Advanced Glycation End Products

Subjects: Health Care Sciences & Services

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Diabetes mellitus (DM) is considered one of the most massive epidemics of the twenty-first century due to its high mortality rates caused mainly due to its complications; therefore, the early identification of such complications becomes a race against time to establish a prompt diagnosis. The research of complications of DM over the years has allowed the development of numerous alternatives for diagnosis. Among these emerge the quantification of advanced glycation end products (AGEs) given their increased levels due to chronic hyperglycemia, while also being related to the induction of different stress-associated cellular responses and proinflammatory mechanisms involved in the progression of chronic complications of DM. Additionally, the investigation for more valuable and safe techniques has led to developing a newer, noninvasive, and effective tool, termed skin fluorescence (SAF).

Keywords: advanced glycation end products ; diabetes mellitus ; chronic complications ; skin fluorescence

1. Introduction

Diabetes Mellitus (DM) is a metabolic disease characterized by chronic hyperglycemia due to absent or inadequate insulin secretion, combining with defective action on target tissues, depending on the type of diabetes [1]. DM has many categories; however, the main subtypes are type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), and gestational diabetes mellitus [2]. Diabetes is currently considered one of the largest epidemics of the twenty-first century. In 2015, according to the International Diabetes Federation (IDF), 415 million people worldwide were estimated to have diabetes, and there were approximately 5 million deaths attributable to diabetes, which is estimated as a death every 6 s [3]. However, it is to emphasize that the leading cause of death is not diabetes per se but DM-derived complications that lead to systemic dysfunction [4].

As a result, the prompt identification of DM-associated complications has become significantly relevant. DM complications can be divided into two main types, acute and chronic complications. Acute complications involve hypoglycemia and hyperglycemic crises, which tend to onset abruptly [5], instead of the slow and steady progression of chronic complications over the years [6]. Regardless of the type of diabetes mellitus, the chronic complications are likewise divided into two categories depending on the vascular damage. Macrovascular complications include cardiovascular disease (CVD); meanwhile, microvascular complications include chronic kidney disease (CKD), neuropathy, and diabetic retinopathy [7].

Diverse studies have determined that advanced glycation end products (AGEs) are involved in the pathophysiological mechanisms of DM complications [8]. These derive from nonenzymatic reactions between carbohydrate residues and protein, lipids, or nucleic acids, along with oxidative processes [9]. The development mechanism of DM complications through AGEs is varied, since these can generate structural changes to different macromolecules, altering their function and leading to intracellular pathways that trigger inflammatory responses and endothelial damage [10]. Thus, measuring these changes works both as a diagnostic method of DM and as a biochemical marker of glycemic control, being the determination of hemoglobin A1c (HbA1c), the most known marker tested [11].

The quantification of AGEs can also serve to assess the risk of developing DM complications and measure their degree of progression [9]. Although multiple measurement techniques have been developed, the search for more accurate, selective, and safe procedures is still ongoing [11]. Luckily, skin fluorescence (SAF) has recently been described in several studies as a noninvasive method [12]. Here, we analyze the pathophysiological mechanisms induced by AGEs that trigger the progression of chronic complications of DM and describe the newer measurement techniques available, focusing on SAF, a possible tool to measure the risk of developing DM complications.

2. Protein Glycation and Formation of Advanced Glycation End Products

Advanced glycation end products (AGEs) are an heterogeneous group of oxidative molecules with pathogenic capability [13]. The synthesis of these compounds begins with common metabolic pathways that occurred during the storage of food-

derived products in the organism due to nonenzymatic reactions between reduced carbohydrates and free amino acids, peptides, lipids, or nucleic acids [14]. These reactions mentioned earlier are called Maillard reaction, glycation, or “nonenzymatic glycosylation” [15].

The generation of AGEs is completed through three stages [16], starting with the production of Schiff Bases [17], which emerge from the covalent bond established between the amino group of the free amino acid (generally composed by lysine and less frequently by arginine and cysteine residues), lipids, and nucleic acids with glucose [18][19]. This stage takes place in a time-lapse of hours following the postprandial glycemic increase, and it is characterized as a reversible reaction, since it can be re-established if the glycemic levels decrease [13].

Afterward, Schiff Bases submit to a molecular rearrangement, generating Amadori products, which are more stable compounds, although this stage is still reversible from carbohydrate oxidation [20]. The most recognized product is $HbA1_c$, assembled through the junction of a valine residue of one of the β chain of this hemeprotein with plasma glucose [11]. Later, Amadori products accumulate in the organism; these go through reduction–oxidation reactions to eventually associate with secondary proteins through covalent bonds, altering their tertiary and quaternary structures and forming AGEs such as 3,4-*N*-carboxymethyl-lysine (CML), 3-deoxyglucosone (3DG), and Methylglyoxal (MG) [18]. AGEs have a brown-yellowish pigmentation, and some of them even have fluorescent properties, especially pyrrolidine, CML, imidazoline, and pentosidine [21]. Under physiological conditions, the glycation process occurs in weeks to years; nonetheless, in some pathological states such as hyperglycemia, oxidative stress, and temperature increase, the needed time can be reduced to hours [22] (**Figure 1**).

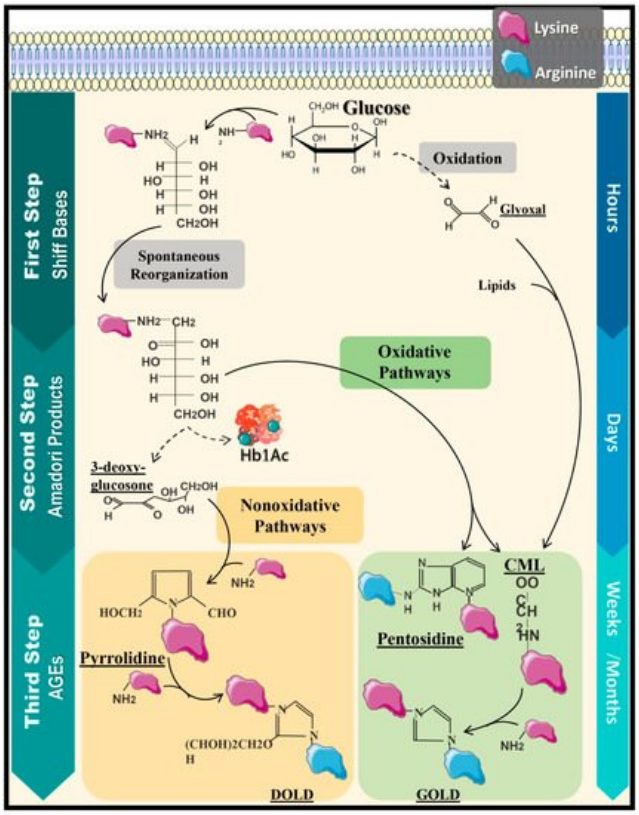

Figure 1. Maillard Reaction: production of AGEs. Production of AGEs initiates from a three-staged metabolic process denominated by a Maillard reaction, starting with the reversible formation of Schiff Bases, followed by a molecular rearrangement that results in the generation of Amadori products and, finally, leading to the formation of AGEs due to a posterior binding to secondary proteins, establishing as nonreversible structures. This can occur due to oxidative processes such as the formation of pyrrolidine and, also, nonoxidative processes such as the formation of pentosidine and CML; however, other proteins can be added to these molecules, allowing the formation of products such as DOLD and GOLD. Additionally, there are alternative pathways to form AGEs; for instance, the oxidation of glucose and subsequent glyoxal formation can generate CML by the binding of glyoxal to lipids. Hb1Ac: glycated hemoglobin and CML: 3,4-*N*-carboxymethyl-lysine.

Comparatively, glucose has the slowest glycation rate of carbohydrate within these compounds, unlike fructose, glucose 6-phosphate, and threose (intracellular carbohydrates), which have a faster oxidation capacity [15]. Additionally, the formation of AGEs is also exogenous, since they can be found in food, like primarily animal-derived high-fat food such as beef [14]. Different studies have demonstrated that these types of food induce an increase in plasma levels of AGEs, since up to 10% of food rich in AGEs is absorbed into the bloodstream [13]. Despite the existence of discrepancies regarding the

effects of exogenous compounds, studies have shown that a higher consumption of these food is correlated with weight gain [23], insulin sensitivity alteration [24], and albuminuria [25]. Therefore, AGE-rich diets, favoring oxidative stress and chronic inflammation states due to interactions with cellular compounds, are a substantial risk factor to the development of metabolic and cardiovascular complications [26].

3. AGEs and Their Implication in Chronic Complications of Diabetes Mellitus

Chronic complications of DM derive from structural and functional modifications of blood vessels due to hyperglycemia, affecting the heart, kidneys, and nervous system [27]. Among the mechanisms implied in developing these complications are the structural modifications induced by AGEs in vulnerable molecules such as proteins, lipids, and DNA, altering their stability and functions [28].

Activation of the receptor for advanced glycation end products (RAGE) represents the main mechanism involved between DM and AGEs [8]. RAGE is a cell surface receptor composed of three extracellular domains, a transmembrane domain, and a cytoplasmic tail [8], which belongs to the immunoglobulin superfamily [29], since its expression derives from the major histocompatibility complex class III (MHC-III) [30]. Thus, RAGE expression predominates in specific cells such as monocytes, macrophages, proximal tubular cells, podocytes, and mesangial cells [29].

As a result of the AGE–RAGE interaction, the cytoplasmic domain of RAGE leads to different signaling pathways. In particular, it can activate the p21 protein [31], triggering other signaling compounds to eventually stimulate kinases such as the extracellular signal-regulated kinase (ERK), c-Jun *N*-terminal kinase (JNK), and mitogen-activated protein kinase (MAP) [29], along with Janus kinase 1 and 2/Signal transducer and activators of transcription (JAK/STAT1) [32]. Finally, the consequences of these signal transduction pathways consist of the activation of transcription factors such as nuclear factor kappa B (NF-kB) [33] and the interferon-sensitive response element (ISRE) [34], which lead to the synthesis of proinflammatory cytokines as tumor necrosis factor-alpha (TNF-α) [34] and interleukins (IL) 1, 6, and 17 [35][36], as well as vascular cell adhesion molecule-1 (VCAM-1) [29].

Additionally, NADH oxidase's activation directly and indirectly generates reactive oxygen species (ROS) due to RAGE stimulation [37]. Furthermore, RAGE can be activated by other types of ligands aside from AGEs, including S 100 or Calgranulin, Mac-1, High-mobility group box 1 (HMBG1), and β-amyloids, predominantly when their levels increase during inflammatory reactions (**Figure 2**) [31]. The discovery of RAGE's multiligand nature explains its elevated and persistent activity in diabetes complications [36][37].

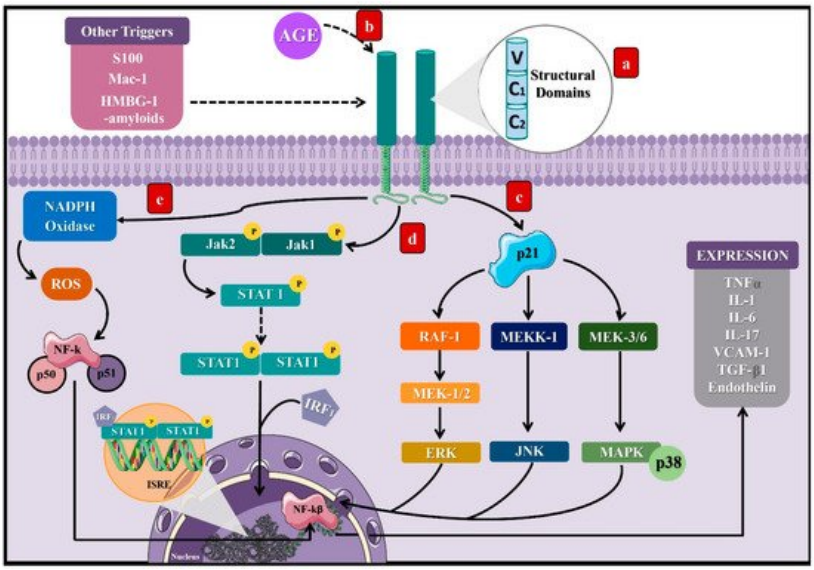

Figure 2. Signaling pathways induced by the activation of the receptor of AGEs. (**a**) RAGE is a cell surface receptor composed of three extracellular domains, a transmembrane domain, and a short cytoplasmic tail. (**b**) AGEs bind to RAGE's extracellular portion and induce activation of the cytoplasmic domain, leading to different signaling pathways, which will finally result in the stimulation of transcription factors such as NF-KB and ISRE. Three pathways that can lead to such a response: (**c**) activation of the protein p21, which induces RAF-1, MEKK-1, and MEK 3/6 proteins that activate the factors ERK, JNK, and MAPK, which translocate to the cell nucleus. (**d**) Activation of the JAK2/STAT1 pathway, where STAT1 dimerizes and binds to the IRF1 sequence to translocate to the cell nucleus, binding to the ISRE segment and inducing transcription of proinflammatory cytokines. (**e**) Activation of the NADPH oxidase that leads to the stimulation of

NF-KB. These processes can be activated by other molecules such as S100, Mac-1, HMBG-1, and β-amyloids. NF-kB: nuclear factor kappa light chain enhancer of activated B cells, ISRE: interferon-sensitive response element, TNFα: tumor necrosis factor-alpha, IL: interleukins, VCAM-1: adherence and growth factors as the vascular cell adhesion molecule-1, TGF-β1: transforming growth factor β, RAF-1: proto-oncogene serine/threonine kinase, MEKK-1: mitogen-activated protein kinase kinase kinase 1, MEK 3/6: mitogen-activated protein kinase kinase, ERK: extracellular signal-regulated kinase, JNK: c-Jun N-terminal kinase, MAPK: mitogen-activated protein kinase, JAK: Janus kinase, STAT: signal transducer and activators of transcription, IRF1: interferon regulatory factor-1, S 100: calgranulin, and HMBG1: high-mobility group box 1.

There are different types of these receptors that have been studied, known as soluble forms of RAGE (RAGEs), which are composed of extracellular domains without their intracellular portion, so they can be transported and found free in the plasma [38]. Of note, two types of receptors have been identified, cleaved RAGE(cRAGE) and endogenous secretory RAGE (esRAGE) or RAGE_V1, depending on how they were created [39]. cRAGE is formed from the action of matrix metalloproteases (MMP) and α-disintegrin metalloprotease (ADAM)-10; these enzymes cleave from the cell surface to RAGE, thus losing its transmembrane and cytosolic portions, but it conserves the V1-C1-C2 domains of RAGE. On the other hand, esRAGE is generated by the alternative splicing of the RNAm RAGE gene, changing its structure by adding a 16-amino acid extension at the c-terminal end [40].

Although the distribution and function of these receptors are not yet clear, there are multiple hypotheses about their role in the pathophysiology of inflammatory and metabolic diseases, such as DM. Among the most managed actions, their role as “decoys” for AGEs is evaluated, generating a downregulation effect in inflammation and preventing cell damage due to the sequestration of RAGE ligands that leads to the pathways not activated being intracellularly related to these receptors not only by AGEs but other ligands such as HMB1 or S100, postulating a possible regulatory action on the AGEs–RAGE axis [40]. In addition, studies have established an inversely proportional relationship between the levels of sRAGE and the markers of metabolic syndrome and atherosclerosis in patients with DM, used as a biomarker in inflammatory processes and complications associated with this disease [41].

3.1. Molecular Mechanisms of AGEs in Microvascular Complications of DM

The presence of diabetic retinopathy, neuropathy, or (micro) albuminuria defines the existence of microvascular complications of DM [42]; despite affecting different organs, these complications mutually relate to each other [43]. Diverse studies have associated AGEs with the progression of those complications, mainly given the direct action of these products on tissues or via stimulation of the AGE–RAGE axis and the subsequent inflammatory response [44][45][46].

Diabetic kidney disease (DKD) is characterized by renal hypertrophy, proteinuria, decreased glomerular filtration rate, and renal fibrosis [47], ultimately progressing to chronic kidney disease (CDK) [48]. Induction of the AGE–RAGE pathways deriving from the accumulation of these products in renal tissue leads to inflammatory activity [49]. Thus, triggering the migration of macrophages that agglomerate in the renal glomerulus’s mesangium and establishing an inflammatory microenvironment led by IL-6 synthesis with the consequent expansion of this layer eventually causes the compression of capillaries and reduction of the body surface area of renal filtration [50]. Additionally, increased expression of transforming growth factor β (TGF-β) has been correlated with fibrogenesis activation, collagen synthesis stimulation, and renal tubular cell apoptosis, therefore explaining both glomerular sclerosis and dysfunction [51].

Other mechanisms induced by the AGE–RAGE pathway arise specifically through CML, which constitutes a higher AGE accumulation in vivo [52], the renal epithelium being continuously exposed to these changes [53]. It has been recently determined that AGEs generate lipid accumulation in this tissue deriving from altered cholesterol metabolism, since AGEs activate the sterol-regulatory element-binding protein 2 (SREBP-2) and, correspondingly, the expression of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase) increases, concluding in an increased cholesterol synthesis. Additionally, this molecule’s access to cells benefits from the stimulation of low-density lipoprotein (LDLc) activity in conjunction with the decrease of the ATP-binding cassette transporter A1 (ABCA1), which results in tissue dysfunction [44] (**Figure 3**).

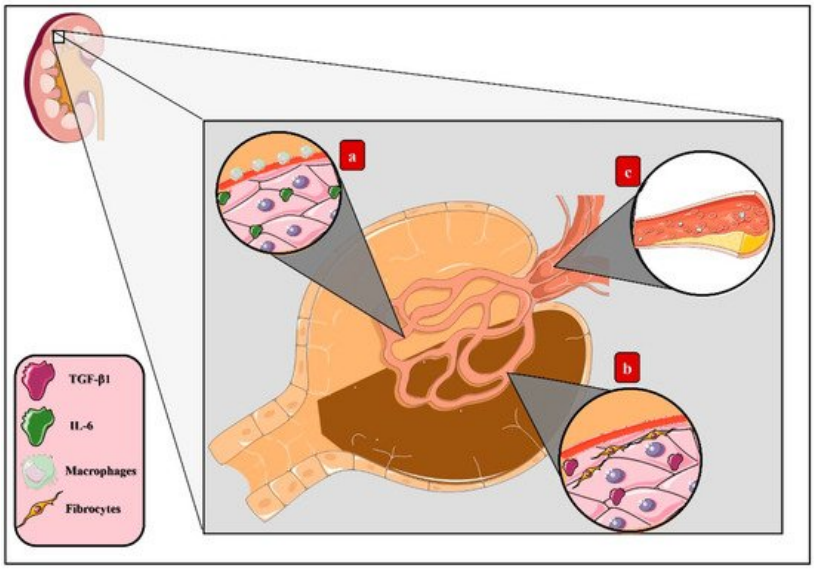

Figure 3. AGEs in diabetic kidney disease. Activation of the AGE–RAGE axis derived from the accumulation of AGEs in renal tissue induces tissue dysfunction through diverse mechanisms: (**a**) macrophage migration, which agglomerates in the renal glomerulus's mesangium, establishing an inflammatory microenvironment led by IL-6 synthesis and, eventually, causing the expansion of this layer, compression of the capillary, and reduction of the body surface area of filtration. (**b**) Increased expression of transforming growth factor β (TGF-β), which stimulates fibrogenesis, collagen synthesis, and renal tubular cell apoptosis, leading to glomerular sclerosis. (**c**) Lipids storage from altered cholesterol metabolism as a result of the activation of sterol-regulatory element-binding protein 2 (SREBP-2), increasing the expression of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase) and, finally, concluding in increased cholesterol synthesis.

Diabetic neuropathy is defined by the progressive loss of axons within peripheral nerves, clinically manifested by severe pain and sensory impairment [54]. The accumulation of AGEs in the endoneurium, Schwann cells, extracellular matrix, and capillary within these nervous structures cause the glycation of proteins such as fibronectin and laminin [55], inducing structural and functional modifications that decrease the regenerative capacity related to axonal atrophy [56]. Likewise, oxidative stress and, thereby, neuronal cytotoxicity are induced through the AGE–RAGE pathway [57], given the increased levels of superoxide and hydrogen peroxide [58] and decreased intracellular glutathione (GSH) [46], which is an essential antioxidant tripeptide composed of glutamate, cysteine, and glycine [59].

The loss of peripheral sensation and the increase of mechanical pressure in the feet are the primary cause of diabetic foot [60]. Secondly, the oxidative stress, proinflammatory cytokines presence, and glycation of proteins such as collagen lead to the hardening of epithelial cells' basement membranes, concluding in skin tissue frailty and impaired wound healing [61].

On the other hand, diabetic retinopathy (DR) constitutes a degenerative vascular process that progresses through different stages [62]. First, a blood flow imbalance emerges, in addition to an increased vascular permeability and capillary basement membrane hardening, advancing to the formation of microaneurysms and establishing a microvascular injury that produces ischemia due to decreased retinal blood flow, thus representing a significant cause of blindness [63][64]. The development of these pathological changes results from pericyte apoptosis induced by the AGE–RAGE pathway. Likewise, increased oxidative stress produced by NF-kB expression produces free radicals such as peroxynitrite inside the subretinal membrane and microvasculature, damaging the DNA [65].

Moreover, the regulatory function of Müller cells inside the retina [66] becomes affected in DM by exposure to hyperglycemia [67], and the inflammatory process, alongside its effects on the microvasculature, is also a consequence of activation of the AGE–RAGE pathway [45]. Furthermore, this pathway increases the expression of cytokines and proangiogenic factors such as the vascular endothelial growth factor (VEGF) [68], basic fibroblast growth factor (bFGF) [69], and TGF-β [70], leading to the distinguished neovascularization of DR and significantly exacerbated by the high accumulation capacity of AGEs in the vitreous humor [69].

3.2. AGEs and the Macrovascular Alterations in DM

Cardiovascular complications of DM arise as a consequence of the damage to large-diameter vascular structures. They are mostly the leading cause of death among diabetic patients, representing 50% of the deaths related to this disease [27]. Diabetic cardiomyopathy is characterized by ventricular dysfunction originating from myocyte hypertrophy [71][72] and myocardial fibrosis [73]. The AGE–RAGE axis has been admitted as one of the contributing factors to this incompletely elucidated chronic complication (**Figure 4**) [29].

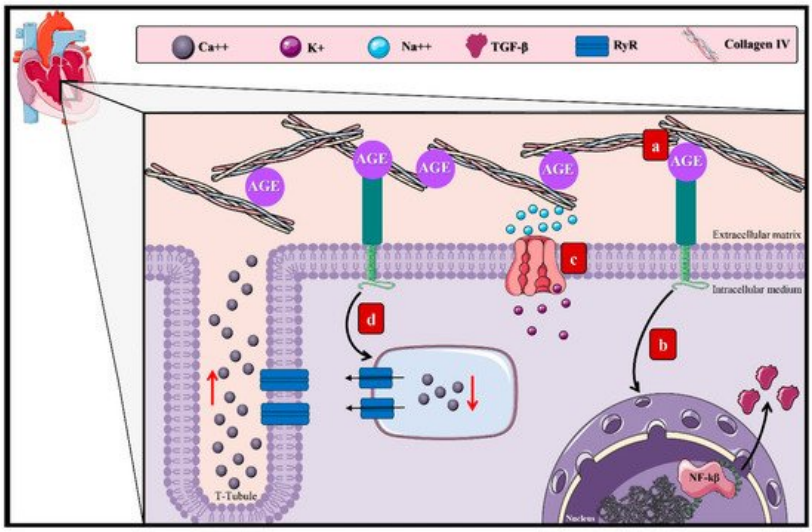

Figure 4. AGEs in diabetic cardiomyopathy. The effect of the AGEs in diabetic cardiomyopathy arises through diverse mechanisms: (**a**) accumulation in the extracellular matrix of cardiac tissue due to the interaction with structural proteins, inducing reticulation between collagen fibers and laminin and decreasing the elastic properties of the cardiac tissue. (**b**) Activation of the AGE–RAGE pathway by the induction of TGF-β and other proinflammatory cytokines that allow the proliferation of fibroblasts conducive to myocardial hypertrophy. (**c**) Activation of the AGE–RAGE pathway and ionic imbalance due to inhibition of the SIRT1/NAD+ pathway, disturbing the function of the Na^{++}/K^{+} ATPase. (**d**) Overstimulation of the RyR, generating irregular modifications of the Ca++ levels, favoring its exit and causing an alteration of the cardiac cycle that advances to diastolic dysfunction. Ca^{++}: calcium, K^{+}: potassium, Na^{++}: sodium, TGF-β1: transforming growth factor β, and RyR: ryanodine receptors.

This process may cause the deterioration of cardiac functions by myocyte hypertrophy [74]. Lately, it has been established that this cardiac remodeling process occurs through the connection within the AGE–RAGE pathway and dendritic cells (DC) [75], which are antigen-presenting cells with essential functions in T-cell regulation and homeostasis [76]. However, it has been reported that the accumulation of matured DC during myocardial infarction could aggravate the tissue remodel [77]. Equally, during in vitro studies, it was determined that the AGE–RAGE pathway promotes DC's maturation and, therefore, the expression of genes that develop hypertrophy, such as *MYH7*, which encodes the cardiac beta-myosin heavy chain (β-MHC) [75][78].

The increment in fibroblast numbers after the increase of AGEs in the extracellular matrix [74] promotes interactions with structural proteins, inducing reticulation between collagen fibers and laminin, deriving in a loss of the cardiac tissue's elastic properties, rigidity, and increased cardiac volume, conductive to diastolic dysfunction [79][80]. The AGE–RAGE pathway intervenes in fibroblast proliferation by stimulating proinflammatory genes and TGF-β, amplifying the adverse effect on the cardiac elastic properties [81].

Separately, the accumulation of AGEs in cardiac tissue is also related to the inhibition of the sirtuin-1 protein (SIRT1) expression. SIRT1, a member of the class III deacetylase family, is an antioxidant protein capable of delaying fibrosis and apoptosis of cardiac cells through its activation by NAD^{+} [82]. Besides, the adenosine monophosphate-activated protein kinase (AMPK) keeps a cellular energetic balance and enhances the NAD^{+} levels and can also regulate SIRT1 functions [83]. In conclusion, it has been established that Na^{++}/K^{+} ATPase alterations are due to dysregulation of the SIRT1/AMPK pathway, modifying cellular ionic homeostasis [84].

Moreover, the Ca^{2+} levels decrease due to the increased activity of the ryanodine receptors induced by AGE–RAGE [85]. These receptors manage to equilibrate the ion levels during diastole and systole [86]; however, their hyperactivity allows a Ca^{2+} leak from the sarcoplasmic reticulum during diastole, diminishing the Ca^{2+} levels during systole and, thus, disturbing the cardiac cycle [87], driving to cardiac dysfunction [85].

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