Diabetes & its Complications

Advanced glycation end-products and their relationship with complications of Diabetes Mellitus

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Diabetes mellitus is the collective term to refer to heterogeneous metabolic disorders, the main finding of which is chronic hyperglycemia. The cause is an altered secretion of insulin or an altered effect of it, or mainly both [1]. According to the American Diabetes association, diabetes is classically subdivided into 4 entities [2]:

- Type 1 diabetes (DM1)
- Type 2 diabetes (DM2)
- Gestational diabetes (GD)
- · Specific types of DM due to other causes

The importance of this disease is vital in most countries of the world, it is estimated that 62 million people in the Americas have Diabetes Mellitus (DM) type 2, generating high costs for the health system. It was estimated that it generates expenses calculated in \$ 382.6 billion (or 12-14% of the health budget) and this number will increase to \$ 445.6 billion by 2040. Also, it is a large direct cause of death etiology. It is estimated worldwide that in 2016 diabetes was the direct cause of 1.6 million deaths. Diabetes generates multiple complications that affect the quality of life and can even lead to the death of the patient. The best known are myocardial infarction, stroke, lower limb amputation and end-stage kidney disease [3,4].

Due to the previous facts, in recent decades promotion and prevention methods have taken on importance in order to reduce the incidence of complications associated with diabetes mellitus. However, with the classic methods (Changes in lifestyle associated with pharmacological management) it has been observed that certain patients despite the previous prevention continue to present complications of the disease, which is why the world scientific community has been interested in understanding the genesis of complications derived from Diabetes Mellitus. Several theories have been proposed, such as the role of glycation end products in the development of these complications, which will be the study objective of this article.

What are advanced glycation end products?

Advanced glycation end products (AGEs) are a heterogeneous group of compounds generated through the non-enzymatic glycosylation of proteins, lipids, and nucleic acids. The structural chemical changes that give rise to these compounds often take months or years so that proteins and other substances that have a long half-life are more susceptible to being modified by exposure to glucose; These include extracellular matrix proteins, myelin, cartilage, and proteins [5].

This process begins with an initial chemical reaction called "early glycation" that occurs between reducing sugars or their byproducts and amino groups in proteins, lipids, or nucleic acids. The compounds originating from this reversible reaction are unstable and are called Schiff's bases. They are subsequently subjected to a structural rearrangement to form Amadori products, the best known of which are glycosylated hemoglobin and fructosamine. However, none of these are AGEs; For this to occur, Amadori products must undergo further dehydration, lensing, oxidation, rearrangement and fragmentation reactions (Figure 1) [5].



Figure 1: Formation of advanced glycation end products. Adapted from Advanced glycation end products in cardiovascular disease as a complication of diabetes [5].

This process, also known as the Maillard reaction, was described in the early 1900s, when it was observed that amino acids subjected to high temperatures in the presence of reducing sugars developed a characteristic yellowish-brown color [6].

Approximately twenty have been chemically characterized in human tissues, which are named according to the protein they are modifying (Figure 2), the best known are: [7]

- 1. Pentoxide
- 2. Ne-carboxymethyl lysine (CML)
- 3. Nɛ-carboxyethyl lysine (CEL)

The accumulation of these products depends on the balance between formation and elimination at the renal level by a process that is still unknown. Therefore, factors in which production is high, such as Diabetes mellitus, lead to an increase in them. Other factors that influence serum concentration are shown in Table 1 [9].

Endogenous factors	Exogenous factors
Age	AGEs of the diet
Hyperglycemia	Ionizing radiation
Obesity	UV radiation
Autoimmunity and inflammatory reactions	Air pollution
Chronic kidney disease	Cigarette exposure
Glyoxhalase I and II deficiency	
Oxidative stress and chronic inflammation	

Table 1: Adapted from The Development of Maillard Reaction, and Advanced Glycation End Product (AGE)-Receptor for AGE (RAGE) Signaling Inhibitors as Novel Therapeutic Strategies for Patients with AGE-Related Diseases [10].

What is the relationship of these products with the complications of diabetes?

Morbidity caused by diabetes has traditionally been classified into macro and microvascular complications. Although macrovascular complications have received increased attention, microvascular complications are unique to diabetes and hyperglycemia contributes to their development. It has been hypothesized that numerous mechanisms related to hyperglycemia mediate micro and macrovascular complications. These include the aldose reductasemediated polyol pathway, the hexosamine pathway, protein kinase C activation, generation of reactive oxidative stress, poly (ADP



Figure 2: Nomenclature of Advanced Glycation End Products adapted from Toxicity of advanced glycation end products [8].

ribose) polymerase (PARP) activation, and the focus of this article: accumulation of the AGEs [11]. It been found in diabetic patients. A study conducted by Kathryn Tan and colleagues in Hong Kong in patients diagnosed with type II diabetes mellitus found an elevated serum concentration of AGE. Similarly, in another study carried out by Berg et al. In patients with type I DM, serum elevations were found. This increase precedes the development of micro and macrovascular complications [12,13]. Another study was carried out by Garay and collaborators in Mexico in 2005 in which the measurement of these products in different body fluids (skin, saliva, urine and at the serum level) were useful when evaluating the complications of diabetes [14].

Microvascular complications Diabetic nephropathy

Renal nephropathy is the most frequent cause of chronic kidney disease and It constitutes an important cause of morbidity and mortality in the world. (15) Despite the introduction of new drugs for the prevention of this complication, patients with diabetes continue to develop Chronic Kidney Disease, therefore, in recent years its pathophysiology has been studied. One of the main molecules involved in the genesis of this pathology are the advanced glycation end products since it could accumulate in the glomerular basement membrane, mesangial cells, endothelial cells and podocytes in patients with diabetes and / or end-stage renal failure due to the intrinsic hyperglycemic state that this pathology entails, generating alteration in the structure and function [16].

The mechanism by which these products alter structure and function has been studied, experimentally found to act at the receptor for advanced glycosylation compounds (RAGE). A study in which transgenic mice that overexpressed this receptor were compared showed glomerular hypertrophy, increased albuminuria, mesangial expansion, advanced glomerulosclerosis, and increased serum creatinine, compared to non-transgenic mice [17]. Likewise, in 2010 a study was conducted by Sourris et al. In mice that presented a receptor deficiency, had less albuminuria, and fewer histological changes such as glomerulosclerosis compared to mice that did express the RAGE receptor [18,19].

Through the use of the RAGE receptor, AGEs generate an inflammatory response by releasing reactive oxygen species, which are cytotoxic to kidney cells, due to the fact that they stimulate pro-sclerotic factors such as transforming growth factor beta, growth factor of the connective tissue, through the mitogenactivated protein kinase pathway, the nuclear transcription factor kappa and the protein kinase C pathway, generating fibrogenic reactions in the kidney [20].

Another way in which AGEs contribute to diabetic nephropathy is by increasing the accumulation of kidney lipids, this was corroborated in a study carried out by Yang Yuan et al., Where it was found that N ε - (carboxymethyl) lysine, increased intracellular cholesterol in mice. The theory of the genesis of this elevation could be due to the alteration of the regulation of intracellular feedback of cholesterol [21].

Understanding this has led multiple researchers to make it a promising therapeutic target for the prevention and management of diabetic nephropathy. These have been called inhibitors of the formation and accumulation of advanced glycosylation products, the effect they exert is not clear, it is believed that they can act in 4 ways either directly or indirectly: [10,22,23]

- 1. Stimulate the antioxidant effect
- 2. Reduce the formation of reactive oxygen species
- 3. Modification of lipid profiles
- 4. Inhibit the inflammation process

Among those that act indirectly, we find drugs known as metformin and SGLT2. However, those that have undergone further development and studies are those that act directly, among which we find molecules such as salvianolic acid, berberine, chryscin, the guanyl nucleotide-releasing protein Ras 2 (RasGRP2), astragaloside, among others, in which it has been shown in studies that they have had a protective role in diabetic nephropathy [22,24-28].

Diabetic retinopathy

Diabetic retinopathy is a common and specific microvascular complication of diabetes, and it remains the leading cause of preventable blindness in people of reproductive age [29]. Several biochemical mechanisms have been proposed to understand the pathogenesis of retinopathy through effects on cell metabolism, signaling and growth factors, among which we have the advanced glycation end products. These molecules have been found to accumulate in cells that are responsible for homeostasis at the retineal level, called pericytes. In this way, they cause endothelial dysfunction and alteration of the blood-retinal barrier [30]. How do you generate all these changes? It has been observed that it induces the migration and accumulation of monocytes through the endothelial cell monolayer, added to the activation of NADPH oxidase, generating oxidative stress and activating the nuclear factor-Kb in both ways. All this is done through the receptors of advanced glycosylation compounds, which are naturally expressed in retinal cells and are positively regulated in diabetic patients, resulting in the activation of pro-oxidant and pro-inflammatory signaling pathways, Thus, the interaction between AGEs and their receptor is an important axis in the changes of diabetic retinopathy [31,32].

Another of the theories of how AGEs interfere in the genesis of diabetic retinopathy, was evidenced in a study carried out by TM Curtis and colleagues in mice in which Müllerian glial dysfunction during diabetic retinopathy is related to the accumulation of these products [33]. There is even evidence of drugs such as the acrolein scavenger, 2-hydrazino-4,6-dimethylpyrimidine, which in the study carried out by Rosemary E McDowell et al., Was found to decrease the concentrations of AGEs, and which could be a promising therapeutic target [34].

Possible therapeutic targets in the prevention of diabetic retinopathy have been studied taking into account the previously exposed biochemical mechanisms, and molecules such as Fangquinoline, Zerumbone, among others, have been found, which through animal studies have shown the inhibition of the AGE axis and its receptor exert a protective effect on the genesis of diabetic retinopathy [35-37].

Diabetic neuropathy

Diabetic neuropathy is a heterogeneous condition that has multiple presentation spectra, it can affect proximal or distal nerve fibers, mononeuropathy or polyneuropathy. Distal symmetric poly neuropathy is the most common form of diabetic neuropathy, it consists of a chronic sensory motor poly neuropathy dependent on the length of the nerve [38]. The pathogenesis of these complications has not been fully understood, however, it is believed to be of multifactorial origin. Among the factors involved are glycemic control, duration of diabetes, age-related neuronal wear, among others [39]. It has been found that the advanced glycation end products, as in the other complications mentioned, increase reactive oxygen species by interacting with its receptor RAGE, thus activating the nuclear factor kappa beta, generating inflammatory processes that induce to the alteration of the blood flow of the nerves and the decrease of the neurotrophic support, which leads to the neuronal dysfunction characteristic of this clinical entity [40]. Another mechanism in which AGEs contribute to this is by decreasing the biological function of proteins, thus inhibiting neuronal activity [41].

Diabetic Cardiomyopathy

It is defined as myocardial dysfunction in patients with diabetes mellitus, in the absence of hypertension and structural heart diseases, such as valvular heart disease and coronary artery disease. It could also be defined as myocardial disease in people with diabetes that cannot be attributed to the individual effect of coronary artery disease, hypertension, or other known heart disease [42].

The mechanism of how hyperglycemia generates cardiomyopathy has been exhaustively studied in the last 30 years, more specifically in 1999. The possible harmful effects that hyperglycemia could have at the cardiac level was evidenced in the study carried out by Avendaño et al. In this study, it was found that glycosylation linked to collagen affected diastolic function [43]. Another study, carried out a year earlier, showed improvement in cardiac dysfunction in animals treated with metformin, whereas non-treated animals showed greater rigidity of the diastolic chamber [44].

Currently, the mechanism of the genesis of diabetic cardiomyopathy is not fully understood, but it is believed that it is due to the effects of glucotoxicity, within which AGEs play an important role, individually and jointly with their receptor RAGE. Individually, it has been found that the interlinking of connective tissue increases, generating fibrosis and cardiac stiffness, which leads to an alteration in cardiac diastole [45]. Within the theories of how it alters the latter, it has been proposed that it affects physiological aspects in cardiomyocytes. Multiple studies have suggested that it generates a dysfunction in the sarcoplasmic reticulum that leads to alterations in calcium management, thus generating a decrease in contractile performance [46-48]. Together with their receptor RAGE, they generate an inflammatory reaction by increasing proteins of matrix, through the activation of pathways such as the mitogen-activated protein kinase (MAPK) and Janus kinase (JAK) pathways in vascular and cardiac tissues leading to increased production of reactive oxygen species, which promote inflammation and fibrosis [45].

Molecules that inhibit in vitro the formation of AGEs and their interaction with RAGES have been studied, among which are:

chrysin, pioglitazone, mangiferin, curcumin, among others. All with evidence in reducing fibrosis, oxidative stress, inflammation and cell death, especially curcumurin, which Neha Rani and collaborators in their study state that it is a promising therapeutic target in the treatment of diabetic cardiomyopathy [49-52].

Macrovascular complications Atherosclerosis

Atherosclerosis is a chronic, generalized and progressive disease that mainly affects medium-sized arteries. Clinically it will have multiple spectra of presentations, among which is ischemic heart disease, cerebrovascular disease, peripheral arterial disease, among others. Annually, these complications lead to a high mortality rate in most countries of the world, including Colombia [53].

The AGEs in this entity are believed to play an important role in the genesis of macrovascular complications of diabetes through different mechanisms:

Endothelial dysfunction and vascular inflammation

A molecule that plays an important role within the factors that prevent the formation of atherosclerotic plaques is nitric oxide through 3 actions: vasodilation, inhibition of inflammatory reactions and inhibition of platelet aggregation, AGEs have been found to have an inhibitory effect in the enzyme nitric oxide synthase at the level of the endothelium. In addition, by interacting with its receptor RAGE generates a greater formation of toxic byproducts of nitric oxide such as peroxynitrite. On the other hand, it is believed that the interaction with its receptor also generates an endogenous product called asymmetric dimethylarginine, which is a natural inhibitor of nitric oxide in endothelial cells, mesangial cells and cells of the proximal convoluted tubule, all this leading to endothelial dysfunction [54]. It was evidenced in a study by S. Yamagishi et al. That the factor derived from the pigment epithelium is a protective factor against atherosclerosis by preventing the reduction of endothelial nitric oxide synthase caused by AGEs [55].

It has been found for decades that the inflammatory process in the genesis of atherosclerosis plays a very important role, as well as it has also been proven that it leads to macrovascular complications. There are studies that have suggested this relationship, N Tahara et al., Found in their study that serum AGE level is independently associated with vascular inflammation [56]. In another study by K. Nakamura et al. They suggest that the AGEs-RAGE system may be involved in the elevation of monocyte 1 chemoattractant protein in type 2 diabetic patients, an important molecule in the migration of monocytes to the subendothelium [57]. One of the theories of how AGEs contribute to the inflammatory process at the vascular level is through the generation of reactive oxygen species via the nuclear factor kappa beta [54].

Arterial stiffness

AGEs have been related to tissue aging processes, which increases the concentration of these products, manifesting itself with arterial stiffness. One of the most studied is pentosidine, it is believed that it contributes through the formation of cross-links with extracellular matrix proteins such as collagen and elastin [54,58,59].

Plaque formation and angiogenesis

Low-density lipoproteins, also called LDL, are an initiating factor of atherosclerosis, the accumulation of cholesterol-laden macrophages, traditionally called foam cells in the intima of the arteries, is one of the incipient changes that lead to atherosclerosis. It has been found in various studies that AGEs induce changes that make them more atherogenic. A study by R Bucala et al. Revealed that the modification made by glycosylation products significantly alters the clearance mechanisms mediated by the LDL receptor, and this in turn could contribute to the elevation of LDL in diabetic patients. On the other hand, the elevation of these molecules when encountering a higher serum concentration could contribute to a greater generation of atherosclerosis [60,61]. Another study by W. Cai found that exogenous glycosylation products increase LDL-induced vascular toxicity [62].

There are certain mechanisms that the body develops to prevent the formation of atherosclerosis, one of them are the proteins ABCA1 and ABCG1, which are responsible for the efflux mechanisms at the macrophage level, it is believed that the Advanced Glycation End Products inhibit these proteins, leading to cholesterol-induced cellular toxicity and increased formation of atheromas [63-65]. In addition, they contribute to promote states predisposing to atherogenesis, it has been found that a high level of AGEs could cause instability of the atherosclerotic plaque, this was suggested in the study carried out by Y. Fujino et al. indirectly (skin auto fluorescence) it was found that a high value of these products was associated with greater plaque vulnerability in patients [66].

Platelet activation, thrombosis, and hypercoagulability

In addition to the complications mentioned, diabetes has also been found to generate a pro-thrombotic environment, among the findings is evidence of greater platelet activation, greater activity of procoagulant proteins together with a compromised function of the fibrinolytic system [67]. Within the studied pathophysiological mechanisms of the genesis of this environment, the AGE-RAGE axis has been included, it is believed this axis inhibits an antithrombotic prostanoid, the production of prostacyclin by endothelial cells, while stimulating the plasminogen activator, inhibitor-1, stabilizing arterial thrombi. Furthermore, it has been shown that AGEs can induce platelet activation and aggregation and stimulate the coagulation cascade, which in concert could play a crucial role in the development of atherothrombotic CVD [54,68].

Abnormality in endothelial cell repair

Another of the mechanisms proposed in the last decades with respect to the prevention of the progression of atherosclerotic disease, is the adequate repair of the endothelium at the vascular level. Endothelial progenitor cells play a crucial role in this mechanism; these cells have been experimentally shown to incorporate into neovascularization sites and harbor endothelial denudation sites [69].

Endothelial progenitor cells have been found to exhibit impaired function in the context of diabetes, AGEs are believed to contribute to this. In a study carried out by Qin Chen et al., The mechanism in which these products contributed to the alteration of the function of these cells was investigated, the authors suggested that RAGE mediates the deterioration induced through the negative regulation of Akt and COX-2 in these cells. cells [70].

Conclusions

Diabetes is a disease that causes multiple complications associated with macro and microvascular level, where the interaction between AGEs and their receptor RAGE plays a very important role, which as a common pathway generate a pro-inflammatory state through the production of reactive oxygen species. The understanding of the role of AGEs has opened the way to inhibitory molecules of AGEs, which will be a promising therapeutic target in the prevention and management of complications derived from diabetes.

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