Review Article

Microvascular Complications Associated with Advanced Glycation End Products in Diabetes

Abstract

Diabetes is a frequent metabolic complaint associated with increasing blood sugar levels, it also has a connection to long- term vascular problems that can damage blood vessels, urinary tract, sight, and neurons. By adding amino acid breakdown and ultimately accumulating complex end products of glycation in the organs, hyperglycemia is a crucial factor in the progression of complications related to diabetes. The breakdown process, which entails free of enzymes couplings of polysaccharides to lipids, proteins, or inheritable material, produces miscellaneous motes known to be sophisticated glycation end products.The root cause of diabetes-related difficulties such as atherosclerosis, retinopathy, nephropathy, and nephropathy are greatly impacted by the development of complex end products of glycation and the glycation of proteins.Glycation of proteins hinders molecules from behaving as anticipated by altering the functioning of enzymes,altering the structure of molecules, and impeding sensory interaction.In order to aid in the development of diabetes problems.Recent research suggests that AGEs interact with RAGEs on the plasma membrane to change gene expression, intracellular signaling, and the release of free radicals and pro-inflammatory chemicals.The formation of several AGE types from the glycation of plasma proteins is covered in the current review. The pathogenesis of diabetes sequelae such as retinal degeneration, glaucoma nerve damage, kidney failure, and myocardium are also discussed in relation to AGEs. This study includes an update on the disease's vascular consequences, underlying causes, and available therapeutic options. A summary of illness management techniques is also provided in this article.

Key Words: Hyperglycemia Microvascular Complications, Protein Glycation, Advanced Glycation End Products

Introduction:

Diabetes:A collection of metabolic illnesses known as diabetes are characterized by high blood sugar levels (hyperglycemia), making it a chronic (lifelong) disease.It results from either an insulin deficit, an insulin resistance, or both. Blood sugar levels are regulated by beta cells of pancreas which releasesinsulin[1].Sight blurring, increased thirst, exhaustion, urinary tract infections, starvation, and decreased appetite are some of the symptoms that diabetics regularly suffer[2]..Diabetic patients are more likely to have hypoglycemia (low blood glucose), which occurs when the body receives too much insulin. Hyperglycemia (high blood glucose) is a result of body receiving insufficient insulin[3,4]. A hyperglycemia condition, commonly known as Type 2 diabetes, arises when the amount of sugar in the blood rise above 180 milligrams deciliter (10 mmol/l)[2].

Types of Diabetes:

Diabetes develops in a trio of different forms. It's them, the condition known as "gestational diabetes mellitus" (GDM) pertains to various levels of insensitivity to glucose typically emerges or is first seen during pregnancy. Type II diabetes (T2D), also known as adult-onset diabetes or non-insulin-dependent diabetes mellitus (NIDDM), is a condition in which a person has low or no amounts of insulin or elevated levels of insulin (IR). Type I diabetes (T1D), also known as insulin-dependent diabetes mellitus (IDDM), is brought on by a form of autoimmune disease on the body's cells and results in an inhibition or cessation of the release of insulin[2].

Cause: Obesity, inflammation, and immunity are all major sequelae that have diabetes as their primary cause[2]. Albumin is changed into glycated albumin via Amadori glucose adducts, which is associated with complications of diabetes on its own[2]. If patient is untreated for a few days, hyperglycemia can result in the dangerous disease known as diabetic ketoacidosis (DKA)[3]. Some diabetic persons develop the non-inflammatory corneal condition keratoconus[5]. Insulinoma, a tumor produced from islet beta cells that exhibits a variety of clinical signs, is brought on by hypoglycemia. Proinsulin levels are used to diagnose insulinoma[2].

Diabetic Complications:

From a third to a half of people suffering from diabetes develop organs and cellular damage as a result of the substantial association between diabetes and combined microscopic and macrovascular problems. Diabetes-related changes to the circulatory system's body structure, framework, and performance may end up in malfunction of multiple organs[6].Addison's syndrome, also known as Addison, Grave's, a excessive thyroid function, thyroid dysfunction, hypo testosterone, celiac disorder, pernicious anemia, which causes anemia, and eczema are a few of the autoimmune disorders connected to diabetes[7].A same etiology underlies both diabetes-related macroscopic vascular (containing large vessels like artery or vein) and microscopic vascular (which involves small vessels like capillaries) issues.Chronic hyperglycemia contributes significantly to the development of diabetic arterial disease through a variety of energy expenditure and structural variations, including the generation of advanced end products of glycation, unusual induction of signaling networks (which includes the pathway of protein kinase C [PKC]), a higher level of reactive oxygen substances (ROS), a class of oxygen-rich molecules that may combine with various biological molecules. and trigger impairment, and unusual stimuli for the production of hem[6].

Advanced Glycation End Products:

Glycation is an irrevocable free of enzymes reaction among converting carbohydrates and proteins, fatty acids, or genetic material that results in the formation of complex molecules known as AGEs[8]. AGEs are produced either endogenously or exogenously[9]. The complex Maillard process, which occurs when molecules of aldehyde on lowering carbohydrates such as fructose, glucose, or ribose combine without enzymes to the terminal amino groupings of nucleic acids, protein, along with fatty acids resulting in reactive carbonyl compounds, is principally responsible for the production of internal AGEs[10]. Exogenous AGEs are derived from food,particularly in western diets and also food having high pH, low hydration, and prolonged high temperatures produce enormous amounts of numerous classes of AGEs[11].

Mailard Reaction:AGEs are formed by multistep molecular reaction process known as Mailardreaction. The unbound amino acid groups of polypeptides or the carbonyl chains of reducing sugars are involved in a series of chain events[9].There are three main phases to this reaction: early, moderate, and late. The unattached amino group of the peptide reacts without enzymes with a sugar that reduces, like fructose, in the earliest stages to form the Schiff base. The Amadori product, a more stable molecule, is produced by undergoing a rearrangement on the Schiff base.At alater step, glyoxal, methylglyoxal (MGO), and deoxyglucosones are formed from the Amadori product (keto-amine), which is subsequently broken down into a variety of strong carbonyl and dicarbonyl chemicals through oxidation and polymerization reactions[12,13].

The AGE radicals' capacity to interact with particular proteins and form connections that impair the functioning of cells in the human body and tissues. The hydroxyl cascade and the breakdown of lipids by oxidation process are two additional minor pathways for the generation of AGEs in addition to the Maillard process[9].

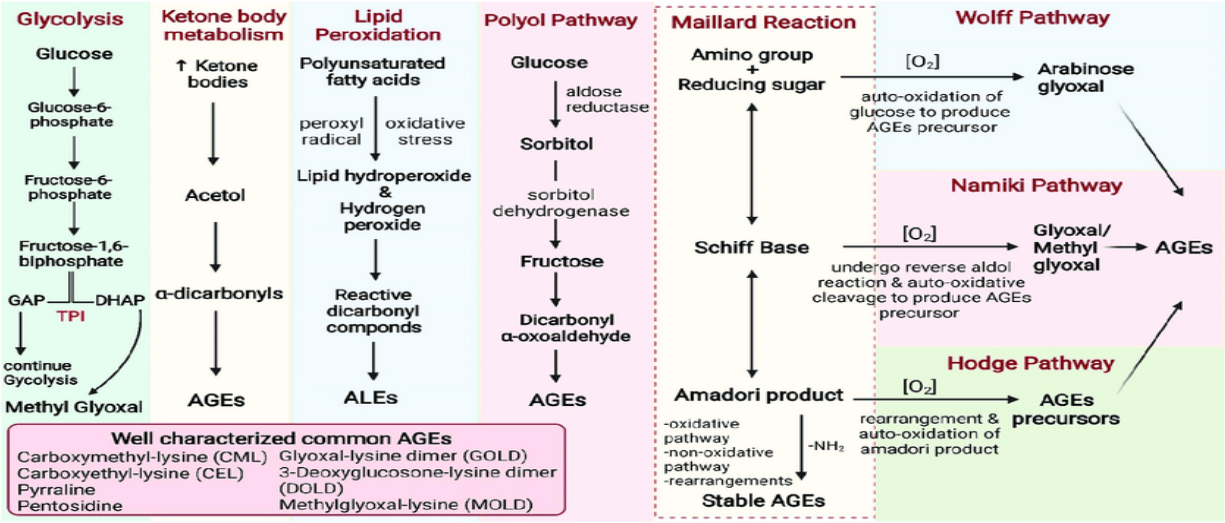

Figure 1: AGEs formation pathways. The Maillard processes process often produces advanced glycation end products. Reverse aldol reaction, Schiff base undergoes oxidation itself, metallic triggered autooxidation of carbohydrates (Wolff pathway), and Amadori product splitting undergoes oxidation in the absence of oxygen (Hodge process), all contribute significantly to the formation of active dicarbonyls and AGEs predecessors. In the Polyol route, an enzyme called aldol reductase converts a large quantity of carbohydrates to a substance called sorbitol which is then converted into sucrose by polyol enzyme. AGEs are produced as a result of the powerful glycating properties of fructose and its metabolites. When polyunsaturated fatty acids are subjected to lipid peroxidation, lipid peroxides are created, which later change into reactive dicarbonyls and advanced lipid peroxidation end products (ALEs). For creating the intermediary AGEs progenitor reacting dicarbonyls, the breakdown of ketone molecules made from protein also results in the production of AGEs. Methylglyoxal is produced naturally during a process called cellular respiration known as triose phosphate isomerase.

AGEs RAGE in diabetic complications:

The etiology of diabetes problems is significantly influenced by the interaction of AGEs with their cellular receptors. RAGE was once referred to as an AGE receptor. Numerous AGE receptors have been found, including oligosaccharyl transferase-48 (OST-48), lactoferrin, scavenger receptor types I and II. On smooth muscle cells, macrophages, endothelial cells, and astrocytes. RAGE is a multiligand receptor that belongs to the immunoglobulin superfamily of cell surface molecules. RAGE was previously discovered to adhere to the beta-amyloid protein, as well as - amphoterin,beta sheet filaments, S100/calgranulin, & Mac-1. The three extrinsic regions, including a V-type with ligand-binding capabilities, two C-type antibody regions (C 1 and C 2), a trans membrane helix, and a short cytosolic tail, form RAGE.Additionally, the fourth trans membrane domain that binds RAGE in the plasma membrane is connected to a high-voltage fifth internal domain which increases interaction between cytosol transducer molecules[14].

The most prevalent AGE in living cells, N3-carboxy-methyl-lysine (CML), performs primarily an impulse propagation sensor for RAGE and is expected to engage with different AGEs. Merely the V region, of RAGE gets attached by AGEs, and chronic stimulation of cells controlled by receptor-dependent transduction leads to swelling. It is hypothesized that RAGE activation is crucial to AGE pathogenesis. Aside from AGEs, additional ligands that may activate RAGE include S100-calgranulins, a group of cytokine mediators that promote inflammation, amyloid, amphoterin, and various other fibrillar molecules. The combination of AGEs and RAGE on macrophage induces oxidative harm and the induction of nuclear factor-B (NF-B) by triggering the stimulation of both the mitogen-activated protein (MAP) kinase, as well as p21ras transduction pathway.NF-B controls the synthesis of cytokines that promote inflammation like IL-1, IL-6, and tumor necrosis factor-alpha, as well as endothelin-1, tissue factors, thrombomodulin, and other cytokines. Enhanced generation of binding molecules include vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) occurs along with additional impacts include enhanced permeability to blood vessels[14].NF-B and heme oxygenase mRNA are stimulated as a result of a connection between RAGE and AGEs inside the endothelial cells, which are indications of oxidative

stress[12]. NF-B encourages the synthesis of TNF under conditions of glycoxidative stress, which consequently boosts the creation of ROS. Type II diabetes, neurological disorders, and cardiovascular ailments are all mostly caused by ROS[15]. Findings show that cells of the blood vessels that are actively subjected to diabetes levels of sugar develops increased reactive oxygen substances (ROS), which then stimulate the protein known as NADPH oxidase enzyme[16]. Another treatment option for diabetes that is independent of blood glucose management is the reduction of AGEs generation, which could help prevent some diabetic complications[17].

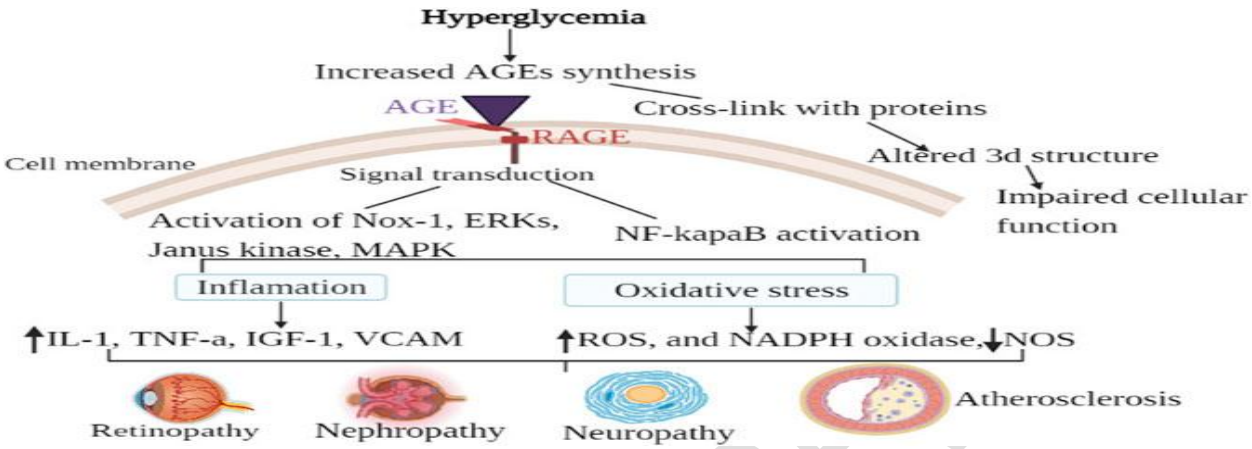

Figure 2: The broad function of the AGEs in persistent diabetes problems. The more prevalent cause of indigenous complex glycation metabolites production in diabetics is hyperglycemia. The main process of advanced end-products of glycation in diabetes-related vascular issues is the stimulation of multiple pathways that transmit signals as a consequence of RAGE/AGE association or by interconnect building with proteins in cells.The signal transduction pathways are all stimulated in conjunction with RAGE. If these processes are engaged (a smaller amount of NOS, higher ROS, and increased NADPH oxidase), factors associated with inflammation and oxidative stress all becomes operative. The 3- dimensional configuration of the peptide was altered by the formation of cross-links (adducts), which hampered the activity of cells. Cardiovascular disease, nerve disease, kidney failure, and blindness are just a few of the diabetic vascular issues that can occur as a result of the cumulative action.

AGEs and RAGE as indicators in vascular complications:

It is well established that individuals with diabetes who have type 2 diabetes (T2DM) have bloodstream AGE concentrations which solely put them into danger by developing endothelial failure. The blood concentrations of AGEs have been demonstrated to serve as a reliable indicator for fatalities by heart disease in women having Type 2 diabetes or people without diabetes in an 18-year subsequent studies. Additionally, it is understood that in individuals with T1DM, serum AGE levels are associated with vascular stiffness and dysfunction of the left ventricle.RAGE contains three distinct splice variants: C-terminal variant without transmembrane and effector domains, N-terminal variant without the AGE-binding domain, and a soluble receptor for advanced glycation end-product (sRAGE).It is understood that it is generated by the splitting of cellular-surface RAGE and is believed to depict endothelial cell damage. However, it is known that the AGE-RAGE system can be impacted by sRAGE, a completely RAGE antagonist[18].Even though serum RAGE contents only make up 1/1,000 to 1/5,000 of the total circulatory AGE concentrations, they however depict RAGE activity in tissues and can be utilized for determining the extent of vascular disorders[19]. In contrast to non-diabetics, individuals with T2DM, serum sRAGE concentrations were substantially higher, and this additionally had a favorable correlation with heart failure[20].

Agents known to modulate AGEs:

Numerous drugs have the ability to modify AGEs. Statin may hinder the stimulation of NADPH oxidase by AGE-RAGE and hence halt post-RAGE-induced transduction of signals by inhibiting Rac1 from getting prenylated. Pravastatin has been recognized for reducing damage to tubular cells in diabetic kidney disease and inhibiting AGEs-induced apoptosis. Atorvastatin also has the ability to stop the production of AGE due to its anti-oxidative characteristics[18].

Table 1: Agents known to modulate AGEs

Agents	Recommended outcomes

Atorvastatin	By virtue of its anti-oxidative activities, prevent AGE development.
Linagliptin	decrease AGE-induced oxidative damage generation-RAGE.
Rosiglitazone	Decrease heart hygroma, coronary RAGE expression, along with ventricular diastolic activity.
Telmisartan	One can lessen the activity of cellular oxidative stress and inflammation markers by stopping AGEs from delivering impulses along with the generation of DNA related to coronary heart disease.
Aminoguanidine	Avoid diabetic cardiomyopathy's heart enlargement and arterial rigidity.
Exendin-4	Suppress AGE-RAGE-mediated degradation in renal cells to decrease the beginning as well as advancement of diabetes-related kidney disease

AGEs in Diabetic Complications:

Diabetic Retinopathy: Diabetes-related retinopathy(DR), can be defined by damages in the lens of the eye caused by modifications in blood vessel permeability, microvascular microaneurysms, a decrease of pericytes, and an overly rapid pace of blood vessel development, is an extremely frequent root cause of vision impairment in people having diabetes mellitus[21].The retina is particularly susceptible to OS, and its oxygenated compounds are toxic results in damaging to the walls of the vascular vessels, leading to diabetes vascular injury[22].Skin AGEs levels have a strong correlation with DR in T2DM and can significantly predict how much DR willoccur[9]. Diabetic retinopathy comes in two different forms. Non-proliferative forms of the sickness emerge first, whereas Proliferative forms of the illness are more severe and advanced[2].

Causes of DR:DR symptoms include vision that is fuzzy, progressive decrease in vision gradually, floating objects shadowy figures or deficient areas of vision, and difficulties perceiving during darkness. The vascular involvement is the most serious and often occurring DM disease. The key factors contributing to microvascular impairment in hyperglycemia are inadequate control of glycemia, abnormal lipids, elevated blood pressure, oxidative stresses (OS), swelling, and intermediate products of glycation. The foundation for diagnosing retina is to identify preliminary retinal indications during fundoscopy inspections of the eyes[2].

AGEs in DR: The early dilation (occlusion) of vasculature is a consequence of the build-up of AGEs caused by long-term glucose exposures to the ocular epithelial blood flow[9]. They raise intrinsic cell adhesion molecule levels (ICAM), which facilitate the disintegration of the internal blood-retinal barrier attachment of ocular leucocyte capillaries, eventually leading to visual injury[23]. A rise in AGEs leads to a strong expression ofRAGE mRNA in the retinal cells of diabetic patients. RAGE mRNA expression and oxidative markers are favorably correlated with circulating AGE levels in type 2 DM patients. It has been shown that proinflammatory processes may be aggravated and RAGE expression may increase in an enriched ligand environment (AGEs aggregation). Whenever AGEs adhere to RAGE, crucial cellular signaling channels are triggered. These include the tyrosine phosphorylation procedure of signal transducer JAK & catalysts of translation (STAT), the stimulation of PKC, as well as the generation of OS through NF-B protein. Lastly, it encourages the generation of adhesive molecules as well as the synthesis of cytokine including VEGF and TNF-alpha. Although the condition known as proliferative retinopathyis causedby the formationoffresh blood vessels(angiogenesis) in the optical epithelium mediators including interleukin inflammatory illness in the optic nerve. AGEs can enhance TNF- mRNA levels in human blood vessel cells simultaneously loweringendothelialNOSmRNAexpression, andthismightplayaroleinimpairedmicrovascularactioninprolonged hyperglycemia[9]

Diabetes cataract: Cataract formation, or the loss of lens transparency[9], is also significantly influenced by AGEs. One of the mechanisms generating diabetic cataracts has been identified as the glycation of lens proteins (crystallin). An irreversible change in structural proteins caused by AGEs causes ocular polypeptides to combine & produce high-molecular-weight complexes which disperse illumination & decrease eyesight[24].

Diabetic Nephropathy: Diabetes Nephropathy (DN) is a very frequent cause of progressive kidney failure in people with diabetes. When it manifests medically, albuminuria starts to develop, while its GFR gradually decreases as time passes. It is also a substantial trigger factor in developing macrovascular problems if not controlled[25].

AGEs in DN: The synthesis and breakdown of collagen and other components of the extracellular matrix (ECM) in the glomerular basement membrane are both disturbed by AGEs[9]. As AGE and collagen cross-link in the basement membrane, the membrane will thicken, filtration will be hampered, and finally glomerular function will be lost[27].A crucial part in DN is also played by the AGE-RAGE axis. AGE-RAGE pathway encourages TGF- production in lacis cells as well as visceral cells of glomerular capillaries& cells of the tubule[9]. The JAK/STAT transduction system is used by TGF-a pro-fibrotic aspect, because to increase the synthesis of fibronectin, type IV collagen, & laminin consequently strengthen the membrane in the basement[14].Additionally, AGE causes kidney fibrosis and inflammation. The expression of many cytokines is also induced in kidney cells by RAGE activation. These cytokines then encourage the development of MCP-I (monocyte chemoattractant protein-1), which is connected to

the infiltration of monocytes and macrophages into renal cells[26].AGEs can cause podocytopathy as well. A size-selective sifting hurdle made up of specially designed cells known as renal podocytes regulates the flow of plasma amino acids from the blood into the urinary bladder[27]. The amount of pod cells per glomerulus diminishes and proteinuria sets in as a result of the separation of podocytes from the bottom membrane throughout the epithelial-mesenchymal transformation[28]. In DM patients, AGEs, notably CML, were found to significantly contribute to podocyte damage, proteinuria, and decreased kidney function[29].

Diabetic Neuropathy: Myelin loss from the internode regions & degenerative axons in the peripheral nervous system's voluntary and visceral nervous system lobes are two symptoms of the illness known as diabetes-related neuropathy[9].Diabetesrelated cardiovascular dysfunction, erectile dysfunction, and decreased wound healing are largely caused by neuropathy. Neurotoxicity is typically diagnosed using the emergence of vascular anomalies, which includes enlargement within the vascular basement layer and endothelium excessive growth, combined with a resulting decline in oxygen supply. In the therapeutic setting, nerve conduction velocities are improved by renin-angiotensin system inhibitorsand 1-antagonists, which is thought to be due to an increase in neuronal blood flow.It results in functional problems such diminished nerve transmission and blood flow, which raises a diabetic's lifetime risk of lower extremity amputations.Diabetes-related nerve fiber degeneration causes advanced neuropathy, which is characterized by increased vibration and heat threshold sensitivities that eventually lead to sensory perception loss. A portion of individuals also have hyperalgesia, paresthesias and allodynia, with pain being noticeable in 40–50% of people with diabetic neuropathy[30].

AGEs in Diabetic Neuropathy: Recently, it has been discovered that another risk factor for the development of diabetic neuropathy is the production of AGEs in peripheral nerves. Diabetes causes an increase in the glycation of myelin. Glycated myelin increases the phagocytosis of macrophages susceptibility and triggers enzyme release, that may lead to neuronal degeneration[31]. Axon atrophy/degeneration and decreased transportation of axons are caused by AGE's modification of crucial neuronal cytoskeletal amino acids such as actin, neurofilament and tubulin[9]. Research done in the laboratory revealed the fact that Na+/K+ ATPase polypeptide becomes more glycated under OS. Motor nerve conduction velocity may drop as a result of Na+/K+ ATPase becoming inactive due to glycation[14]. Observational studies have shown that AGEs are increased in T2 DM patients with distal sensorimotor polyneuropathy (DSPN) and are related to the severity of DSPN.Patients with T2 DM who had elevated serum AGEs levels also showed a decrease in relative muscular strength[9].

Diabetic cardiomyopathy: The impairment of the kidney continues to be an important indicator for early-stage heart disease (CVD) in patients withT2D,along with a high level of lipid disorders, inadequate control of glucose levels, and persistently raisedarterial pressure[32]. Hyperglycemia is connected with cardiovascular disorders such as early plaque buildup, it can cause impaired functioning of the heart, mainly affecting diastolic function and myocardial infarction, a stroke[26]. Apolipoprotein-B and the phospholipids which comprises ofLDL components become more glycated as a result of diabetes. The domain that binds to receptors of the LDL membrane proteins Apo B has a positive-charged lysine nucleotide that has been glycosylated. Because of this, the LDL receptor does not identify glycated LDL, although intake by macrophages is enhanced. High-density lipoprotein (HDL) turnover is increased by glycation, while reverse cholesterol transfer efficiency is decreased.The highdensity lipoprotein-associated enzymes paraoxonase is also less active as a result of HDL glycation, that restricts the breakdown of LDL and leukocyte adherence to the walls of blood vessels[9].

AGEs in Diabetic cardiomyopathy: Research studies have shown that AGE-RAGE interaction decreases endothelium cell production of NO, and increases OS. Endothelium disorder, a precursor to plaque buildup, could get worsen if endothelium cell derived NO synthesis &/or BA are reduced[33]. The conjugation of AGEs to proteins from the basement membrane includes both elastin and collagen has been additionally linked to stiffened arteries. By the way they communicate with RAGE, AGEs also increase the synthesis of VEGF in cells of the endothelialsystem. Additionally, VEGF increases atherosclerosis swelling by promoting calcification pathological angiogenesis[19]. Inducing OS, the stimulation of nuclear factor (NF-B), the formation of clinging and VCAM-1, and increased endothelium cell permeation and lipids intrusion in the sub-endothelium are all effects of AGE binding to sensors. AGEs in DM also activate the RAGE/toll-like receptor 4 (TLR4) pathway in atherosclerotic macrophage.Inhibiting the AGE-RAGE axis earlier in the course of developing diabetes might be more beneficial in preventing the onset of related blood vessel issues[9]. Additionally, recent research has shown that compounds (phytochemicals) that occur naturally with high bioactive molecules react with AGEs and their associated intermediates via a number of signaling pathways, possibly limiting and inhibiting the course of hyperglycemia[34].

The results of existing and forthcoming clinical studies may be helpful in identifying the best target for therapy for AGEs in diabetes-related complications.

Regulating blood sugar involving different organs:

The prolonged blood glucose surge, often known as "hyperglycemia," is the principal biochemical diagnostic indicator for both of the main kinds of diabetes. In the type 1 & type 2 diabetes, the ideal way to determine optimum glucose regulation and decrease the potential of microvascular complications is to reach normoglycemia as early in the process of the disease as is practical. Diabetes with type 1 is associated with absolute insulin reliance, and up to fifty percent of people having T2D ultimately require insulin therapy to control hyperglycemia. Those T1D patients who received prolonged therapy with insulin, possibly through enhancing the regular number of administrations or by switching to anongoinginsulininfusionmethodusingadeviceknownasapump,saw benefitsinmicro &macrovascularcomplications. Instead of a specific autonomous effect of the hormone insulin, these enhancements of T1D chances of survival have been linked to a significant enhancement of total glucose management across many different organs.External treatment with insulin is being shown to help patients with diabetes delay the start & development of the two types of complications.The situation is still more complicated with type 2 diabetes because a variety of pharmaceutical techniques are utilized to manage hyperglycemia in this disease, as is shown in below. When a person has T2D, diabetes is managed with a wide variety of drugs. They involve medications that work to improve the uptake of glucose by the peripheral blood vessels and lower levels of insulin resistance, such as thiazolidinediones & metformin. GLP-1 agonists, dipeptidyl peptidase - IV & sulfonylureas are inhibiting agents are a few of the medications that encourage the cells of the pancreas to secrete insulin and are often employed in clinical trials to deal with the associated inadequate insulin observed in the context of resistance to insulin simultaneously[35].

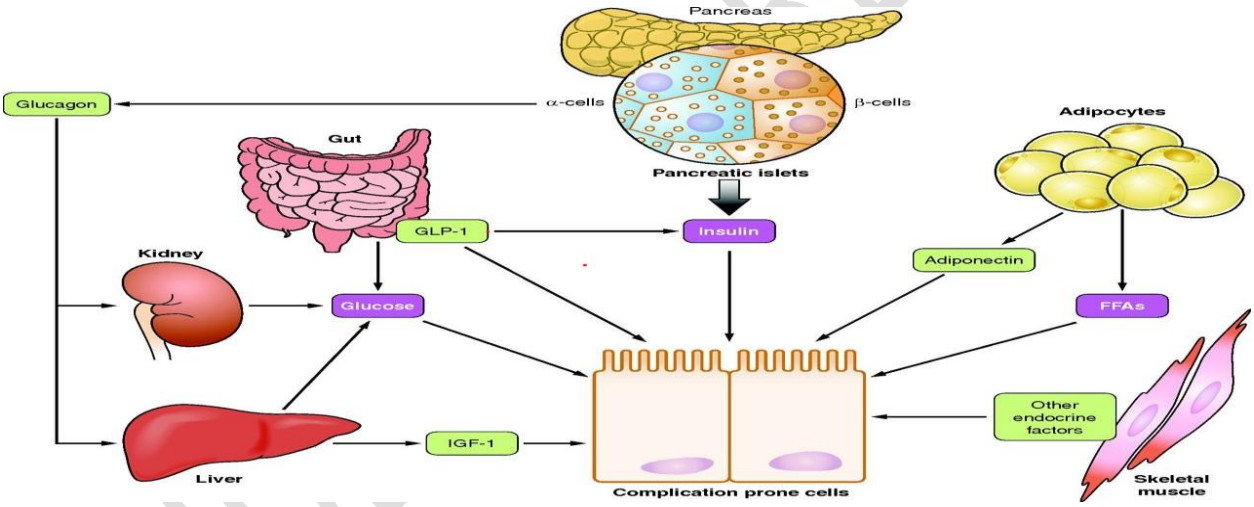

Figure 3: The relationships between cells of interest that are susceptible to the detrimental effects of type 2 diabetes and the mechanisms that regulate glucose.Neuronal cells, proximal tubular, endothelium, Muller & podocytes are among the possible list of target cells. Glucagon-like peptide-1 (GLP-1), IGF-1, and FFA are examples of these molecules.

The onset and course of diabetes problems are directly impacted by certain of these antihyperglycemic medications.Thiazolidinediones, which are PPAR agonists and peroxisome proliferator activated receptors, have had positive effects on complications apart from their capacity to decrease blood sugar. In fact, the PPAR agonists' protective effects on the diabetic kidney seem to be regulated by preventing proximal tubular cellactivation and reducing the release ofprofibrotic cytokines such as HGF and different substances. The effectiveness of thiazolidinediones has been overshadowed by the rise in the incidence of heart-related instances, notablyMI (cardiac infarction), associated with the use of the rosiglitazone PPAR agonist[35].

Regarding the problems of diabetes, metformin has shown mixed results. Patients on the diabetes medicine metformin have reported that their peripheral nerve damage has gotten more severe, it is believed to be related to how it affects vitamin B12[36]. It's interesting to note that human diabetic nephropathy has been negatively impacted by vitamin B modification. In contrast, metformin appears to have positive benefits on macrovascular consequences

in type 2 diabetic patients, including plaque development in arteries and formation of blood clot in coronary artery and MI.The drug metformin has positive benefits on renal disease.Metformin's favorable impacts on diabetes-related issues appear to be associated with gains in lipid disorders a fall in inflammatory substances characteristics, a decrease in carbonyl & oxidative stress and a regaining of the functioning of endothelial cells within the endothelium[35].

The latest development of oral antihyperglycemic drugs for T2D are sodium-dependent glucose transporter 2 (SGLT2) inhibiting agents, that utilize the advantages of the renal function in regulating the equilibrium of glucose and are currently in a sophisticated phase of clinical study. The amount of glucose in the plasma declines as an outcome of the medical strategy, more especially the specific therapeutic inhibition of renal SGLT2, that prevents reuptake of carbohydrates and increases the urinary elimination of sugars[37]. A lot of research is presently being done on this method of treating type 2 diabetes by reducing plasma blood sugar levels. Due to the fact that the inhibition of SGLT2 does not rely on the amount of insulin or its effects, one is unable to entirely rule away an eventual role to this newly developed group of anti- diabetic medications in T1D[35].

Advantages of pharmacological intervention in distinct diabetic complications:

The use of pharmaceutical treatments that can (directly or indirectly) interfere with AGEs has positive impact on a number of diabetic problems. By preventing ADMA production in tubular cells and reducing AGEs ability to cause apoptosis, pravastatin lessens tubular damage in diabetic nephropathy.To slow the onset and progression of diabetic nephropathy, a GLP-1 receptor agonist prevents the production of ADMA in tubular cells.In an experimental animal model of diabetic cardiomyopathy, aminoguanidine has been found to prevent heart hypertrophy and arterial rigidity.It has been demonstrated that administering grape seed pro-anthocyanidins extracts (GSPE) reduces AGEs, making it an excellent treatment for diabetic peripheral neuropathic pain. By preventing AGE buildup, hesperidin protects streptozotocin-induced diabetic rats against retinal and plasma abnormalities.By preventing AGEs from building up in db/db Mice, the extract of Litsea japonica slows the progression of diabetic nephropathy. In diabetes caused by STZ, AGEs-mediated kidney damage is lessened by Korean red ginseng extract. Telmisartan prevents diabetic nephropathy's AGE-induced podocyte separation and destruction[14].

Table 2: Pharmacological therapies having positive impact on long-term diabetes repercussions by interfering with AGEs.

Sr. No.	Intervention	Comments
1	Pravastatin	Reduces tubular damage in diabetic nephropathy by inhibiting ADMA generation in tubular cells and attenuating AGEs-induced apoptosis
2	GLP-1 receptor agonist	Inhibits the generation of ADMA generation in tubular cells to attenuate the development and progression of the diabetic nephropathy
3	Aminoguanidine	Prevent cardiac hypertrophy and arterial stiffening in diabetic cardiomyopathy
4	Rosiglitazone	Reduces the expression of RAGE on myocardium and attenuates cardiac fibrosis and left ventricular diastolic function in experimental models of diabetic myocardial fibrosis
5	Grape seed proanthocyanidins extracts	Effective against diabetic peripheral neuropathic pain by decreasing AGEs
6	Hesperidin	Prevents retinal and plasma abnormalities in diabetic rats by inhibiting accumulation of AGEs
7	Epalrestat	Suppresses the deterioration of diabetic peripheral neuropathy, by inhibiting the polyol pathway and suppressing the production of AGEs
8	Curcumin	Produces beneficial effects in hepatic fibrosis in type 2 diabetes mellitus by suppressing AGEs-mediated induction of the RAGE gene expression by increasing PPARγ activity
9	Pyridoxamine	Produce beneficial effects in relation to microalbuminuria and proinflammatory cytokines in experimental diabetic nephropathy
10	*Litsea japonica*	Reduces the development of diabetic nephropathy via inhibition of AGEs accumulation
11	Korean red ginseng extract	Alleviates AGEs-mediated renal injury in STZ-induced diabetes
12	Telmisartan	Inhibits AGE-induced podocyte damage and detachment in diabetic nephropathy

Herbal Treatment:

The known botanicals for treating diabetes are **B**ael (Aegle marmelos), Bitter gourd (Momordica charantia), Turmeric (Curcuma longa), and a few other species. Polyphenols that occur organically in fruits and nuts, has shown to perform a number of functions, includingthose of an antioxidant, antibacterial, and antimutagenic agent[2,38].Recent research has demonstrated that a leaf extract from the ayurvedic plant Terminalia arjuna (Combretaceae) possesses antihyperglycemic action in streptozotocin-induced diabetic rats. It has been demonstrated that a number of plant-derived chemicals increase transport of carbohydrates through leaves extort by

the activation of AMPK.There have also been reports that the main curcuminoid in turmeric, curcumin, salidroside from Rhodiola rosea, and cryptotanshinone from quinoids have stimulatory effects on glucose uptake in adipocytes and muscles through AMPK[2].

PhysicalExercise

Bodilyexerciseandtrainingarecrucialforpreventingandmanagementofhyperglycemia because they improve the ability to tolerate glucose and reduce the resistance to insulin. Daily physical activity also helps to reduce the effects of hyperglycemia. Individuals suffering from diabetes have to concentrate on controlling their everyday energy consumption and utilization (energy flux) in addition to administering treatment to reduce the BMI (Body Mass Index)[1,39]

Alcohol

Alcohol use at moderate levels aids in the management of diabetes, according to a study that discovered a quadratic curve (U-shaped) association between the two. When compared to the non-drinking group, alcohol consumption of 26 to 50 grams per day was negatively connected with T2D risk, but consumption of more than 50 grams per day was not linked to the disease, which seemed to suggest that moderate alcohol consumption may workas a preventative measure for T2D. The mechanisms underlying the preventive effects of moderate alcohol consumption on T2D and CVD may be similar [2].

Management

To people with diabetes, knowing hyperglycemia management is essential since it assists in managing the illness and avert issues. Managing appropriate blood sugar levels in T1D patients reduces the onset and development of vasculature and neural disorders. Dietary habits, physical activity, and managing stress are all effective and widely recommended ways to deal with T2D [2]. Between such things, diet has attracted a lot of focus in the treatment of hyperglycemia associated with T2D. The ADA (American Diabetes Association) and the European Association for the study of Diabetes (EASD) together published an accord on the approach for controlling diabetes in patients with T2D. According to these recommendations, metformin should be used as an initial treatment together with exercise and MNT (medical nutrition therapy) to modify one's lifestyle [2,40]. Patients with T2D frequently have low self-esteem and a sense of hopelessness, which makes them less diligent about sticking to their regimen.Obesity prevention and management strategies will aid to control and therapy of T2DM. Diabetic individuals must give up smoking and, overweight people, reduce weight. Blood pressure in hypertensive patients needs to be lowered to less than 130/80 mm Hg. Less than 70 mg/dL of cholesterol should be the target [41]. Because topical steroids can influence blood glucose levels, diabetic individuals getting treatment for longer period with steroid eye drops are advised to monitor the amount of sugar levels. To educate people with diabetes on correct cleanliness, diet, and adherence to dietary guidance, exercise guidelines, and medication, it is encouraged to set up programs of instruction in hospitals [2].

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