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ADVANCED GLYCATION END PRODUCTS (AGEs) AND LATE COMPLICATIONS IN DIABETES

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ABSTRACT

The pathophysiological condition of hyperglycemia found in diabetic patients promotes significant changes in the metabolism of carbohydrates, proteins and lipids. The significant increase in the availability of glucose in the intracellular medium directly affects glucose metabolism by diverting some of its intermediates to alternative routes, generating elevated levels of end products that are normally produced in small amounts during normal metabolism. The greatest impact of action as the body's response to hyperglycemia is the production of a class of heterogeneous molecules known as advanced glycation end products (AGEs). Persistent hyperglycemia results in progressive non-enzymatic glycation of intra- and extracellular components such as proteins, lipids, and nucleic acids, or AGEs, which play a central role in the late complications found in diabetes. Because they are located at the interface between blood and tissues, the endothelium plays an important role in the maintenance of systemic physiology, being extremely susceptible to pathogenic stimuli that lead to cellular senescence. Endothelial cells are secretors of pro-inflammatory cytokines, contributing to various cardiovascular and metabolic pathologies, mainly involving retinal hair cells, Schwann cells in peripheral nerves, renal glomerulus, and neurons. The accumulation of AGEs in cells causes abnormal glycation of proteins, leading to their misfolding and abnormal aggregation, as well as increasing oxidative stress and pro-inflammatory events. These events induce chronic complications in the micro- and microcirculation, resulting in progressive endothelial damage and are associated with capillary occlusion, ischemia, and organ failure.

Keywords: Diabetes. Glycation of biomolecules. Free radicals. Diabetic angiopathy.

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1 INTRODUCTION

The occurrence of diabetes in contemporary society is considered one of the main threats to human health, significantly impacting people's quality of life and longevity. *Diabetes mellitus* is a heterogeneous group of diseases whose common denominator is hyperglycemia due to resistance to insulin action, insufficient secretion of this hormone, or both. It is also associated with disorders of lipid and protein metabolism. It is a prevalent disorder, affecting about 7% of the Brazilian population (≅15.1 million people) (Fráguas *et al.*, 2009). Such an excessively high incidence evidences the clinical importance and relevance of the disease in contemporary society.

This is the main disease associated with glucose metabolism, which is divided into two types: Type 1 Diabetes Mellitus (DM1) and Type 2 Diabetes Mellitus (DM2). DM1 is an autoimmune disease of high morbidity, characterized by the destruction of insulin-producing pancreatic beta cells (Lucier, Mathias, 2025). DM2 is a heterogeneous syndrome that originates from defects in insulin secretion and action, where environmental and genetic factors are involved in this type of disease (Demir, *et al*. 2021).

2 ALTERNATIVE METABOLISM IN HYPERGLYCEMIA

Hyperglycemia is the pathophysiological condition in which blood sugar levels are above normal and, in most cases, is directly associated with all subtypes of diabetes. A priori, what may seem harmless, becomes highly harmful as the disease progresses, since its complications result in severe damage to metabolic and hormonal functions, culminating in the derangement of the body's protein, lipid, and enzymatic metabolism (Sanches, et al. 2023).

Diabetes has become one of the biggest concerns of health authorities, due to the vascular complications it causes and, mainly, the cellular and tissue damage that are consequences of the disease. In addition, the factor that has the greatest impact on action as the body's response to hyperglycemia is the diversion from conventional metabolic pathways to alternative routes that generate a heterogeneous class of molecules, the advanced glycation end products (AGEs), (Vlassara, Uribarri, 2014).

2.1 FORMATION OF THE AGES

AGEs are products that occur naturally in the body, but in tiny proportions, affecting, according to Barbosa et al. (2008), molecules that have a long half-life, such as collagen, for example, exerting their action on the natural aging process. However, under hyperglycemic

conditions, serum concentrations of AGEs in diabetic individuals are significantly higher when compared to non-diabetic individuals. In addition, AGEs are "considered important pathogenic mediators of diabetic complications, capable of irreversibly modifying the chemical and functional properties of the most diverse biological structures". Persistent hyperglycemia results in the progressive non-enzymatic glycation of intra- and extracellular components such as proteins, lipids, and nucleic acids, generating chemical fractions, the AGEs, with a central role in the late complications found in diabetes (Khalid, et al., 2022)

According to Mohamadizadeh et al. (2004), chronic hyperglycemia is also one of the primary sources for the generation of ROS (reactive oxygen species), which in turn are contributing elements to oxidative stress and then, when added to the hyperglycemic factor, induces a dysfunction in beta cells and causes an increase in insulin resistance, in addition to potentiating the increase of more AGEs. These are formed as a normal consequence of metabolism or are absorbed into the diet. These increased levels contribute to the abnormalities in metabolism, as seen by the Western diet, which is rich in processed foods. Although AGEs are products of diabetic hyperglycemia, they compromise insulin signaling and pancreatic beta cell function. In addition, AGEs also contribute to hypothalamic inflammation, disrupting the central control of energy balance (Sergi, et al., 2021)

In addition, high serum glucose levels will promote a deviation in the body's biochemical pathways, causing the known pathophysiology of diabetes, such as "polyol pathway, hexosamine pathway, AGEs pathway, and protein kinase C pathway" (Barbosa et al., 2008)

In the first studies, as defended by Mohamadizadeh et al. (2004), it was believed that AGEs were formed due to the Maillard process, consisting of a series of non-enzymatic reactions in which ketone groups (carbonyls) of glucose molecules or aldehydes reacted with the amino groups of proteins, lipids, amino acids, and nucleic acids, i.e., extracellular elements. Other studies indicate that the primary initiating event for the formation of AGEs is the high concentration of intracellular glucose, due to the greater reactivity of intracellularly generated glucose-derived dicarbonyl precursors (glyoxal, methylglyoxal, and 3-deoxyglucosone), which culminate in the formation of intra- and extracellular AGEs (Barbosa et al., 2008). Therefore, AGEs continue to be elements formed from aminocarbonyl reactions of a non-enzymatic nature, which occur rapidly in the hyperglycemic state of diabetes, in which the idea that increased levels of circulating glucose, precursors of AGE and oxidative stress lead to the formation of AGE in patients with diabetes is still maintained (Mohamadizadeh et al., 2004). Briefly, the process occurs from the post-translation of these modified proteins, in which two successive steps are encompassed, starting with the

formation of an aldymine (Schiff base - coming from the binding of carbonyls and amino groups), followed by an isomerization process (Amadori rearrangement), forming a stable ketamine (Christidis et al. 2024).

The alternative metabolism in hyperglycemia is then associated with the "carbonyl stress" pathway, being the pathway that generates highly reactive intermediate dicarbonyl compounds through the oxidation of lipids and/or sugars, with reaction power 20 thousand times greater when compared to glucose (and therefore they are the main intermediate elements for the formation of AGEs), such as methylglyoxal and glyoxal, from glycolysis and glucose autooxidation, which when interacting with amino acids form AGEs. In turn, due to these reactions mentioned above, AGEs can also be called products of lipoxidation or advanced glycoxidation. It is also worth mentioning the production of Reactive Oxygen Species (ROS), which intensify oxidative stress and structural and functional damage caused to the body (Barbosa et al. 2008). Concomitant with the occurrence of these reactions, the formation of AGEs can still involve neutrophils, monocytes and macrophages, where myeloperoxidase and NADPH oxidase, involved in the inflammatory process, produce other AGEs from the oxidation of amino acids.

As a primary defense mechanism, the body has enzymatic systems that act protectively on the degenerative accumulation of AGEs. These systems are based on the kinetic balance (endogenous pool) between the sum of endogenous formation and exogenous attainment of AGEs, and their degradation and elimination through specialized systems. The enzymes involved in this defense system include oxaldehyde reductase and aldose reductase, which are efficient in detoxifying these reactive dicarbonyl intermediates. According to Barbosa et al. (2008), some of the known enzyme systems are goxylase I and II, fructosamine-3-kinase and fructosamine oxidase, which are also responsible for ceasing glycation reactions at different stages. Even so, in pathological situations such as diabetes (hyperglycemia), kidney failure, hyperlipidemia, and in cases of high exogenous intake of AGEs, in which there is an excess of it within the body, these enzymatic defense systems can be defeated. In short, it is essential to diagnose and monitor diabetes for its treatment and, as Christidis et al. (2024) states, glycated hemoglobin (HbA1c) monitoring is the gold standard for this purpose.

The body has systems capable of promoting tissue removal of specific levels of AGEs in the body, using means such as extracellular proteolysis or scavenger receptors that activate macrophages to perform endocytosis and intracellular degradation of AGEs, finally releasing into the circulation small soluble peptides (named as "second generation of AGEs") that, Although there may still be highly reactive intermediates, their effects are limited by

renal excretion and will later be excreted in the urine. Thus, Barbosa et al. (2008) safely state that "the efficiency of AGEs removal systems depends, ultimately, on the efficiency of renal *clearance*", and the failure to remove circulating AGEs and their consequent accumulation in the blood and tissues is due to renal dysfunction diagnosed in individuals with nephropathy, for example.

3 ADVANCED GLYCATION END PRODUCTS FORMED

Briefly, some of the main products formed from the advanced glycation reactions previously described in the face of diabetes pathology should be highlighted. It is important to remember that both endogenous and exogenous factors are capable of producing AGEs, resulting in the physiological alteration of proteins and lipids. The protein albumin is the most affected in the interaction of the AGEs formation process, since it has a high tendency to glycation due to contact with lysine and arginine, which irreversibly alter its structure, giving rise to a type of AGE known as human serum albumin. This binding is relatively acceptable and common in about 10% of the albumin present in the body, however, in diabetic individuals, this binding tends to be about 2 to 3 times greater.

In endogenous situations, resulting from hyperglycemia or processes related to oxidative stress, also known as "carbonyl stress" mechanisms, free amino groups are obtained from proteins and nucleic acids, as well as carbonyl groups from reducing sugars, reactive metabolites and oxidized lipids, which result in compounds such as AGEs and ROS, already identified as pentosidine and carboxymethyl-lysine (CML), being the most frequent types in humans, according to Rosas (2015) apud (Barbosa, *et al*., 2008).

In exogenous situations, AGEs commonly come from compounds related to food and smoking. Studies have the information that foods exposed to high temperatures in the cooking process and thermal processes are sources of EFAs. In the case of smoking, the formation of advanced glycation end products is associated with the combustion process, causing the biomolecules to be volatilized in the lungs, then interacting with plasma proteins and triggering the mechanisms of AGEs.

There are three most well-known pathways that generate the end products of advanced glycation, which are Maillard Reaction, Carbonyl Stress Pathway and Polyol Pathway. In the Maillard Reaction, the products obtained are glycated hemoglobin and fructosamine (Amadori products), being considered products of stable structures, but which have highly reactive carbonyl groups, which generate groups of primary amines resulting in AGEs, as described by Rosas (2015) apud (Bierhaus *et al*., 1998). In the Carbonyl Stress Pathway, the oxidation of lipids and/or sugars occurs, generating highly reactive dicarbonyl

compounds, known as methylglyoxal and glyoxal, for example, which, when united with amino acids, form the AGEs pyrryline, carboxymethyllysine (CML) and pentosidene. Last but not least, there is the Polyol Pathway, extremely favorable to the formation of AGEs due to promoting the conversion of glucose into sorbitol, through the enzyme aldose reductase, and later promoting the conversion of sorbitol into fructose, using the enzyme sorbitol-dehydrogenase. As a result, fructose metabolites are converted into α-oxaldehydes, which, when interacting with monoacids, form AGEs (Rosas, 2015 apud Contreras, 2010).

The accumulation of methylglyoxal, a highly reactive dicarbonyl, is related to the pathogenesis of diabetes and other chronic inflammatory diseases such as cardiovascular diseases, cancer, and age-associated central nervous system disorders (Schalkwijk, Stehouwer, 2020)

Another factor that also has a high responsibility in the activation of chain reactions is the interaction of AGEs with RAGEs, which are the beginning of the signaling of the pathways that will later activate protein kinases (such as ERK1/2, JNK, Akt and p38), and the phosphatidylinositol-3-kinase (PI3-K) pathway that will activate nuclear factor kappa B (NF-κB).

4 AGE RECEIVERS

The receptor for advanced glycation end products (RAGE) is a member of the immunoglobulin superfamily. It is composed of an extracellular portion, a transmembrane part, and an intracellular domain. The extracellular region is made up of one variable domain (V) and two constant domains (C1 and C2). The variable domain and V-C1 are important for the interaction of ligands with RAGE. The first identified ligands of RAGE were non-enzymatic glycoxidation products called advanced glycation end products (Neeper, 1992).

In addition to fl-RAGE, recently, numerous isoforms of the naturally occurring RAGE protein have also been described. The primary RAGE transcript undergoes alternative splicing and proteolytic cleavage of fl-RAGE under the control of as-yet-unknown pathways to produce truncated RAGE (Jiang *et al.* 2018; Hudson *et al.*, 2008; Sterenczak *et al.*, 2013). N-terminal truncation lacks the ligand-binding domain and is unable to involve glycated end products. C-terminal truncation primarily forms a soluble RAGE pool (sRAGE), including endogenous secretory RAGE (esRAGE) generated from alternative splicing and cleaved RAGE (cRAGE) derived from the proteolysis of membrane-bound fl-RAGE by metalloproteases (Jiang *et al*., 2018; Chuah *et al*., 2023). Membrane-bound fl-RAGE is responsible for intracellular RAGE signaling in response to extracellular ligands that lead to the activation of proinflammatory events (Garay-Sevilla *et al.*, 2021).

The human RAGE gene is located on chromosome 6, close to major histocompatibility complex III (MHC class III), which indicates its involvement in immune responses (Hudson *et al*., 2008). It is expressed in several cell types, such as vascular endothelium, monocytes, macrophages, smooth muscle, glomerular epithelium cells, and neurons; however, at low levels in homeostasis. However, in situations of increased cellular activity (metabolism) or in response to stress, inflammation and Alzheimer's disease, RAGE expression is increased in affected cells, becoming a marker of inflammatory processes (Schmidt *et al*. 2000).

During chronic diabetes, persistent hyperglycemia leads to elevated levels of AGEs in the bloodstream, which by involvement with RAGE induces a series of signaling events. The AGEs/RAGE interaction triggers a variety of downstream effectors, including mitogen-activated protein kinase (MAPK), p38, stress-activated protein kinase/c-Jun N-terminal kinase (SAPK/JNK), Ras-mediated extracellular signal-regulated kinase (ERK1/2), and Janus signal transducer kinase and transcription activator pathway (JAK/STAT) which, in turn, will lead to sustained activation transcription factors such as NF-κB, STAT3, HIF-1α, and AP-1 (Sergi *et al*. 2021; Gasiowski *et al*., 2018).

The hyperglycemia-induced burden of AGEs in the pancreas contributes to beta cell toxicity through the activation of inflammatory cascades and oxidative stress (Le Bagge *et al*. 2020). High levels of AGEs upregulate RAGE expression in pancreatic islets, as observed in several studies. The AGEs/RAGE axis triggers intracellular signal transduction and activates NF-κB transcription, resulting in chronic inflammation, mitochondrial dysfunction, beta-cell impairment, and apoptosis (Khalid *et al*., 2021; Guan *et al*., 2016; Zhu *et al*., 2011).

JNK activation promotes phosphorylation of the insulin receptor substrate (IRS-1) into serine residues which leads to downregulation of insulin signal transduction and induces insulin resistance (Sutherland *et al*., 2004).

5 EFFECTS OF AGES

5.1 INTRA- AND EXTRACELLULAR

Advanced Glycation End Products (AGEs) exert significant effects on both the intracellular and extracellular environment, impacting several biological processes.

5.1.1 Intracellular AGEs

Advanced glycation end products (AGEs) accumulate progressively during aging as a consequence of normal metabolic activities and the glycation process. This accumulation of AGEs, originating from both endogenous and exogenous sources, can compromise the functioning of several cells in the body, resulting in a variety of cellular reactions and,

eventually, cell damage and degeneration. When AGEs accumulate within cells, they can cause abnormal protein glycation, cause protein misfolding and the formation of anomalous or oligomeric protein aggregates, and increase oxidative stress and inflammation. These factors can also activate signaling pathways that lead to apoptosis, resulting in protein dysfunction, stress on the endoplasmic reticulum, mitochondrial problems, cell death, and organ damage (Chan et al., 2016; Yamabe et al., 2013).

In the nervous system, for example, the accumulation of AGEs can modify key proteins, such as α-synuclein and TAU, resulting in protein dysfunctions and the formation of harmful aggregates. These protein aggregates are associated with the development of neurodegenerative diseases, such as Alzheimer's and Parkinson's disease, reinforcing the importance of controlling intracellular AGEs levels (Kontaxi et al., 2017).

5.1.2 Extracellular AGEs

AGEs are long-lived molecules that form irreversibly and can be found both in the circulation and in tissues, especially in structures with long-lived proteins, such as the crystalline proteins of the eye, cartilage, glomerular basement membrane, and extracellular matrix (SINGH, 2014). The binding of AGEs with extracellular matrix proteins, such as laminin, elastin, and collagen, can alter the elasticity and function of tissues. In fact, elevated levels of interconnected AGEs are often observed in experimental animal models, as well as in autopsy tissue samples from individuals who are aging or who have conditions such as cancer, obesity, or diabetic complications (Turner, 2015).

In addition to affecting long-lasting proteins, AGEs also bind to short-lived proteins such as serum albumin. This interaction activates specific receptors, such as RAGEs (Receptors for Advanced Glycation End Products), which trigger inflammatory responses and result in protein dysfunction and cellular damage (Rondeau, Bourdon 2011). The activation of RAGEs is associated with the amplification of oxidative stress and chronic inflammation, which aggravates pathologies such as atherosclerosis and diabetes.

5.2 IN THE CELLS OF THE ENDOTHELIUM

Cells that are overly affected due to hyperglycemic states are those that are relatively unable to deal with the regulation of glucose transport within them, and therefore become vulnerable to high levels of blood sugar. Because they are located at the interface between blood and tissues, the endothelium plays an important role in the maintenance of systemic physiology, being extremely susceptible to pathogenic stimuli that lead to cellular

senescence. Endothelial cells secrete pro-inflammatory cytokines, contributing to various cardiovascular and metabolic pathologies (Bloom *et al.*, 2023).

In line with Barbosa *et al*. (2008), the known structures that suffer such influence are the endothelial cells of the retinal capillaries, *Schwann cells* in the peripheral nerves, mesangial cells of the renal glomerulus and neurons.

The thickening of the glomerular basement membrane seen in diabetic nephropathy, for example, is due to the increased release of β growth factors (TGF-β), influenced by AGEs through RAGEs (receptors for advanced glycation end products), in which the synthesis of collagen matrix elements is stimulated. In addition to the endothelial cells of the basement membrane, "mesangial cells, podocytes and renal tubular cells" are also involved in this process (Barbosa *et al*., 2008).

Another impact of AGEs through the RAGEs, in addition to the accumulation of ROS in vascular endothelial cells, is vascular endothelial dysfunction, while there is inhibition of the dilation of endothelium-dependent arteries, which is caused by K+ channels, which in turn are activated by Ca2+ and have great conductance in the arteries. This inhibition is due to the fact that ROS interact with NO (nitric oxide), an element necessary for endothelium-dependent vasodilation. This interaction forms peroxynitrite, thus using all available source of NO, in addition to also uncoupling the active dimers, preventing the formation of more NO, promoting an excess in the serum load of ROS. Concern about this factor is high because endothelium-dependent vasodilation is essential for regulating blood flow in the body and controlling microvascular tone, as discussed by Naser *et al*. (2024).

5.3 PATHOLOGIES RELATED TO LAGS

AGEs are the main factor in the pathophysiological causes of vascular complications in diabetic individuals, since in hyperglycemic states, the formation of AGEs increases significantly, leading to an imbalance in body vascular homeostasis and reflecting in several late complications, such as increased arterial stiffness, endothelial changes, oxidative stress, inflammation, increased thrombogenicity, vascular hyperpermeability, and reduced vasorelaxation, factors that increase the risk of hypertension in diabetic individuals, as pointed out by Fuhr et al. (2022). Its pathological effects occur since AGEs have the ability to modify chemical and functional properties of the body, in a practically irreversible way depending on their degree of progression. In diabetes, the activation of alternative glucose utilization pathways causes damage to the endothelial cell, accompanied by the violation of its functions. Metabolic disorders produce oxidative stress, contributing to the progression of endothelial dysfunction and vascular complications (Ilkhomovich, 2024).

AGEs, under conditions of oxidative stress, are involved in a number of pathologies, including diabetes, atherosclerosis, Alzheimer's disease, as well as secondary stages of traumatic brain injury. These AGEs, when they cross-link intra- and interproteins, deactivate enzymes, exacerbating the progression of the disease. Binding to RAGEs may also result in more pro-inflammatory events, with overexpression of these receptors being involved in neurodegenerative diseases such as Alzheimer's and amniotrophic lateral sclerosis (Reddy et al., 2022)

The most studied consequences of persistent hyperglycemia with the production of AGEs are associated with chronic complications in micro and macrovascular conditions, classified as micro and macroangiopathies, in which they have undesirable effects that negatively affect the quality of life of their patients. Diabetic microangiopathies are associated with changes in the function of microvascular beds, resulting in progressive damage to the endothelium and associated cells, culminating, for example, in capillary occlusion, ischemia, and organ failure. Microangiopathy appears to be related to the mechanism of cellular senescence due to the high-glucose environment found in diabetes. Cellular senescence is a state of permanent cell cycle arrest and is involved in many vascular lesions (Liu et al., 2024).

Diabetic macroangiopathies, on the other hand, are associated with damage to cardiovascular tissues, which in turn are potentiated by cases of hypertension, constituting the main cause of mortality and morbidity in patients with diabetes. Diabetic macroangiopathy is a serious and prevalent complication, contributing significantly to the increase in morbidity and mortality rates of affected patients. The pathogenesis of macroangiopathy involves molecular mechanisms related to an intricate interaction between inflammatory mechanisms, oxidative stress, endothelial dysfunction, and dysregulated angiogenesis (Yin, et al., 2024).

5.3.1 Impaired healing

One of the most well-known characteristics of diabetes is impaired skin healing, which is also the main cause of the high number of amputations related to the disease, reflecting in the increase in the morbidity and mortality rate associated with it. It is known that the natural process for wound healing begins with the migration of specific cells to the site in question, followed by inflammation, proliferation of necessary cells, angiogenesis, production of extracellular matrix components, tissue remodeling, and finally, closure of the lesion. This inflammatory response is the key to rapid wound healing, and it is precisely at this point that AGEs interfere.

In pathological situations, such as diabetes, the healing process already begins with a delay in the proliferation of inflammatory cells at the site of the injury, however, when these cells in question reach the site of the injury, they initiate the process of chronic inflammation, preventing the arrival of the components of the extracellular matrix and impairing the rest of the process. making it difficult to close the wound. This chronic inflammatory process occurs due to the interaction between AGEs and their receptors, which promotes the stimulation of pro-inflammatory molecules (such as TNF-α and metalloproteinases) that cause the destruction of the extracellular matrix, in addition to also affecting fibroblasts, impairing the performance of collagen in the healing process, as demonstrated by Barbosa et al. (2008).

5.3.2 Nephropathy

Diabetic nephropathy is characterized by hyperfiltration and albuninuria in the early stages, followed by a progressive decline in renal function, and may vary with other glomerular/tubular pathologies and severe peripheral vascular disease (Sagoo, Gnudi, 2020). End-stage kidney disease is highly associated with cases of diabetic nephropathy, resulting in conditions such as proteinuria (presence of protein in the urine), increased blood pressure, and of course, impaired kidney function.

As already seen, one of the strong characteristics of diabetic nephropathy is the thickening of the glomerular basement membrane, due to the increased synthesis of components of the extracellular matrix (type IV collagen and its respective proteins), influenced by the β growth factor (TGF-β) that is stimulated by AGEs through RAGEs. In addition to the thickening of the basement membrane, there are also changes in the glomerular filtration capacity, since there is compression of the filtration capillaries and a decrease in the area of action, which can even culminate in the total loss of glomerular function (Barbosa et al., 2008).

5.3.3 Neuropathy

As is induced by the name itself, diabetic neuropathies directly affect neuronal segmentations, impairing cognitive and motor functions of their patients. Its incidence in diabetic patients is considered high.

Diabetic neuropathy is characterized by damage to sensory neurons, with central and peripheral neuropathic syndromes of different patterns, such as pain and numbness. Clinically, it is more common to find distal symmetrical polyneuropathy of the feet and hands. At least 50% of patients with diabetes develop neuropathy over time. Nerve cells that have limited ability to receive glucose, such as vascular cells, Schwann cells, and central and

peripheral neurons. In the early stage of diabetes, there is an abnormality in blood flow and vascular permeability due to hyperglycemia. Over time, altered glucose metabolism reduces intracellular levels of NADPH and myo-inositol, which is critical for nervous function. Diabetic neuropathy is usually caused by a direct effect of hyperglycemia on damaged cells and an indirect effect on cellular functions. Microvascular degeneration occurs in conjunction with reduced production of endothelial and neuronal cells. In the condition of hyperglycemia, glucose or glycolysis intermediates are diverted to other routes, consuming NADPH, increasing oxidative stress that causes mitochondrial injury allowing the return of protons without ATP production. Axons, rich in mitochondria, are susceptible to this damage (Pang et al. 2020).

Due to the hyperglycemic condition of diabetes, there is an increase in myelin glycation and, in turn, glycated myelin is more prone to phagocytosis by macrophages that undergo stimuli to secrete proteases, further contributing to nerve demyelination. In addition, the AGEs present in glycated myelin bind to plasma proteins (such as IgG and IgM), stimulating increased immune reactions to CML and RAGE, further enhancing neuronal demyelination. Studies analyzed by Barbosa et al. (2008) showed that this neuronal dysfunction is associated with the AGE-RAGE interaction, which results in the activation of NF-κB and the production of pro-inflammatory cytokines, such as IL-6 and TNF-α. In addition, AGEs also influence the process of vascular ischemia (which acts directly on neural changes), while they promote the thickening of the blood vessels that supply the nerve in question.

5.3.4 Retinopathy

Vision loss caused by diabetic retinopathy can be one of the main impacts for diabetic patients. The retina is a metabolically very active tissue, with photoreceptor interactions with neurons, which transfer the electrochemical signal to the brain with the support of glia and vascular tissue. Diabetes negatively impacts the blood-retinal barrier, affecting these interactions between cells, promoting vascular abnormalities, loss of blood barriers, and impairment of neuronal function. Changes in retinal blood flow and permeability, basement membrane thickening, loss of pericytes, and acellular capillary formation contribute to clinically visible lesions in nonproliferative retinopathy such as microaneurysms, venous beading, and microvascular abnormalities. The great influence of AGEs is characterized by their existence in blood vessels, causing an increase in the permeability of endothelial cells, which intensifies vascular obstruction. In addition, the AGE-RAGE ratio intensely stimulates the production of vascular endothelial cell growth factor (VEGF), promoting angiogenesis and neovascularization. Mesenchymal cells also have a great influence on this process, such as

pericytes, which express RAGEs. With increased ischemia, patients may develop proliferative retinopathy, with a risk of visual loss due to neovascular complications with vitreous hemorrhage or retinal displacement (Antonetti et al., 2021).

6 DIAGNOSIS AND THERAPY

The increase in the number of structures of AGEs has been detailed in studies, and measuring these compounds in the serum or tissues of diabetic patients can help in assessing the risk of disease progression.

Glycated Hemoglobin (HbA1c) is widely used as an indirect marker of long-term glycemic control. HbA1c reflects the average blood glucose levels over the past two to three months, and is an important measure in the management of diabetes. Although not a direct marker of AGEs, elevated HbA1c levels indicate increased exposure to glucose and, consequently, the formation of AGEs (Rohlfing *et al.*, 2002).

The high structural variability of AGEs represents a challenge for the creation of a single quantification method for this group of molecules. Some AGEs, such as carboxymethyllysine (CML) and pentosidene, have well-established quantification methods. Pentosidine can be measured using high-performance liquid chromatography (HPLC), while carboxymethyllysine (CML) is often quantified by mass spectrometry. In addition, enzyme-linked immunosorbent assays (ELISA) with specific antibodies are used to quantify AGEs, such as carboxyethyllysine (CEL) and CML, which are present in higher concentrations in serum (Taneda; Monnier, 1994; Teerlink *et al*., 2004; Scheije *et al*., 2009). These assays offer a less invasive approach and are useful in assessing long-term exposure to AGEs.

Some AGEs have fluorescence at specific wavelengths, allowing its quantification through this property. Although fluorescence-based methods are well characterized, they often have low specificity (Makita *et al*., 1992). An innovative approach in clinical trials involves the use of an autofluorescence reader (AFR), which allows non-invasive quantification of the accumulation of AGEs in the skin. This recently validated technology has demonstrated significant correlations between skin autofluorescence, age, glycemic control, and renal function in preliminary studies with diabetic patients. A positive correlation between FA and CML, CEL and pentosidine concentrations has already been demonstrated (Meerwaldt *et al*., 2004). FA was higher in individuals with microalbuminuria, an indicator of early kidney injury, and endothelial dysfunction, compared to healthy individuals. Studies indicate that PA is higher in diabetic patients than in non-diabetic patients (Gerrits *et al*., 2008; Genevieve *et al*., 2013). This method has the advantage of being simple, fast and non-

invasive, although it is subject to multiple interferences (Bos, *et al.* 2011; De Ranitz-Greven *et al*., 2012).

The detection and quantification of AGEs play an essential role in the evaluation of late complications associated with diabetes. To monitor these complications, several complementary tests are also used to assess the severity and progression of clinical conditions. Diabetic retinopathy, diabetic nephropathy, and diabetic neuropathy are common complications that can be evaluated through specific tests.

Complete ophthalmologic examination, including ophthalmoscopy (direct and indirect) and retinal biomicroscopy under mydriasis medicamentosa, is critical for detection (86%) and staging of retinopathy. Photographic documentation (retinography) is also important for detection, i.e., the assessment of disease progression and treatment outcomes (Ferris, 1993).

The early diagnosis of diabetic neuropathy (DN) is carried out through the quantification of microalbuminuria, a test that detects the presence of small amounts of albumin in the urine, starting to be released from stage 2 of DN. In more advanced stages of DN, an increase in blood creatinine and urea levels, changes in creatinine clearance, and the presence of proteins in urine collected over 24 hours can be observed (Brito *et al.* 2016).

The evaluation of diabetic neuropathy is carried out through a series of clinical tests and neurological examinations. Nerve conduction, which measures the speed and amplitude of electrical impulse conduction along nerves, is a key method for assessing the presence and severity of neuropathy. In addition, sensitivity tests, such as the monofilament test and the evaluation of tendon reflexes, are used to identify the sensory and motor deterioration associated with neuropathy. Periodic monitoring of these tests is essential to detect diabetic neuropathy early and to guide the implementation of appropriate management strategies, ensuring an effective approach to managing the condition (Pop-Busui, *et al.*, 2017).

Advanced glycation end products (AGEs) play a crucial role in the development and worsening of complications associated with diabetes, and are considered promising targets for new therapies. Currently, several agents with anti-AGE properties are under investigation and can act in different ways, such as: reducing the absorption of AGEs, decreasing oxidative stress, neutralizing and detoxifying dicarbonyl intermediates, and disrupting biochemical pathways that affect AGEs levels. These agents include medications, supplements, and dietary interventions.

Aminoguanidine, also known as Pimagedine, was one of the first inhibitors of AGEs formation to be studied (Brownlee, 1986). It is believed to act as a nucleophilic trap for carbonyl intermediates. Animal studies have shown that aminoguanidine prevents several

diabetic vascular complications, including improving proteinuria, vessel elasticity, and preventing diabetic retinopathy. Clinical trials have shown a reduction in hemoglobin AGE levels independently of the reduction in HbA_1c (Bucala, Vlassara, 1995). However, side effects associated with chronic use, such as a higher incidence of glomerulonephritis and vitamin B6 deficiency, have led researchers to seek a safe dosage for its therapeutic application in patients with diabetes (Mceniery, 2006; Goldin, 2006).

Research has also revealed that pyridoxamine, a vitamin B6 derivative, can antagonize angiotensin II-induced increase in AGEs, as well as protect against renal hypertrophy and salt retention (Thomas, 2005). It has shown benefits in preventing retinal vascular damage caused by diabetes. Animal experiments suggest that pyridoxamine may reduce plasma creatinine and albuminuria, which makes it promising for the treatment of diabetic nephropathy (Degenhardt, *et al.*, 2002). Early clinical trials in patients with type 1 and type 2 diabetes indicated that pyridoxamine may be effective in reducing AGEs, although concerns have also been raised about the safety of its use (Williams, *et al.*, 2007).

In in vitro experiments, LR-90 proved to be efficient in the interaction with reactive carbonyl compounds and showed a superior metal complexation capacity in relation to pyridoxamine and aminoguanidine. In the context of studies with diabetic rats, LR-90 was able to reduce albumin and creatinine levels and circulating AGEs, without affecting glycemic control. Mice treated with this compound also demonstrated an increase in body weight compared to untreated mice, suggesting that this substance may have some other metabolic effect that is still unknown. In addition, LR-90 prevented glomerulosclerosis, tubular degeneration, and collagen deposition in the kidneys, and led to a reduction in cross-linking by AGEs and fluorescence of tail collagen. Treatment with LR-90 also decreased the accumulation of AGEs in the renal glomeruli and the deposition of nitrotyrosine in the renal cortex (Figarola, *et al.*, 2003).

GLP-1 (glucagon-like peptide-1) is a hormone produced in the gut that plays a crucial role in glucose regulation. Recently, GLP-1 has been identified as a potential therapy for type 2 diabetes, since it stimulates insulin release and inhibits glucagon secretion. In addition to its effect on controlling glucose levels, GLP-1 also offers protection against the damage caused by AGEs by promoting an increase in antioxidant defenses and blocking the positive feedback effect of AGEs on RAGE receptor expression (Puddu, *et al.*, 2013).

ACE inhibitors and angiotensin II antagonists have been shown to reduce the formation of AGEs, as evidenced by a number of in vitro studies and in animal models of diabetes. These agents also appear to promote sRAGE expression, as observed in vitro,

preclinical, and clinical research, providing an additional mechanism to inhibit AGE-induced organic injury (Forbes, *et al.*, 2005).

Oral hypoglycemic agents, such as metformin and pioglitazone, not only reduce the formation of AGEs by controlling hyperglycemia, but have also demonstrated in in vitro studies the ability to prevent the formation and cross-linking of AGEs (Rahbar, *et al.*, 2000), regardless of their direct effects on glucose levels.

The scientific community has been very keen to find therapeutic alternatives to reduce the harmful effects of Advanced Glycation End Products (AGEs) in humans, as demonstrated by the extensive amount of research conducted in this field. Although most of these studies are still in the preclinical phase, there is a growing expectation that antagonists of the formation and/or action of AGEs may soon be integrated into clinical practice to treat related diseases, especially diabetes mellitus (Goh, Cooper, 2008).

7 FINAL CONSIDERATIONS

Long-term exposure to hyperglycemia results in a significant increase in the production of Advanced Glycation End Products (AGEs), which are strongly linked to the late complications of diabetes. The AGE-RAGE axis plays a crucial role in intensifying inflammation, oxidative stress, and endothelial dysfunction, factors that aggravate vascular, renal, neuropathic, and retinopathic problems (Vlassara, Palace, 2002).

In this sense, AGEs should be considered a relevant factor in the chronic complications of diabetes. Effective blood glucose control and the implementation of therapeutic strategies aimed at reducing AGEs are essential for the prevention and management of these complications (Neves, et al., 2023).

Continued research on the modulation of AGEs will be key to enhancing therapeutic approaches and improving the quality of life of diabetic patients by targeting advanced glycation as a strategy to reduce diabetic complications.

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