceutical Sciences, Visakhapatnam - 530003, Andhra Pradesh, India*

[3]*Department of Pharmacology, Sree Dattha Institute of Pharmacy, Sheriguda, Ibrahimpatnam, Hyderabad - 501510, Telangana, India*

[4]*Aditya College of Pharmacy, Surampalem - 533437, Andhra Pradesh, India*

Abstract:

Advanced Glycation End products (AGEs) are formed through non-enzymatic interactions between reducing sugars and cellular macromolecules, a process substantially enhanced under sustained hyperglycemic and oxidative stress conditions. Under normal physiology, AGEs are detoxified by the glyoxalase system; however, their pathological accumulation is closely linked to aging, diabetes mellitus, and associated metabolic disorders. The biological effects of AGEs are primarily mediated through binding to the Receptor for Advanced Glycation End products (RAGE), which activates downstream signalling pathways that promote oxidative stress, inflammatory responses, immune dysfunction, and metabolic imbalance. Insulin resistance, a central feature of diabetes, results from the combined influence of obesity, chronic hyperinsulinemia, and cellular stress, leading to disruption of Insulin Receptor Substrate-1 (IRS-1) signalling. Persistent hyperglycemia further aggravates metabolic dysregulation by enhancing protein glycation and stimulating the hexosamine biosynthetic pathway, thereby increasing Reactive Oxygen Species (ROS) generation. Excessive ROS impairs pancreatic β-cell integrity by altering redox homeostasis and essential cellular processes. Diabetes mellitus is increasingly recognised as a systemic vascular disorder affecting both microvascular and macrovascular networks, resulting in complications involving the nervous system, kidneys, heart, brain, and major arteries. Aberrant activation of signalling molecules such as ERK, JNK, IKKβ, PKCβ, PKC zeta, and mTOR contributes to defective insulin signalling and secretion. Advanced Glycation End products (AGEs) accumulate under chronic hyperglycemic and oxidative stress conditions and contribute to metabolic dysfunction by activating the RAGE signalling pathway. This activation promotes oxidative stress, inflammation, and impaired insulin signalling, leading to insulin resistance and β-cell damage. Consequently, persistent hyperglycemia and ROS generation contribute to the progression of diabetes and its systemic vascular complications.

Key Findings: This review highlights the molecular basis of AGE-RAGE-driven signalling and its gene-associated contributions to the development and progression of diabetic vascular complications.

Keywords: Advanced Glycation End Products, Diabetic Complications, Hyperglycemia, Inflammation, Oxidative Stress

Article Received on: 09.11.2024 **Revised on:** 10.02.2026 **Accepted on:** 12.02.2026

**Author for correspondence*

1. Introduction

Carbohydrates with a free aldehyde (-CHO) or ketone (>C=O) functional group in their structure are known as reducing sugars. They can transfer electrons to other compounds by acting as reducing agents thanks to their chemical structure. The aldehyde or ketone group is accessible for reaction because these cyclic sugar molecules are in equilibrium with an open-chain form. Because they have these reactive groups by nature, all monosaccharides-single sugar units-are regarded as reducing sugars. This also applies to some disaccharides, which are made up of two sugar units, if one of their constituent sugar units still has a free aldehyde or ketone group. Reducing sugars is a redox (reduction-oxidation) chemical reaction. Another molecule gets reduced as a result of the reducing sugar giving it electrons during this reaction. The sugar itself experiences oxidation at the same time, losing electrons and changing from an aldehyde or ketone group to a carboxylic acid group. All monosaccharides, such as glucose, fructose, and galactose, are typical examples of reducing sugars. Reducing sugars include disaccharides like lactose, which is present in milk, and maltose, which is produced when starch is broken down. Sugar reduction is important for both food science and biological systems. They participate in metabolic processes like glycolysis, which breaks down glucose to produce energy, and are a major source of energy for living things in biology. Blood glucose levels can rise quickly as a result of limiting carbohydrates quick absorption, which is important in diseases like diabetes. On the other hand, not every sugar is a lowering sugar. Table sugar, or sucrose, is a non-reducing sugar. This is because neither of its glucose or fructose units can open into a straight-chain form with a free aldehyde or ketone group due to the glycosidic bond between them. The reason sucrose does not react in tests for lowering sugars can be explained by this structural difference[1].

Advanced Glycation End products (AGEs) represent a heterogeneous group of irreversible adducts generated through non-enzymatic reactions between reducing sugars and nucleophilic groups of proteins, lipids, and nucleic acids. Although AGE formation occurs at a low rate under physiological conditions, persistent hyperglycemia and enhanced oxidative stress markedly accelerate this process, leading to pathological accumulation. In healthy systems, reactive dicarbonyl intermediates such as methylglyoxal are efficiently detoxified by the glyoxalase pathway; (The two primary enzymes in the glyoxalase pathway, glyoxalase I and glyoxalase II, work together to detoxify methylglyoxal, a hazardous consequence of glycolysis.

The two essential enzymes in the glyoxalase system, Glyoxalase I (GLO1) and Glyoxalase II (GLO2), cooperate to transform Methylglyoxal (MG) into non-toxic byproducts. By detoxifying harmful aldehydes generated during regular metabolism, this route is crucial for preserving cellular health. Methylglyoxal and Glutathione (GSH) are converted by GLO1 into the hemithioacetal intermediate S-D-lactoylglutathione. This intermediate is subsequently hydrolysed by GLO2 to create D-lactate and replenish GSH, which can be used again). However, impairment of this defense mechanism under diabetic conditions promotes excessive AGE burden and cellular dysfunction. Highly reactive dicarbonyl metabolites are generated from sugars in circulation or formed during the glycolytic process undergo the Maillard reaction, a condensation between reducing sugars (*e.g.* glucose, fructose, ribose) and the free amino groups of proteins, leading to the formation of reversible unstable Schiff bases that finally may evolve into more stable Amadori products. Amadori products have the tendency to undergo oxidation re-arrangement, dehydration, and cyclisation, and over time, form the dicarbonyl intermediates that react with arginine and lysine residues to irreversibly generate crosslinked AGEs. Some of the AGEs are CML: Nε-(Carboxymethyl)-Lysine; CMA: Nε-(Carboxymethyl)-Arginine; GOLD: Glyoxal-derived Lysyl Dimer; 3-DG: 3-Deoxyglucosone; GH-1,2,3: Glyoxal-derived Hydroimidazolone; MGH-1,2,3: Methylglyoxal-derived Hydroimidazolone; CEL: Nε-(Carboxyethyl)-Lysine; CEA: Nε-(Carboxyethyl)-Arginine; MOLD: Methylglyoxal-derived Lysine Dimer; GdG: 3-(2′-deoxyribosyl)-6,7-dihydro-6,7-dihydroxyimidazo-[2,3-*b*]purin-9(8)one; CMdG: N2-Carboxymethyl-deoxyguanosine;MGdG:3-(2′-deoxyribosyl)-6,7-dihydro-6,7-dihydroxyimidazo-[2,3-*b*]purin-9(8)one; CEdG: N2-(1-Carboxyethyl)-deoxyguanosine; Glucosepane; Pentosidine; Pyrraline; Argpyrimidine. Under High Glycemia diets (HG, right), proteolytic capacities are insufficient and AGEs accelerate the formation of aggregates/oligomers, leading to the onset of age-related diseases[1].

The pathological relevance of AGEs is largely mediated through their interaction with the Receptor for Advanced

Glycation End products (RAGE), a multiligand pattern-recognition receptor expressed on endothelial cells, immune cells, smooth muscle cells, and pancreatic β-cells. Engagement of AGEs with RAGE initiates a cascade of intracellular signalling events, including activation of Nuclear Factor-κB (NF-κB), Mitogen-Activated Protein Kinases (MAPKs), and Protein Kinase C (PKC) isoforms, thereby amplifying oxidative stress and inflammatory gene expression. This sustained signalling establishes a feed-forward loop that perpetuates metabolic and vascular injury. Many studies have reported the involvement of glycated proteins in multiple degenerative and inflammatory diseases: Glycation of Cerebro-Spinal Fluid (CSF) proteins in Alzheimer's disease; glycation of Low-Density Lipoprotein (LDL), collagen and elastin in diabetic arteriosclerosis leading to cerebrovascular and cardiovascular occlusion; glycation of lens crystallins in diabetic cataract; elevated carboxymethyl lysine in CSF of Amyotropic Lateral Sclerosis (ALS); presence of argpyrimidine and carboxymethyl lysine in cancer tissues; with implications of glycated High-Density Lipoprotein (HDL) in diabetes and cancer; glucose, glyceraldehyde and methyl glyoxal AGEs in cancer proliferation and invasion. Protein glycation promotes the conversion of α-helix to β-sheet structure reported in β-amyloid protein of Alzheimer's and β-synuclein of Parkinson's diseases[2,3].

Dysregulation of Insulin Receptor Substrate-1 (IRS-1) through serine phosphorylation by stress-activated kinases such as JNK, IKKβ, and mTOR disrupts downstream insulin signalling, impairing glucose uptake and metabolic homeostasis. Concurrently, hyperglycemia-driven activation of alternative metabolic pathways, including the hexosamine biosynthetic pathway, further exacerbates oxidative stress and inflammatory signalling.

Diabetes is a serious metabolic disease characterised by elevated blood glucose levels that are believed to be caused by impaired insulin synthesis or insulin resistance in the body which is responsible for Type II diabetes mellitus. Abnormal glucose states are common in the elderly. One third of senior citizens has diabetes, and three quarters have either pre-diabetes or diabetes. Nevertheless, a large number of elderly individuals with Type 2 diabetes go undiagnosed. 45.6% of diabetic patients who have not received a diagnosis and are 65 years of age or older. Men were more likely than women to have undetected diabetes, and those who did reported feeling better about their health. Over the past few decades, the prevalence of diabetes has significantly increased in almost every corner of the world; 415 million people worldwide today have the disease. Over the past few decades, the prevalence of diabetes has been rising substantially. According to the International Diabetes Federation (IDF), around 500 million. Diabetes currently affects 30% of people worldwide, and by 2045, that number is predicted to rise by an additional 30%. Diabetes is a common cause of morbidity, a lower quality of life, and early mortality when combined with its numerous micro and macrovascular consequences. Diabetes is expected to be responsible for around 10% of all-cause mortality worldwide in the 20-99 age group[4]. Between 1990 and 2022, the number of people with diabetes increased from 200 million to 830 million. In comparison to high-income nations, prevalence has been increasing more quickly in low-and middle-income nations. In 2022, over half of diabetics did not take their medicine. Low-and middle-income nations have the lowest rates of diabetes treatment coverage. Diabetes results in lower limb amputation, heart attacks, stroke, blindness, and renal failure.

Over two million people died from diabetes and renal disease in 2021. Furthermore, elevated blood glucose was a contributing factor in around 11% of cardiovascular fatalities[5].

In the present review, the Kyoto Encyclopedia of Genes and Genomes (KEGG) used which is a comprehensive database resource for the biological interpretation of genomic sequences and other high-throughput data[5]. With reference to this database several genetic pathways responsible for diabetes related complications was enlisted in this review.

2. KEGG Analysis for Diabetic Complications

ERK1/2 are MAP kinases activated by growth factors, stress, and inflammatory signals. In metabolic tissues, ERK becomes aberrantly phosphorylated in conditions of lipid overload and hyperglycemia, contributing to impaired phosphorylation of insulin receptor substrates and downstream signalling dysfunction. Elevated ERK signalling is associated with increased serine phosphorylation of IRS proteins, reducing insulin-stimulated PI3K-Akt signalling and glucose uptake in insulin-responsive tissues. The MAPK cascade, including ERK, is activated by free fatty acids and high glucose, making it a relevant contributor to hepatic and muscle insulin resistance[6]. JNK, another stress-activated MAP

kinase, integrates signals from inflammatory cytokines and metabolic stress. In skeletal muscle and adipose tissue of insulin-resistant states, JNK is activated by oxidative stress and nutrient overload, promoting inhibitory serine phosphorylation of IRS-1 and dampening insulin receptor signalling. Proteomic studies of insulin-resistant human muscle have also highlighted enrichment of JNK and related p38 kinase signaling pathways, implicating them in the phosphoproteomic signature of reduced insulin sensitivity[7].

IKKβ is a central component of the NF-κB activation cascade. Chronic metabolic inflammation seen in obesity and diabetes leads to persistent IKKβ activation, which in turn promotes NF-κB-driven inflammatory gene expression and contributes to insulin resistance by enhancing serine phosphorylation of IRS proteins. IKKβ also crosstalks with nutrient-sensing pathways; recent studies show that NF-κB signaling remains a key mediator of inflammatory stress in metabolic tissues, although direct diabetes-specific experimental articles remain limited in public indexing[8,9]. PKCζ is an atypical protein kinase C isoform implicated in insulin signalling and β-cell adaptation. While much of the classical literature predates 2020, recent mechanistic work underscores its potential role in transmitting glucose-stimulated signals in β-cells and in coordinating growth responses mediated through mTOR and cyclin-D2 during compensatory β-cell proliferation. Continued activation of PKCζ in metabolic stress may influence insulin secretory capacity and β-cell mass, although contemporary original studies specifically focusing on PKCζ in human diabetes remain limited[10].

PKCθ is implicated in lipid-induced insulin resistance in skeletal muscle. Although many foundational PKCθ studies predate 2020, the mechanistic consensus remains that PKCθ is activated by lipid accumulation and diacylglycerol in muscle cells, leading to increased serine phosphorylation of IRS-1 and impaired glucose transport. This molecular mechanism is still widely invoked in recent mechanistic reviews of free fatty acid-induced insulin resistance[11]. mTOR functions as a nutrient and energy sensor integrating signalls from insulin, amino acids, and growth factors. Chronic nutrient excess and hyperinsulinemia activate mTORC1, which, *via* feedback mechanisms, enhances serine phosphorylation of IRS proteins and reduces PI3K signaling, contributing to systemic insulin resistance. Recent clinical and experimental data note that in high-insulin and high-glucose conditions, mTOR is upregulated along with inflammatory markers and correlates with insulin resistance indices[12,13].

Some of the best chemically characterised AGEs include N-epsilon-Carboxy-Methyl-Lysine (CML), N-epsilon-Carboxy-Ethyl-Lysine (CEL) and Imidazolone.

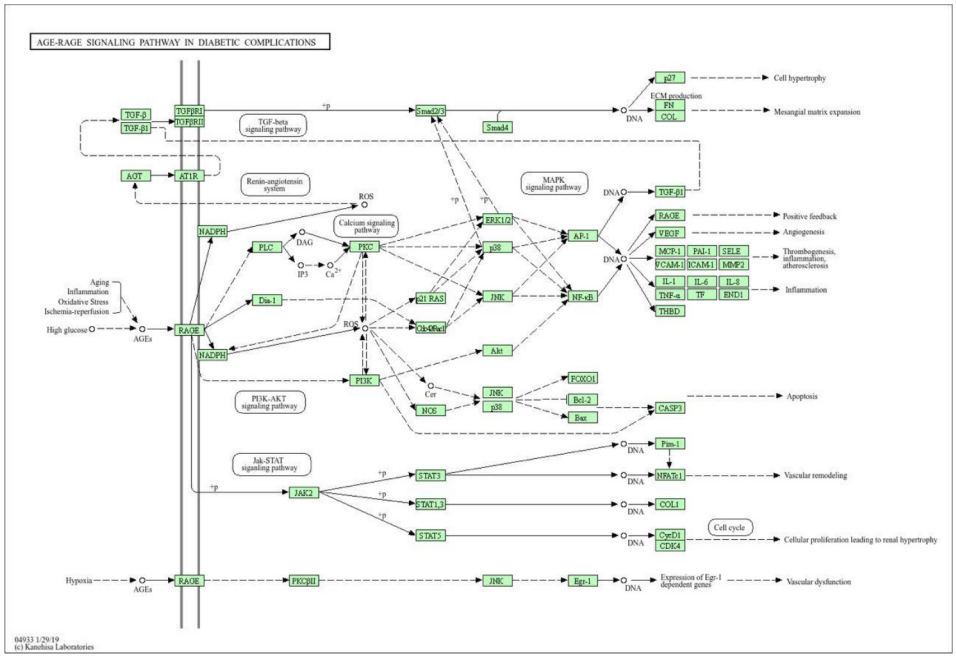


Figure 1. KEGG analysis for diabetic complications[61].

The major receptor for AGEs, known as Receptor for Advanced Glycation End products (RAGE or AGER), belongs to the immunoglobulin superfamily and has been described as a pattern recognition receptor. AGE/RAGE signalling elicits activation of multiple intracellular signal pathways involving NADPH oxidase, protein kinase C, and MAPKs, then resulting in NF-kappaB activity. NF-kappa B promotes the expression of pro-inflammatory cytokines such as IL-1, IL-6 and TNF-alpha and a variety of atherosclerosis-related genes, including VCAM-1, tissue factor, VEGF, and RAGE. In addition, JAK-STAT-mediated and PI3K-Akt-dependent pathways are induced *via* RAGE, which in turn participate in cell proliferation and apoptosis respectively. Hypoxia-mediated induction of Egr-1 was also shown to require the AGE-RAGE interaction. The results of these signal transductions have been reported to be the possible mechanism that initiates diabetic complications[14].

3. Mechanism of Hyperglycemia-induced Impairment of Insulin Secretion

Chronic hyperglycemia disrupts glucose homeostasis by simultaneously impairing pancreatic β-cell insulin secretion and reducing insulin sensitivity in peripheral tissues. Sustained elevation of intracellular glucose enhances oxidative stress through excessive generation of Reactive Oxygen Species (ROS), leading to mitochondrial dysfunction and altered redox balance in β-cells, which possess limited antioxidant capacity. This oxidative burden interferes with glucose-stimulated insulin secretion by impairing ATP production, calcium signalling, and insulin granule exocytosis. Insulin resistance was induced by several diabetogenic factors such as obesity, hyperinsulinism and cellular stress leads to inhibition of IRS 1 (Insulin Receptor Substrate 1) function. The genes responsible for impaired insulin secretion and effecting IRS1 function are[15]. (ERK, JNK, IKKbeta, PKC zeta, PKC theta and mTOR) the mechanism was represented in Figure 1.

Prolonged hyperglycemia is also responsible for insulin resistance by the mechanism of beta cell dysfunction. Hyperglycemia by the mechanism of glycation, hexosamine pathway leads to huge approach of Reactive Oxygen Species (ROS) to beta cells of pancreas causing damage to cellular component PDX-1 (Pancreatic and Duodenal Homeobox 1)[16]. The two candidate genes Kir6.2 and IRS play a central role in insulin secretion and signalling transmission[17,18].

4. Diabetic Complications

These days, diabetes mellitus is recognised as a vascular disease that affects nerves, other organs, kidney, retina, and other small and big microvascular blood vessels as well as the heart, brain, and peripheral arteries. Cardiovascular issues account for 23.6% of cases, renal complications for 21.1%, ocular difficulties for 16.6%, and foot ulcers for 5.1%. There is a higher prevalence of these problems, in many patients experiencing numerous difficulties[19].

There are several pathological mechanisms how hyperglycemia causes several complications. Activation of the Diacylglycerol (DAG)/Protein Kinase C (PKC) approach, raised oxidative stress, elevated AGE's, increased hexosamine pathway, and elevated polyol pathway are some of the most discussed causes represented in Figure 7 [20]. In modern world medication for diabetic complications was available without targeting the mechanism of disease

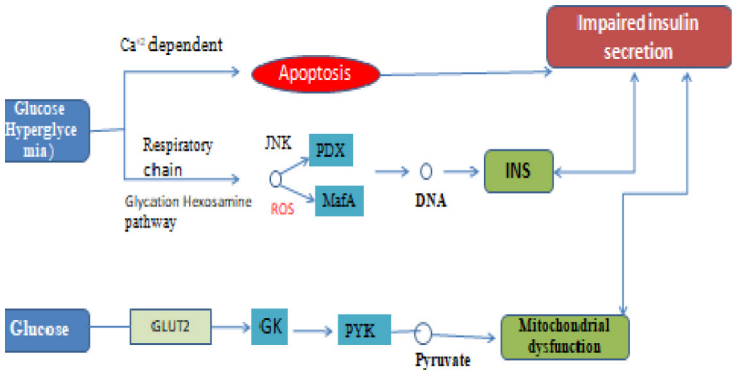


Figure 2. Mechanism of impaired insulin release and insulin resistance due to hyperglycemia.

progression[21]. The present review focuses on various mechanisms responsible for the progression of diabetes to diabetic complications and their mechanisms involved in disease progression. Diabetes mellitus for a prolonged duration can lead vascular tissue damage which can progress to both macrovascular and microvascular problems significantly increase morbidity and death of diabetic subjects shown in Figure 2 [18]. Microvascular complications, such as diabetic retinopathy, neuropathy, and nephropathy, impact small blood vessels. Kidney problems, nerve discomfort, and eyesight impairment might result from these consequences.

Large blood vessels are affected by macrovascular complications, which include peripheral artery disease, coronary artery disease, and stroke. Chest pain, exhaustion, and serious cardiovascular problems are possible outcomes of these conditions. Accelerated atherosclerosis formation, which narrows the artery lumen and may raise the risk of cardiovascular events like stroke and heart attack, is the primary pathogenic process in diabetic macrovascular disease. RAGE activation is one of the ways that ROS can be produced. Advanced glycation, auto-oxidation, glycolysis, glucose-6-phosphate dehydrogenase, sorbitol, polyol pathway flux, hexosamine pathway flux, mitochondrial respiratory xanthine oxidase, uncoupled nitric oxide synthase, and NADPH oxidases are some of the renal sources of ROS that have been implicated in the diabetic kidney[22,23].

4.1 Macrovascualr Complications

4.1.1 Diabetic Cardiomyopathy

The patients of diabetes develop left ventricular dysfunction independent of medical cases such as coronary artery disease. The mechanism involved in the progression of Type II diabetes to diabetic cardiomyopathy involves hyperglycemia induced hexosamine pathway, impaired calcium metabolism, mitochondrial dysfunction represented in Figure 3 [10]. Heart failure, cardiomyocyte malfunction, endothelial dysfunction, cardiac fibrosis, and hypertrophy are the outcomes of effects due to hexosamine pathway[24]. Heart fibroblasts are the last effector cells in the heart fibrosis process. The promoter polymorphisms −429T/C and −374T/A were found to be differently connected with diabetic vascular complications in North Indian T2DM participants; the −429 C allele was linked to increased risk, whereas the −374 A allele was protective against macrovascular disease. The −429CC genotype was associated with higher circulating AGEs and a higher risk of macrovascular problems in Indian T2DM patients; the −374 A allele seemed to provide protection. When compared to healthy persons, the RAGE gene polymorphism significantly affects the level of AGEs and PON1 activity in diabetes subjects. MVC is more likely to occur in diabetic patients with a CC genotype of -429T/C if AGE levels are high and PON1 activity is low[25].

Patients with diabetes mellitus who exhibit failure of the left ventricle without an existing etiology, such as coronary

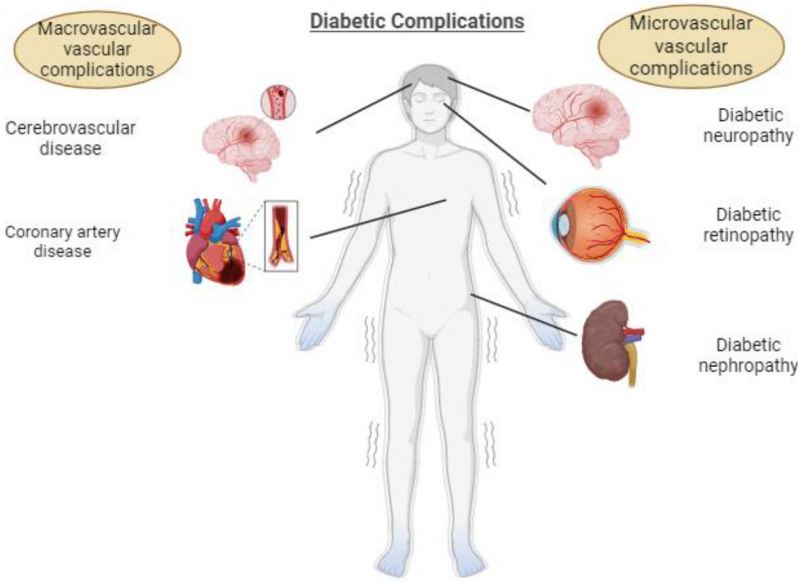


Figure 3. Major diabetic complications.

artery disease or hypertension, are said to have diabetic cardiomyopathy[24]. In general, hyperglycemia, elevated circulating fatty acids, and insulin resistance are involved in the pathophysiology of diabetic cardiomyopathy. These factors contribute to an elevated level of Reactive Oxygen Species (ROS), mitochondrial dysfunction, impaired calcium metabolism, activation of the Renin-Angiotensin System (RAS), and altered substrate metabolism[26-28]. Heart fibrosis, hypertrophy, cardiomyocyte mortality, contractile dysfunction, capillary endothelial cell damage, and eventual heart failure are the implications of these effects. Heart fibroblasts are the last effector cells in the heart fibrosis process[29,30].

4.1.2 Peripheral Vascular Disease (PVD)

Endothelialal dysfunction, vascular smooth muscle damage, inflammation and hypercoagubility due to uncontrolled diabetes mellitus may be the factors responsible for atheroscelrosis, embolism and thrombus formation in large arteries[21]. The formation of embolism in arteries is responsible for peripheral vascular disease or peripheral arterial disease. The promising therapeutic adjunct in the treatment for peripheral arterial disease is therapeutic angiogenesis[31].

4.2 Microvascular Diabetic Complications

Chronic and prolonged hyperglycemia effecting small blood vessels may develop micro vascular complications which include diabetic retinopathy, nephropathy and neuropathy[19,32]. The risks of these complications are elevated by the duration and control of blood glucose.

4.2.1 Diabetic Nephropathy

High blood glucose levels can induce inflammatory response in kidneys which can be the main mechanism of diabetic nephropathy which is the main reason for chronic kidney disease[33]. From the past studies it was reported that diabetic nephropathy is responsible for aging of tubular cells, mesangial cells, endothelial cells and podocytes[34]. High blood glucose, oxidative stress causes the activation of AGEs (Advanced Glycation End products) acting on RAGE/AGER (receptor for advanced glycation end products) induce inflammatory pathway causing the release of as IL-1, IL-6, and TNF-α represented in Figure 4 [27,35]. In addition, RAGE triggers PI3K-Akt-dependent and JAK-STAT-mediated pathways, which result in renal hypertrophy and cell proliferation[36].

4.2.2 Diabetic Neuropathy

Diabetic neuropathy is characterised by sensory loss in lower extremities causing pain and substantial morbidity. Almost half of the Type 2 diabetic patients are affected with diabetic neuropathy[37,38].

The main pathological mechanism responsible for diabetic neuropathy is oxidative stress induced advanced glycation end products shown in Figure 5 [39]. Accumulation of misfolded protein aggregates also responsible for release of RAGES which later activates the Ras /Raf Map Kinase pathway which in turn activates the inflammatory pathway for the release of TNF (tumour necrosis factor)), IL-1 (interleukin -1), IL-6 (interleukin 6), COX-2 (cyclo-oxgynase enzyme) all these inflammatory pathways are responsible for the reduction in LTP (Long Term nerve Potential) which can progress to diabetic neuropathy[40,41].

Methylglyoxal, an AGE precursor, must be detoxified by Glyoxalase-1 (GLO1), and a number of genetic variations affect the enzyme's activity and susceptibility to illness. Although not always disease-specific, a study found correlations between GLO1 rs4746 and enzyme activity levels and suggested risk for microvascular problems. GLO1 SNPs (rs4746, rs1049346, and rs1130534) were associated with reduced enzyme activity and greater plasma methylglyoxal in individuals with acute coronary

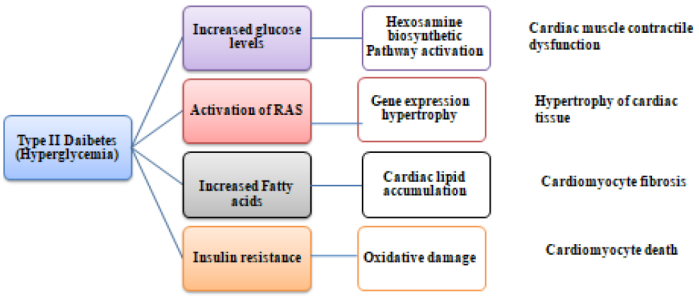


Figure 4. Schematic representation of mechanism involved in the diabetic cardiomyopathy.

syndrome in another investigation involving T2DM patients from South India. In human participants, these variations were linked to lower GLO1 enzyme activity, suggesting a genetic influence on detoxifying ability. Association of C332C-genotype of the glyoxalase 1 gene with diabetic neuropathy in Type 2 diabetes, might be an important mediator of diabetic neuropathy in Type 2 diabetes[42].

4.2.3 Diabetic Retinopathy

Diabetic retinopathy is involved in vision loss and vision impairment in working aged population aged between (45-60 years)[43]. Longer duration and later stages of diabetes leads to vision loss, DR was characterised by the growth of new retinal blood vessels, leakage and breakage of retinal vessels[44]. Several molecular pathways are involved in the progression of DR and severity of DR. Several pathological mechanisms are involved in progression in DR such as VEGF induced MAPK signaling pathway causing proliferation of vascular endothelial cells shown in Figure 6 [45].

5. Mechanisms Responsible for the Progression of Diabetic Complications

Diabetes mellitus is the major cause for diabetic complications causing structural and physiological vascular endothelial changes[46]. Inflammation, ischemic condition and oxidative stress are responsible for signaling inflammatory pathway causing hypertrophy of cells[47].

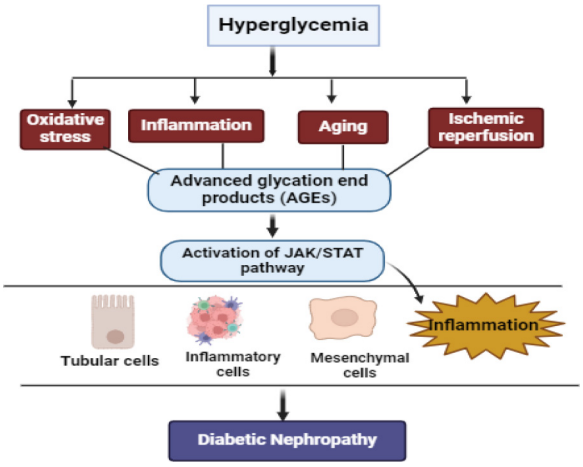


Figure 5. Mechanism of diabetic nephropathy.

Uncontrolled hyperglycemia on prolonged period effects the peripheral nerves, retina and kidneys which leads to diabetic complications. In the pathogenesis of these complications AGEs are mainly responsible for the severity of these complications[48]. Past studies have proposed that modification of cellular proteins due to glucose and amino acids attachment causing irreversible formation of AGE's which leads to glucotoxicity in nerves and reduction of long term potential and nerve conduction[49]. Previous research has shown a connection between high circulating AGEs and a progressive decrease in renal function, even in the absence of diabetes[50]. Additionally, there is a favorable correlation between the incidence of diabetic kidney disease and elevated circulating amounts of sRAGE. AGEs mediated kidney damage was due to the accumulation of AGEs in the renal compartment which was also previously reported[30,51].

A complex collection of substances known as Advanced Glycation End products (AGEs) are generated when proteins, lipids, and nucleic acids undergo non-enzymatic glycation and oxidation. This process is mostly brought on by aging and certain medical conditions including hyperglycemia[52,53]. N-epsilon-Carboxy-Methyl-Lysine (CML), N-epsilon-Carboxy-Ethyl-Lysine (CEL), and Imidazolone are among the best chemically characterised AGEs[54]. The primary AGE receptor, sometimes referred to as the Receptor for Advanced Glycation End products (RAGE or AGER), is a pattern recognition receptor that is a member of the immunoglobulin superfamily[53,55]. The primary AGE receptor, sometimes referred to as the Receptor for Advanced Glycation End products (RAGE or AGER), is a pattern recognition receptor that is a member of the immunoglobulin superfamily. Multiple intracellular signal pathways involving MAPKs, NADPH oxidase, and protein kinase C are activated by AGE/RAGE signaling, which in turn causes NF-kappa B

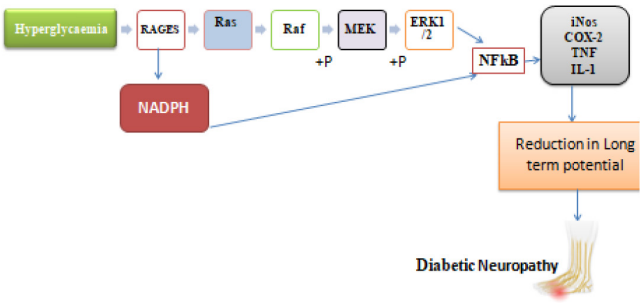


Figure 6. Schematic representation of mechanism involved in the diabetic neuropathy.

activity[56]. Figure 7 illustrates how NF-kappa B stimulates the expression of several atherosclerosis-related genes, including VCAM-1, tissue factor, VEGF, and RAGE as well as pro-inflammatory cytokines including IL-1, IL-6, and TNF-alpha[57]. Furthermore, RAGE triggers PI3K-Akt-dependent and JAK-STAT-mediated pathways, which contribute to apoptosis and cell proliferation, respectively[47,64,54,58]. It was also demonstrated that the AGE-RAGE interaction is necessary for the hypoxia-mediated activation of Egr-1. It has been suggested that the outcomes of these signal transductions may be the mechanism that initiates diabetes issues.

Polymorphisms of Aldose Reductase (AKR1B1): The polyol pathway's initial step is catalysed by AKR1B1, and genetic variation may have an impact on diabetic microvascular problems. AKR1B1 −106C>T(rs759853) was significantly associated with diabetic retinopathy in North Indian T2DM individuals; in particular, the TT genotype increased risk[59].The TT genotype at −106C>T was linked to increased erythrocyte AR levels and diabetic nephropathy in Japanese T2DM[60]. In teenagers with Type 1 diabetes, Z-2 repeat microsatellite (CA) promoter repeat is linked to greater AKR1B1 expression and a higher risk of neuropathy and microvascular damage[61]. In broad cohorts, variant rs9640883 was associated with diabetic retinopathy; however, its independent effect might rely on interactions with clinical risk factors[62].

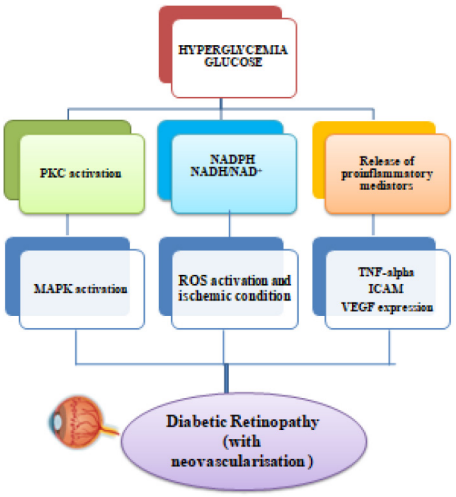


Figure 7. Schematic representation of mechanism involved in diabetic retinopathy.
(TNF-alpha- Tumor Necrosis Factor alpha, ICAM-Intracellular Adhesion Molecule, VEGF-Vascular Endothelial Growth Factor)

RAGE and NF-κB Epigenetic Regulation: While direct polymorphisms are hereditary, AGE-RAGE-mediated inflammation also depends on the epigenetic regulation of NF-κB and AGER/RAGE. Differential methylation of the AGER promoter region can impact transcription and RAGE expression in inflammatory diseases and sequelae from diabetes (several translational research studies, not yet fully resolved at the SNP level)[63].

Numerous signalling pathways are initiated by the AGEs/RAGE axis, and these pathways may trigger a variety of downstream consequences, including oxidative stress, inflammation, disruption of metabolic function, and epigenetic changes[58,64]. Identifying combination of medicinal products that target multiple pathways may be a better choice than focusing on just one when it comes to intervening against AGE accumulation and blocking the AGEs/RAGE axis[65]. Moreover, it has been demonstrated in recent years that naturally occurring substances high in bioactive components (phytochemicals) interact with AGEs and the mediators that are associated with them through a variety of signalling cascades, restricting and impeding the progression of diabetes[47,66].

5.1 AGE Inhibitors

Aminoguanidine, metformin, carnosine, homocarnosine, pyridoxamine, and N-phenacyl thiazolium bromide, Cobalamin (Vitamin B12), Benfotiamine, HMGB1 inhibitors are a few interesting medication options. Aspirin and Tenilsetam, two anti-inflammatory medications, also have AGE inhibiting characteristics. The antioxidants function as 57 species. This procedure, known as AGE inhibitors, most likely via sequestering free radicals and metal-ion chelation, Angiotensin Converting Enzyme

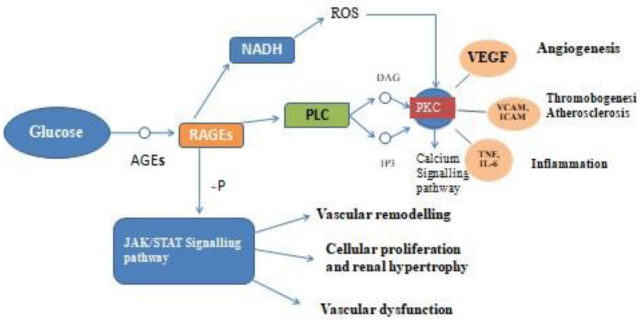


Figure 8. Schematic representation of AGE/RAGE mechanism involved in the progression of diabetic complications.

Inhibitors (ACE-I) and Angiotensin Receptor Blockers (ARB)[67].

5.2 RAGE Antagonists

RAGE can be directly targeted with RAGE inhibitors, RAGE peptides, anti-RAGE antibodies, DNA aptamers, sRAGE, or the intracellular domain of RAGE. Azeliragon (phase 3 clinical trial not proved), RAGE peptides, like the mutant RAGE peptide S391A RAGE362-404 (*in vivo* preclinical trials conducted), aptamers, soluble RAGE[68].

However, the clinical data regarding the drug's efficacy to antagonise AGE-RAGE remains restricted to specific pharmacological categories. Determining the optimal therapeutic goal for AGEs/RAGES in diabetic complications may be made easier by the outcomes of current review.

6. Conclusion

In the present modern world hyperglycemia for a prolonged period can enhance the formation of AGEs. The pathophysiology of diabetic vascular disorders, including atherosclerosis, retinopathy, nephropathy, and neuropathy, is significantly influenced by the accumulation of AGEs and RAGEs in blood and tissues. In addition to their influence on long-lived extracellular proteins through non-receptor-mediated mechanisms, the current review emphasised on the molecular mechanism of AGE-RAGE axis cellular signalling in diabetic complications. Numerous biological substances are produced that seem to activate intracellular signal transduction pathways, resulting in the production of pro-inflammatory mediators and pro-sclerotic cytokines. This raises oxidative stress and gene expression, which helps diabetic vascular complications develop and worsen. These biological mechanisms and molecular pathways may eventually serve as new therapeutic targets for mitigating vascular complications in people with diabetes mellitus[69-76].

7. Acknowledgement

The authors acknowledge the facilities provided by Raghu College of pharmacy, Vishakaptnam, Aditya College of Pharmacy, Sri Datta College of Pharmacy and Maharajah's college of pharmacy.

8. References

1. Rowan S, Bejarano E, Taylor A. Mechanistic targeting of advanced glycation end-products in age-related diseases. Biochim Biophys Acta Mol Basis Dis. 2018; 1864(12):3631-3643. https://doi.org/10.1016/j.bbadis.2018.08.036 PMID: 30279139. PMCID: PMC6822271.
2. Palanissami G, Paul SFD. AGEs and RAGE: Metabolic and molecular signatures of the glycation-inflammation axis in malignant or metastatic cancers. Explor Target Antitumor Ther. 2023; 4:812-849. https://doi.org/10.37349/etat.2023.00170 PMid: 37970208. PMCid: PMC10645465.
3. Reddy VP, Aryal P, Soni P. RAGE inhibitors in neurodegenerative diseases. Biomedicines. 2023; 11(4):1131. https://doi.org/10.3390/biomedicines11041131 PMID: 37189749. PMCID: PMC10136230.
4. Govindaswamy S, Dhivya PS, Sangeetha SKS. Prevalence and complications of diabetes mellitus in India- A systematic review. Indian J Pharm Educ Res. 2023; 57(2s):s213-s225. https://doi.org/10.5530/ijper.57.2s.25
5. Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2021. Results. Institute for Health Metrics and Evaluation. 2024. https://vizhub.healthdata.org/gbd-results/
6. Faria BQ, Calixto PS, Picheth G, Ferreira LM, Rego FGM, Guerra JFC, Sari MHM. Palmitate-induced hepatic insulin resistance as an in vitro model for natural and synthetic drug screening: A scoping review of therapeutic candidates and mechanisms. Chem Biol Interact. 2025; 420:111717. https://doi.org/10.1016/j.cbi.2025.111717 PMID: 40850566.
7. Hwang H, Bowen BP, Lefort N, Flynn CR, De Filippis EA, Roberts C, Smoke CC, Meyer C, Hojlund K, Yi Z, Mandarino LJ. Proteomics analysis of human skeletal muscle reveals novel abnormalities in obesity and Type 2 diabetes. Diabetes. 2010; 59(1):33-42. https://doi.org/10.2337/db09-0214 PMID: 19833877. PMCID: PMC2797941.
8. Guo Q, Jin Y, Chen X, et al. NF-κB in biology and targeted therapy: New insights and translational implications. Sig Transduct Target Ther. 2024; 9:53. https://doi.org/10.1038/s41392-024-01757-9 PMid: 38433280.PMCid: PMC10910037.
9. Mobeen A, Joshi S, Fatima F, et al. NF-κB signaling is the major inflammatory pathway for inducing insulin resistance. 3 Biotech. 2025; 15:47. https://doi.org/10.1007/s13205-024-04202-4 PMid: 39845928.PMCid: PMC11747027.
10. Lakshmipathi J, Alvarez-Perez JC, Rosselot C, Casinelli GP, Stamateris RE, et al. PKCζ is essential for pancreatic β-cell replication during insulin resistance by regulating mTOR and cyclin-D2. Diabetes. 2016; 65(5):1283-1296. https://doi.org/10.2337/db15-1398 PMid: 26868297.PMCid: PMC4839210.

11. Kewalramani G, Fink LN, Asadi F, Klip A. Palmitate-activated macrophages confer insulin resistance to muscle cells by a mechanism involving protein kinase C θ and ε. Plos One. 2011; 6(10):e26947. https://doi.org/10.1371/journal.pone.0026947 PMID: 22046423. PMCID: PMC3202600.
12. Amin NG, Rahim AA, Rohoma K, Elwafa RAA, Dabees HMF, Elrahmany S. The relation of mTOR with diabetic complications and insulin resistance in patients with Type 2 diabetes mellitus. Diabetol Metab Syndr. 2024; 16(1):222. https://doi.org/10.1186/s13098-024-01450-5 PMID: 39261960. PMCID: PMC11389252.
13. Stanciu SM, Jinga M, Miricescu D, Stefani C, Nica RI, *et al*. mTOR dysregulation, insulin resistance, and hypertension. Biomedicines. 2024; 12(8):1802. https://doi.org/10.3390/biomedicines12081802 PMid: 39200267. PMCid: PMC11351979.
14. Kegg Pathway: hsa04933. Kegg.jp. 2026. 2026. https://www.kegg.jp/entry/hsa04933
15. Zhu H, Chen YM, Gong WK, Lai JB, Yao B Bin, Zhao ZJ, *et al*. Shared and specific biological signalling pathways for diabetic retinopathy, peripheral neuropathy and nephropathy by high-throughput sequencing analysis. Diab Vasc Dis Res. 2022; 19(4):0–4. https://doi.org/10.1177/14791641221122918 PMid: 35989592. PMCid: PMC9397373.
16. Paneque A, Fortus H, Zheng J, Werlen G, Jacinto E. The hexosamine biosynthesis pathway: Regulation and function. Genes. 2023; 14(4):933. https://doi.org/10.3390/genes14040933 PMid: 37107691. PMCid: PMC10138107.
17. Burillo J, Marques P, Jimenez B, Gonzalez-Blanco C, Benito M, Guillen C. Insulin resistance and diabetes mellitus in Alzheimer's disease. cells. 2021; 10(5):1236. https://doi.org/10.3390/cells10051236 PMID: 34069890. PMCID: PMC8157600.
18. Banday MZ, Sameer AS, Nissar S. Pathophysiology of diabetes: An overview. Avicenna J Med. 2020; 10(04):174-188. https://doi.org/10.4103/ajm.ajm_53_20 PMid: 33437689. PMCid: PMC7791288.
19. An J, Nichols GA, Qian L, Munis MA, Harrison TN, Li Z, *et al*. Prevalence and incidence of microvascular and macrovascular complications over 15 years among patients with incident Type 2 diabetes. BMJ Open Diabetes Res Care. 2021; 9(1):1-10. https://doi.org/10.1136/bmjdrc-2020-001847 PMid: 33397671. PMCid: PMC7783518.
20. Ohiagu FO, Chikezie PC, Chikezie CM. Pathophysiology of diabetes mellitus complications: Metabolic events and control. Biomed Res Ther. 2021; 8(3):4243-4257. https://doi.org/10.15419/bmrat.v8i3.663
21. Yu MG, Gordin D, Fu J, Park K, Li Q, King GL. Protective factors and the pathogenesis of complications in diabetes. Endocr Rev. 2024; 45(2):227-252. https://doi.org/10.1210/endrev/bnad030 PMid: 37638875. PMCid: PMC10911956.
22. Chawla A, Chawla R, Jaggi S. Microvasular and macrovascular complications in diabetes mellitus: Distinct or continuum? Indian J Endocrinol Metab. 2016; 20(4):546-551. https://doi.org/10.4103/2230-8210.183480 PMid: 27366724. PMCid: PMC4911847.
23. Bereda G. Complication of diabetes mellitus: Microvascular and macrovascular Complications. 2022.
24. Jia G, Hill MA, Sowers JR. Diabetic cardiomyopathy: An update of mechanisms contributing to this clinical entity. Circ Res. 2018; 122(4):624-638. https://doi.org/10.1161/CIRCRESAHA.117.311586 PMid:29449364 PMCid:PMC5819359
25. Bansal S, Chawla D, Banerjee BD, Madhu SV, Tripathi AK. Association of RAGE gene polymorphism with circulating AGEs level and paraoxonase activity in relation to macro-vascular complications in Indian Type 2 diabetes mellitus patients. Gene. 2013; 526(2):325-330. https://doi.org/10.1016/j.gene.2013.05.013 PMid:23721855
26. Batista JPT, Faria AOV, Ribeiro TFS, Silva ACS. The role of renin-angiotensin system in diabetic cardiomyopathy: A narrative review. Life. 2023; 13(7):1598. https://doi.org/10.3390/life13071598 PMid: 37511973. PMCid: PMC10381689.
27. Poloni JAT, Rotta LN. Diabetic kidney disease: Pathophysiological changes and urinalysis contribution to diagnosis-a narrative review. J Lab Precis Med. 2022; 7:1-10. https://doi.org/10.21037/jlpm-21-20
28. Jubaidi FF, Zainalabidin S, Mariappan V, Budin SB. Mitochondrial dysfunction in diabetic cardiomyopathy: The possible therapeutic roles of phenolic acids. Int J Mol Sci. 2020; 21(17):6043. https://doi.org/10.3390/ijms21176043 PMid: 32842567. PMCid: PMC7503847.
29. Pan KL, Hsu YC, Chang ST, Chung CM, Lin CL. The role of cardiac fibrosis in diabetic cardiomyopathy: From pathophysiology to clinical diagnostic tools. Int J Mol Sci. 2023; 24(10):8604. https://doi.org/10.3390/ijms24108604 PMid: 37239956. PMCid: PMC10218088.
30. Lin YC, Chang YH, Yang SY, Wu KD, Chu TS. Update of pathophysiology and management of diabetic kidney disease. J Formos Med Assoc. 2018; 117(8):662-675. https://doi.org/10.1016/j.jfma.2018.02.007 PMid: 29486908.
31. Cooke JP, Meng S. Vascular regeneration in peripheral artery disease. Arterioscler Thromb Vasc Biol. 2020; 40(7):1627-1634. https://doi.org/10.1161/ATVBAHA.120.312862 PMid: 32434408. PMCid: PMC7357605.
32. Yen FS, Wei JCC, Shih YH, Hsu CC, Hwu CM. Impact of individual microvascular disease on the risks of macrovascular complications in Type 2 diabetes: A nationwide population-based cohort study. Cardiovasc Diabetol. 2023; 22(1):1-9. https://doi.org/10.1186/s12933-023-01821-8 PMid: 37161539. PMCid: PMC10170797.

33. Xiong Y, Zhou L. The signaling of cellular senescence in diabetic nephropathy. Oxid Med Cell Longev. 2019. https://doi.org/10.1155/2019/7495629 PMid: 31687085. PMCid: PMC6794967.
34. Hung PH, Hsu YC, Chen TH, Lin CL. Recent advances in diabetic kidney diseases: From kidney injury to kidney fibrosis. Int J Mol Sci. 2021; 22(21):11857. https://doi.org/10.3390/ijms222111857 PMid: 34769288. PMCid: PMC8584225.
35. Mengstie MA, Chekol Abebe E, Behaile Teklemariam A, Tilahun Mulu A, Agidew MM, Teshome Azezew M, *et al*. Endogenous advanced glycation end products in the pathogenesis of chronic diabetic complications. Front Mol Biosci. 2022; 9:1-11. https://doi.org/10.3389/fmolb.2022.1002710 PMid: 36188225. PMCid: PMC9521189.
36. Yuan Q, Tang B, Zhang C. Signaling pathways of chronic kidney diseases, implications for therapeutics. Signal Transduct Target Ther. 2022; 7(1). https://doi.org/10.1038/s41392-022-01036-5 PMid: 35680856. PMCid: PMC9184651.
37. Feldman EL, Callaghan BC, Pop-Busui R, Zochodne DW, Wright DE, Bennett DL, *et al*. Diabetic Neuropathy. Nat Rev Dis Prim. 2019; 5(1). https://doi.org/10.1038/s41572-019-0092-1 PMid:31197153
38. Lu Y, Xing P, Cai X, Luo D, Li R, Lloyd C, *et al*. Prevalence and risk factors for diabetic peripheral neuropathy in Type 2 diabetic patients from 14 countries: Estimates of the INTERPRET-DD study. Front Public Heal. 2020; 8:1-8. https://doi.org/10.3389/fpubh.2020.534372 PMid: 33194943. PMCid: PMC7606804.
39. Oshitari T. Advanced glycation end-products and diabetic neuropathy of the retina. Int J Mol Sci. 2023; 24(3):2927. https://doi.org/10.3390/ijms24032927 PMid: 36769249. PMCid: PMC9917392.
40. Jubaidi FF, Zainalabidin S, Taib IS, Abdul Hamid Z, Anuar NNM, Jalil J, *et al*. The role of PKC-MAPK signalling pathways in the development of hyperglycemia-induced cardiovascular complications. Int J Mol Sci. 2022; 23(15):8582. https://doi.org/10.3390/ijms23158582 PMid: 35955714. PMCid: PMC9369123.
41. Baum P, Toyka KV, Bluher M, Kosacka J, Nowicki M. Inflammatory mechanisms in the pathophysiology of diabetic peripheral neuropathy (DN)-New aspects. Int J Mol Sci. 2021; 22(19):10835. https://doi.org/10.3390/ijms221910835 PMid: 34639176. PMCid: PMC8509236
42. Groener JB, Reismann P, Fleming T, Kalscheuer H, *et al*. C332C genotype of glyoxalase 1 and its association with late diabetic complications. Exp Clin Endocrinol Diabetes. 2013; 121(7):436-439. https://doi.org/10.1055/s-0033-1345124 PMid:23775136
43. Raman R, Vasconcelos JC, Rajalakshmi R, Prevost AT, Ramasamy K, Mohan V, *et al*. Prevalence of diabetic retinopathy in India stratified by known and undiagnosed diabetes, urban-rural locations, and socioeconomic indices: Results from the SMART India population-based cross-sectional screening study. Lancet Glob Heal. 2022; 10(12):e1764-e1773. https://doi.org/10.1016/S2214-109X(22)00411-9 PMid: 36327997.
44. Amoaku WM, Ghanchi F, Bailey C, Banerjee S, Banerjee S, Downey L, *et al*. Diabetic retinopathy and diabetic macular oedema pathways and management : UK consensus working group. Eye. 2020; 34:1-51. https://doi.org/10.1038/s41433-020-0961-6 PMid: 32504038. PMCid: PMC7337227.
45. Ansari P, Tabasumma N, Snigdha NN, Siam NH, Panduru RVNRS, Azam S, *et al*. Diabetic retinopathy: An overview on mechanisms, pathophysiology and pharmacotherapy. Diabetology. 2022; 3(1):159-175. https://doi.org/10.3390/diabetology3010011
46. Demir S, Nawroth PP, Herzig S, Ustunel BE. Emerging targets in Type 2 diabetes and diabetic complications. Adv Sci. 2021; 8(18):1-23. https://doi.org/10.1002/advs.202100275 PMid: 34319011. PMCid: PMC8456215.
47. Rotariu D, Babes EE, Tit DM, Moisi M, Bustea C, Stoicescu M, *et al*. Oxidative stress - Complex pathological issues concerning the hallmark of cardiovascular and metabolic disorders. Biomed Pharmacother. 2022; 152:113238. https://doi.org/10.1016/j.biopha.2022.113238 PMid: 35687909.
48. Garay-Sevilla ME, Rojas A, Portero-Otin M, Uribarri J. Dietary ages as exogenous boosters of inflammation. Nutrients. 2021; 13(8):2802. https://doi.org/10.3390/nu13082802 PMid: 34444961. PMCid: PMC8401706.
49. Katrachanca SM, Koleske AJ. HHS Public Access. Physiology and Behavior. 2017; 176:139-148.
50. Koska J, Gerstein HC, Beisswenger PJ, Reaven PD. Advanced glycation end products predict loss of renal function and high-risk chronic kidney disease in Type 2 diabetes. Diabetes Care. 2022; 45(3):684-691. Doi: 10.2337/dc21-2196.
51. Du C, Whiddett RO, Buckle I, Chen C, Forbes JM, Fotheringham AK. Diabetes Development. 2022: pp. 1-18.
52. Satyadev N, Rivera MI, Nikolov NK, Fakoya AOJ. Exosomes as biomarkers and therapy in Type 2 diabetes mellitus and associated complications. Front Physiol. 2023; 14:1-21. https://doi.org/10.3389/fphys.2023.1241096 PMid: 37745252. PMCid: PMC10515224.
53. Moshapa FT, Riches-Suman K, Palmer TM. Therapeutic targeting of the proinflammatory IL-6-JAK/STAT signalling pathways responsible for vascular restenosis in Type 2 diabetes mellitus. Cardiol Res Pract. 2019; 9846312. https://doi.org/10.1155/2019/9846312 PMid: 30719343. PMCid: PMC6334365.
54. Zhao L, Hu H, Zhang L, Liu Z, Huang Y, Liu Q, *et al*. Inflammation in diabetes complications: Molecular mechanisms and therapeutic interventions. MedComm. 2024; 5(4):e516. https://doi.org/10.1002/mco2.516 PMid: 38617433. PMCid: PMC11014467.

55. Xu N, Liu S, Zhang Y, Chen Y, Zuo Y, Tan X, *et al*. Oxidative stress signaling in the pathogenesis of diabetic cardiomyopathy and the potential therapeutic role of antioxidant naringenin. Redox Rep. 2023; 28(1). https://doi.org/10.1080/13510002.2023.2246720 PMid: 37747066. PMCid: PMC10538464.
56. Jiang J, Zhao C, Han T, Shan H, Cui G, Li S, *et al*. Advanced glycation end products, bone health, and diabetes mellitus. Exp Clin Endocrinol Diabetes. 2022; 130(10):671-677. https://doi.org/10.1055/a-1861-2388 PMid: 36257297.
57. Uceda AB, Marino L, Casasnovas R, Adrover M. An overview on glycation: Molecular mechanisms, impact on proteins, pathogenesis, and inhibition. Biophys Rev. 2024; 16:189-218. https://doi.org/10.1007/s12551-024-01188-4 PMid: 38737201. PMCid: PMC11078917.
58. Choudhuri S, Dutta D, Sen A, Chowdhury IH, Mitra B, Mondal LK, *et al*. Role of N-epsilon- carboxy methyl lysine, advanced glycation end products and reactive oxygen species for the development of nonproliferative and proliferative retinopathy in Type 2 diabetes mellitus. Mol Vis. 2013; 19:100-113. PMID: 23378723. PMCID: PMC3559098.
59. Makiishi T, Araki S, Koya D, Maeda S, Kashiwagi A, Haneda M. C-106T polymorphism of AKR1B1 is associated with diabetic nephropathy and erythrocyte aldose reductase content in Japanese subjects with Type 2 diabetes mellitus. Am J Kidney Dis. 2003; 42(5):943-951 https://doi.org/10.1016/j.ajkd.2003.06.003 PMid: 14582038.
60. Kaur N, Vanita V. Association of aldose reductase gene (AKR1B1) polymorphism with diabetic retinopathy. Diabetes Res Clin Pract. 2016; 121:41-48. https://doi.org/10.1016/j.diabres.2016.08.019 PMid: 27640118.
61. Kallinikou D, Tsentidis C, Kekou K, Katsalouli M, Louraki M, Kanaka-Gantenbein C, Kanavakis E, Karavanaki K. Homozygosity of the Z-2 polymorphic variant in the aldose reductase gene promoter confers increased risk for neuropathy in children and adolescents with Type 1 diabetes. Pediatr Diabetes. 2022; 23:104-114. https://doi.org/10.1111/pedi.13285 PMid: 34773353.
62. Abhary S, Burdon KP, Laurie KJ, Thorpe S, Landers J, Goold L, Lake S, Petrovsky N, Craig JE. Aldose reductase gene polymorphisms and diabetic retinopathy susceptibility. Diabetes Care. 2010; 33(8):1834-1836. https://doi.org/10.2337/dc09-1893 PMid: 20424224. PMCid: PMC2909072.
63. Harris L, McDonagh EM, Zhang X, Fawcett K, Foreman A, Daneck P, Sergouniotis PI, Parkinson H, Mazzarotto F, Inouye M, Hollox EJ, Birney E, Fitzgerald T. Genome-wide association testing beyond SNPs. Nat Rev Genet. 2025; 26(3):156-170. https://doi.org/10.1038/s41576-024-00778-y PMid: 39375560. PMCid: PMC12329314.
64. Chaudhuri J, Bose N, Gugliucci A, Kapahi P, *et al*. Metabolic diseases : Bridging association and causality. Cell Metab. 2019; 28(3):337-352. https://doi.org/10.1016/j.cmet.2018.08.014 PMid: 30184484. PMCid: PMC6355252.
65. Snelson M, Tan SM, Clarke RE, De Pasquale C, Thallas-Bonke V, Nguyen TV, *et al*. Processed foods drive intestinal barrier permeability and microvascular diseases. Sci Adv. 2021; 7(14):1-15. https://doi.org/10.1126/sciadv.abe4841 PMid: 33789895. PMCid: PMC8011970.
66. Rhee SY, Kim YS. The role of advanced glycation end products in diabetic vascular complications. Diabetes Metab J. 2018; 42(3):188-195. https://doi.org/10.4093/dmj.2017.0105 PMid: 29885110. PMCid: PMC6015964.
67. Jud P, Sourij H. Therapeutic options to reduce advanced glycation end products in patients with diabetes mellitus: A review. Diabetes Res Clin Pract. PMID: 30500546. https://doi.org/10.1016/j.diabres.2018.11.016
68. Yepuri G, Hasan SN, Kumar V, Manigrasso MB, Theophall G, Shekhtman A, *et al*. Mechanistic underpinnings of AGEs-RAGE via DIAPH1 in ischemic, diabetic, and failing hearts. Am J Physiol Heart Circ Physiol. 2025. https://doi.org/1 0.1152/ajpheart.00685.2024. PMID: 40132210. PMCID: PMC12354004.
69. Rowan S, Bejarano E, Taylor A. Mechanistic targeting of advanced glycation end-products in age-related diseases. Biochim Biophys Acta Mol Basis Dis. 2018 Dec; 1864(12):3631-3643. doi: 10.1016/j.bbadis.2018.08.036. Epub 2018 Aug 29. PMID: 30279139; PMCID: PMC6822271.
70. Palanissami G, Paul SFD. AGEs and RAGE: metabolic and molecular signatures of the glycation-inflammation axis in malignant or metastatic cancers. Explor Target Antitumor Ther. 2023; 4:812–49. https://doi.org/10.37349/etat.2023.00170.
71. Reddy VP, Aryal P, Soni P. RAGE Inhibitors in Neurodegenerative Diseases. Biomedicines. 2023 Apr 9; 11(4):1131. doi: 10.3390/biomedicines11041131. PMID: 37189749; PMCID: PMC10136230.
72. Roorda MM. Therapeutic interventions against accumulation of advanced glycation end products (AGEs). Glycative Stress Res. 2017; 4(2):132–143. doi: 10.24659/gsr.4.2_132.
73. Jud P, Sourij H. Therapeutic options to reduce advanced glycation end products in patients with diabetes mellitus: A review. Diabetes Res Clin Pract. 2019: 148:54-63. Doi: 10.1016/J.DIABRES.2018.11.016.
74. Yepuri G, Hasan SN, Kumar V, Manigrasso MB, Theophall G, Shekhtman A, *et al*. Mechanistic underpinnings of AGEs-RAGE via DIAPH1 in ischemic, diabetic, and failing hearts. Am J Physiol Heart Circ 10.1152/ajpheart.00685.2024. 62 Physiol. 2025. doi:1 0.1152/ajpheart.00685.2024.
75. Chawla A, Chawla R, Jaggi S. Microvasular and macrovascular complications in diabetes mellitus: Distinct or continuum? Indian J Endocrinol Metab. 2016 Jul-Aug; 20(4):546-51. doi: 10.4103/2230-8210.183480. PMID: 27366724; PMCID: PMC4911847.
76. Bereda, Gudisa. Complication of Diabetes Mellitus: Microvascular and Macrovascular Complications. 2022; 123-128.

Author Contribution

Study concepts and design: Dr. M. Nalini, Madhavi Latha S. Literature search: G. Gowri, M. Teja Sri. Manuscript preparation: Dr. M. Nalini, M. Teja Sri, Nagraju Bandaru. Manuscript review: A. Sasikala, Madhavi Latha S., G. Gowri. Manuscript editing: Dr. M. Nalini, Nagaraju Bandaru. All authors have read and agreed to the published version of the manuscript.

Access this journal online	
Website: https://www.informaticsjournals.co.in/index.php/toxi/	**Quick Response Code**