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ACADEMIC LITERATURE REVIEW

Involvement of advanced glycation end products in the pathogenesis of diabetic complications: the protective role of regular physical activity

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Abstract Advanced glycation end products (AGEs) may play an important role in the pathogenesis of chronic diabetic complications and in the natural process of biological aging. In fact, maintained hyperglycaemia favours the formation of AGEs at the tissue level in diabetic patients, which may influence the triggering of different chronic pathologies of diabetes such as retinopathy, nephropathy, neuropathy and macro- and micro-vascular diseases. Moreover, the literature has also demonstrated the involvement of AGEs in biological aging, which may explain the accelerated process of aging in diabetic patients. The practice of regular physical activity appears to positively influence glycaemic control, particularly in type 2 diabetes mellitus patients. This occurs through the diminution of fasting glycaemia, with a consequent reduction of glycation of plasmatic components suggested by the normalisation of HbA1c plasmatic levels. This exercise-induced positive effect is evident in the blood of diabetic patients and may also reach the endothelium and connective tissues of different organs, such as the kidneys and eyes, and systems, such as the cardiovascular and nervous systems, with a local reduction of AGEs production and further deceleration of organ dysfunction. The aim of this paper was to review the literature concerning this topic to coherently describe the harmful effects of AGEs in organ dysfunction induced by diabetes in advanced age as well as the mechanisms behind the apparent protection given by the practice of regular physical activity.

Keywords Exercise · Type 2 diabetes mellitus · AGEs · Aging

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Introduction

Regarding its genetic predisposition and clinical specificity, type 2 diabetes mellitus (DM2) represents a heterogeneous pathology, characterised by chronic hyperglycaemia induced by deficient insulin production and/or by a resistance of target tissues to this hormone. DM2 affects approximately 2% of the world population [2], and the prevalence of this disease is expected to increase to ~50% by the year 2030 [147].

Prolonged exposure to hyperglycaemia is currently recognised as the first causal factor in the majority of DM2-related late complications [143]. Diabetic patients with poor glycaemic control are particularly at risk for developing associated pathologies described in humans and in animal models, such as cataracts [101], retinopathy, nephropathy, neuropathy [56], micro- and macro-vascular diseases [124], cardiomyopathy [19], and impaired tissue healing [99]. The precise mechanism involved with regard to the role of hyperglycaemia in the pathogenesis of late complications in diabetes is yet to be clarified. Nevertheless, one advanced hypothesis consists of the glycation of proteins, a process which has been widely observed among DM2 patients [35]. In fact, in non-compensated diabetic patients, the blood glucose concentrations are substantially

augmented. Contrasting with an inadequate glucose utilisation observed in muscle and adipose tissues, cells from other organs that do not need insulin for glucose uptake demonstrate elevated concentrations of glucose at the intracellular level. The high amounts of glucose inside and outside of cells favour the occurrence of spontaneous and non-enzymatic reactions between glucose and proteins in both intra- and extra-cellular compartments [25]. This non-enzymatic glycation of proteins by reducing sugars occurs in a cascade of complex reactions, resulting in a heterogeneous class of components usually classified as advanced glycation end products (AGEs). These types of reactions, initially described by Louis-Camille Maillard in 1912 [81], are strongly associated with hyperglycaemia and tissue oxidative stress [4], and suggestions of their implication in the pathogenesis of chronic complications in diabetes and in aging have increased [129]. On the other hand, the natural process of aging favours the appearance and accumulation of AGEs and of products derived from the process of oxidation, resulting in a vicious cycle that is difficult to stop [74]. There is a wide consensus in the literature that the diminution of the antioxidant capacity is the result of biological aging [64]. However, much evidence supports the concept that regular physical exercise chronically augments the antioxidant capacity [102], which may impair the formation of AGEs in diabetic patients or in individuals in advanced age.

Additionally, the practice of regular physical activity has a positive influence on the glycaemic control, particularly in DM2 patients, through the diminution of fasting glycaemia with the consequent reduction of glucose availability for glycation reactions. Accordingly, regular physical activity may constitute an efficient weapon against DM2-related chronic complications potentially associated with AGEs synthesis.

In this review, we intend to analyse the literature regarding the endogenous and exogenous sources of AGEs, discussing the implication of these products on the aging process and on the late complications of diabetes. Finally, the potential protective role of physical exercise in organ dysfunction induced by AGEs and its underling mechanisms will also be highlighted.

AGEs: endogenous and exogenous sources

AGEs consist of a complex and heterogeneous group of molecules, whose formation begins with a non-enzymatic reaction between the carbonyl group of reducing sugars with free primary amino groups of amino acids, peptides, and proteins, or with lipids and nucleic acids [99, 110, 144]. This type of reaction is designated by non-enzymatic glycosylation, Maillard's reaction or also, more recently, glycation (Fig. 1).

Amino acids are the structural units of all proteins and are mainly composed of a primary amino group, by a carboxyl group, and by a lateral chain that characterises each amino acid. The linkage between different amino acids is carried out by the reaction between the carboxyl group of one amino acid with the amino group of the following

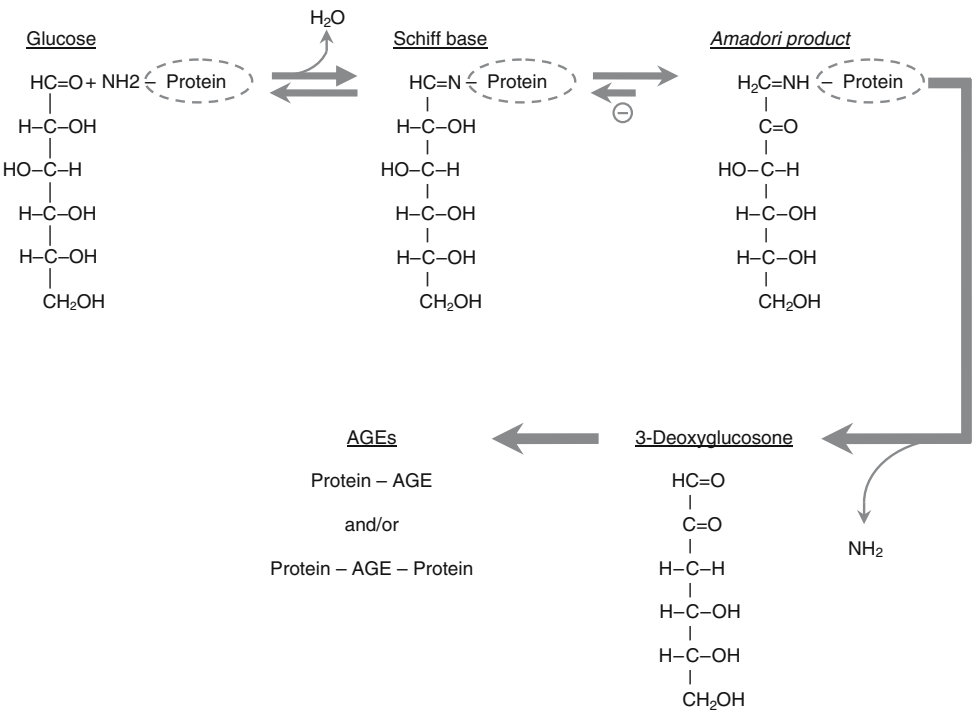

Fig. 1 Sequence of events responsible for the formation of advanced glycation end products (*AGEs*). The reaction between glucose molecules and protein amino groups forms the reversible Schiff base that suffers an intramolecular rearrangement, leading to a less reversible Amadori product. In some conditions, these Amadori products form AGEs through a dicarbonyl intermediate such as 3-deoxyglucosone. According to Ahmed [2]

Table 1 Some cross-linking and non-crossed-linking AGEs that have been most often detected in human tissues

Cross-linking AGEs
Pentosidine
Crossline
Imidazolium dilysine cross-links
1-alkyl-2-formyl-3,4-glycosyl-pyrroles
Arginine–lysine imidazole
Non-cross-linking AGEs
Pyrraline
Nε-carboxymethyl-lysine
Nε-carboxyethyl-lysine

According to Ahmed [2]

amino acid, forming the peptide bond. The establishment of peptide links between different amino acids will create polypeptide chains, within which the primary amino group of the first amino acid, the so-called terminal amino group, is available for further reactions with reducing sugars. Moreover, amino groups belonging to lateral chains of some amino acids, for example lysine and arginine, despite being less reactive than a terminal amino group, may also react with reducing sugars. However, not all the amino groups capable of interacting with sugars actually do so because they can be hidden in the three-dimensional structure of the protein, therefore not permitting access to them [50].

Endogenous glycation reactions occur in a spontaneous way with a small proportion of absorbed simple sugars (glucose, fructose and galactose); the amount of resultant compounds is dependent on the grade and duration of glucose availability, on the body's ability to destroy and excrete them in the urine [95], on the average length of protein life span and on the cellular permeability to free sugars [50]. This type of reaction is carried out in three distinguishable stages (Fig. 1). The initial stage occurs through the association of a sugar with a protein, resulting in a molecular arrangement called the *Schiff* base. These bases are unstable; therefore, they eventually enter into a process of spontaneous restructuring, with the formation of more stable products such as ketoamine or fructosamine, termed *Amadori* compounds, among which HbA1c constitutes a good example [5]. The formation of *Schiff* bases occurs rapidly and reaches thermodynamic equilibrium within a few hours, while in the formation of the *Amadori* products, the thermodynamic equilibrium is only achieved over a period of a few days [2]. *Amadori* products have a carbonyl group that can react with other amino groups. The exact mechanism of this reaction is not known in detail, although it is recognised that it involves complex intramolecular rearrangements and, in some cases, the association between several of these compounds. During this second stage, highly reactive compounds are also formed which have two carbonyl groups acting as reaction propagators [8]. In the final stage, a series of slow and complex transformations occurs involving a series of rearrangements, dehydrations and condensations, which lead to the natural formation of generally coloured (brownish yellow) and/or fluorescent compounds, denominated AGEs. In this phase the reactions have an irreversible character, with the formation of crossed links at the intra- and intermolecular levels, and they occur essentially with proteins of low turnover, as is the case for collagen and myelin (Fig. 1) [141, 150].

Under physiological conditions, the amount of these compounds is determined by the concentration of reducing sugars and by the length of protein exposition to them. With regard to the proteins of rapid turnover, this glycation process does not normally last beyond the initial stage, namely with the formation of *Schiff* bases or *Amadori* products. The main problem lies in the proteins of medium or long life (such as collagen and elastin), which ensure the required time for the AGEs formation and accumulation [55, 138]. Several types of AGEs observed in human tissues are described in Table 1.

Pentosidine consists of a cross-link between the residues of lysine and arginine (Fig. 2), and its content is augmented in diabetic patients [83]. Crossline, initially described in diabetic mice liver, was observed in in vivo and in vitro studies [94]. The imidazolium dilysine cross-links are formed through the reaction between derivates of glyoxal and residues of lysine [52]. The 1-alkyl-2-formyl-3,4-glycosyl-pyrroles are formed through a reaction between two sugars and one unique residue of lysine; their presence is increased in chronic diabetes and they probably contribute to cardiac dysfunction through interaction with type 2 ryanodine receptor calcium-release channels [33]. The arginine–lysine imidazole cross-links were described in Al-Abed and Bucala [7], and it is assumed that they consist of inter-molecular cross-links. Pyrraline is a type of AGE

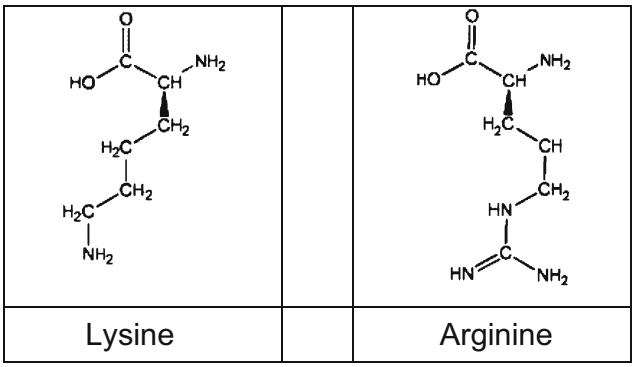

Fig. 2 Chemical structure of lysine and arginine molecules

without cross-links that has been detected in the skin, in plasma, and in the brain of patients with Alzheimer's disease [121]. *Nε*-carboximethyl-lysine (CML) is one of the types of AGEs that is most abundant in vivo and whose concentration in collagen tends to be twice as high in diabetic patients as in non-diabetic individuals. Strong correlations with age are also found, being described augmentations up to fivefold from 20 to 85 years of age [48]. They are formed by the oxidative damage of *Amadori* products and during the oxidation of the methyl group of polyunsaturated fatty acids in the presence of a protein [106].

From the several AGEs species described, CML [61] and pentosidine are the best chemically characterised. The Maillard reaction has been widely used by the food industry due to its implication in the alteration of colour, flavour, aroma and texture of foods [80]. However, it also affects the nutritional properties and toxicity of foods [127]. Additionally, the synthesis of AGEs typically occurs when the sugars are cooked with proteins and/or fats. At temperatures above 120°C (~248°F), an acceleration of protein glycation occurs, but with a longer cooking time at lower temperatures, the formation of AGEs is also promoted. Tobacco can also be a source of AGEs due to the presence of reactive glycated products in its extracts, as well as in the smoke of tobacco in proportions that rapidly react with proteins to form AGEs [34].

A diet rich in AGEs (535 units/mg of CML and 18 nmol/mg of methylglyoxal (MG) derivatives, during 16 weeks, where food and water intake were recorded daily for 1 week and biweekly thereafter) promoted a 53% increase of these substances in the serum of mice; on the other hand, a 7.8% decrease was registered in the low-AGE-diet-mice group (107 units/mg of CML and 3.6 nmol/mg of MG derivatives during the same time period) [99]. In another study carried out on 26 non-diabetic patients with renal insufficiency, an augmentation of CML (29%) and derivates of MG (26%) was also revealed in the blood of the group subjected to an AGE-rich diet, while in the group subjected to a low ingestion of AGEs, a reduction in CML (−34%) and MG (−35%) blood content was observed [137]. These results suggest that a restrictive diet of AGEs could be a reasonable way to reduce excessive overloading of this product in living tissues.

Aging and AGEs formation

At present, the contribution of the Maillard's reaction to the aging process is well known. The augmentation of these compounds is responsible for the acceleration of cellular aging through the alteration of proteins, lipids, and nucleic acids, through the rise in oxidative stress generated in their formation [74] and also by the interaction with the receptors of the advanced glycation end products (RAGEs) [140]. In recent years, these receptors have been the targets of intense research, and a rising rate of its production has been observed in DM2 patients [16]. It has also been suggested that the actual process of aging favours an increase in the formation of AGEs, essentially in the proteins of the extracellular matrix [3]; its accumulation in the tissues is dependent on time and on the concentration of glucose [25]. Moreover, the occurrence of protein glycation is also associated with the physiopathology of some age-related diseases, such as arthritis, arteriosclerosis, diabetes, and other neurodegenerative pathologies [87].

In another way, the total amount of AGEs has been utilised as a marker of oxidative stress that is experienced daily by the tissues. For instance, Yu and collaborators [150] measured the methionine sulphoxide (MetSO) content in the integumentary collagen of type 1 diabetic patients with and without late complications and in normal individuals. An accumulation of MetSO was observed in the collagen with advanced age. Moreover, this product presented significantly higher values in the diabetic subjects especially when late complications of the disease were present [150]. In another study correlating the AGEs tissue content with aging and diabetes [48], a 33% increase of fructose–lysine (FL, an initial compound of glycated products) was observed in the collagen fibres with increased age in non-diabetic individuals, as well as augmentations of 500% in magnitude in CML and in pentosidine, from 20 to 85 years of age. In the same study, diabetic patients evidenced a three-times-greater FL content in the collagen fibres than non-diabetic individuals, which also showed a strong correlation with the levels of glycated haemoglobin. The authors concluded that these chemical alterations in the collagen fibres showed a close association with age, and that glycation reactions were accelerated in diabetes patients. These results support the concept that diabetes is a disease characterised by the acceleration of the degenerative chemical mechanisms associated with biological aging; namely, the disease affects tissue proteins with long life span by the formation of AGEs and by enhanced oxidative stress. The highest AGEs concentrations resulted from both enhanced endogenous synthesis and diet, and can also be directly implicated in the oxidative stress and damage induced on the beta cells of the pancreatic Langerhans islets in diabetic patients [100].

Peripheral resistance to insulin can be the most important factor in triggering DM2, just as it is associated with an increased risk for developing cardiovascular diseases [107]. Many of the molecular mechanisms behind insulin resistance are yet to be determined; however, it is known that they are strongly influenced by age and obesity and, apart from other factors, are dependent on the quantity/quality of

glucose transporting proteins GLUT4 [10, 30, 118] and of intracellular insulin receptor substrate-1 (IRS-1) [30]. Several studies associated the formation of the AGEs with the manifestation of peripheral resistance to insulin in adipose tissue [136] and in skeletal muscle [85]. Enhanced cellular oxidative stress is one of the mechanisms suggested to explain insulin resistance, which may be the result of the AGEs binding to RAGEs; the RAGEs stimulation appears to interfere at various levels of the insulin signalling pathway, and it inhibits the translocation of the GLUT4 to the plasma membrane, with a consequent reduction of glucose uptake [111]. Apart from the influences of age, this mechanism also appears to be present in insulin resistance associated with obesity [136] because a reduction in the glucose transport mediated by insulin was recently observed in the adipocytes of older and obese mice [30].

Oxidative stress, generally accepted as a main conditioning factor for the aging process, appears to reduce the pool of GLUT4 available in cells and the GLUT4 signalling mechanism mediated by insulin, thus harming the cellular glucose uptake capacity [89]. Moreover, MG appears to bind directly to IRS-1 inside the muscle fibres, with the direct consequence of an impairment of insulin-induced IRS-1 tyrosine phosphorylation [108]. These data suggest a direct influence of MG in the induction of insulin resistance, in a way independent of oxidative stress [108].

AGEs and chronic diabetic complications

Much has been postulated in the literature over the implication of the Maillard reaction in the aging process or in the development of late diabetic complications [50].

Vascular diseases Vascular diseases, particularly cardiac coronary disease, are the principal cause of premature death in diabetic patients. Long-term studies comparing intensive and conventional metabolic control in type 1 [56] and type 2 [135] diabetes mellitus has demonstrated a reduction in the incidence and prevalence of cardiovascular events in well-controlled patients. These data suggest a possible role of hyperglycaemia in the pathology of macro-vascular diseases in diabetes, namely through their influence in the formation of AGEs. These products have already been identified in atherosclerotic plaques, suggesting a possible role of AGEs in the development of cardiovascular diseases in diabetic patients [92]. This assumption is reinforced by the enhanced plasmatic concentrations of AGEs found in DM2 patients with cardiac coronary disease [62]. An association between an increased fluorescence of integumentary collagen and arterial rigidity and elevated systolic and diastolic blood pressures has also been reported in diabetic patients [88]. The diminution of arterial and arteriolar elasticity has been associated with AGEs deposits [120], and it could contribute to the development of systemic hypertension and abnormal shear stress, predisposing the endothelial cells to become damaged and to precocious arteriosclerosis [144]. Additionally, it has been demonstrated in experimental diabetic models that aminoguanidine inhibits the formation of this type of crosslink in collagen fibres within the arterial walls, which reinforces the importance of AGEs in this process [27].

The interaction of AGEs with their cellular surface receptors (RAGEs) has been suggested to have causal implications in the pathogenesis of diabetic vascular complications, stimulating the expression of cellular adhesive molecules in the endothelial cells through the formation of reactive oxygen species (ROS) [15]. During the stimulation of RAGE, an increase in the activation of MAP kinases and of nuclear factor-kappaB (NF-κB) has been observed, as well as the expression of adhesion molecules in vascular cells—the so-called vascular cell adhesion molecule-1 (VCAM-1) [51]. With respect to the cellular surface, the endothelium is stimulated by various mediators, such as endotoxins, TNFα, and AGEs, thus promoting an augmentation in the adhesion of mononuclear proinflammatory cells, at least partly under the influence of the VCAM-1. However, some data [144] suggest that the action of the VCAM-1 is not only limited to cellular adhesion events, but also induces the activation of NADPH endothelial oxidase; this process is essential for the migration of lymphocytes through the stimulated cells. These observations should lead to the assumption that the activation of RAGEs on the cell surface can initiate a cascade of events including the activation of NADPH oxidase and of various pro-inflammatory mediators such as VCAM-1, thus aggravating the generated oxidative stress.

RAGEs were initially identified as specific receptors for AGEs [116]. Nowadays, it is known that they are multi-binding receptors, belonging to the super-family of immunoglobulins, which are able to interact with distinct molecules implicated in homeostasis, in inflammatory reactions, and in the development of certain pathologies such as diabetes mellitus and Alzheimer's disease [90]. In diabetic patients, the increased expression of these receptors has been attributed to a wide range of tissues and cells, namely the epithelium, the endothelium, smooth vascular muscle, mononuclear inflammatory cells, the glomerulus and the skin [65]; additionally, AGEs have also been identified in organic fluids of DM2 patients, such as serum and saliva, as well as in skin, confirming an increase in the progression of related complications [53].

The class of S100A12 proteins consists of pro-inflammatory cytokines, mainly expressed by granulocytes, and are involved in the transduction of intercellular signalling events of Ca2+ [16], with a possible influence in the inflammatory

process and in autoimmune diseases [76]. The AGEs and the S100/Calgranulins are those which have been most studied as agents of proinflammatory signalling [43, 105] and which appear to trigger intercellular signalling mechanisms that could participate in some of the pathologies associated with diabetes, such as nephropathy [91], retinopathy [14], cardiovascular diseases [68] and loss of bone mass [42].

The treatment of diabetic mice submitted to accelerated arteriosclerosis, through the soluble extra-cellular domain of the RAGE, completely suppressed diabetic atherosclerosis in a glycaemia- and lipid-independent manner [97]. These findings demonstrate that the interaction of the AGEs with their receptors appears to be involved in the development of accelerated arteriosclerosis in diabetes, reinforcing the attention to be paid to these receptors as possible targets with a therapeutic potential for macro- and micro-vascular diseases in diabetes [115].

Diabetic retinopathy Diabetic complications in the retina result from functional and morphological alterations of the local capillaries, such as an increase in the permeability to albumin and other macro-molecules, vascular dysfunction, loss of pericytes, and thickening of the basal membrane. Capillary occlusion is responsible for the local occurrence of impaired blood perfusion (ischaemic retinopathy), which motivates the secretion of vascular endothelial growth factors with the neoformation of veins (proliferative retinopathy) [109].

The role of the AGEs has also been analysed in diabetic mice treated with an AGE inhibitor: Treatment with aminoguanidine, compared to control animals, resulted in a reduction of 75% in the thickness of the basal membrane of the retinal capillaries [17], in a reduced loss of pericytes [36], in the absence of a development of micro-aneurisms [59] and in the proliferation of endothelial cells [83], in addition to an absence of the accumulation of AGEs in the arterioles [59]. The preventive effect observed in the animal model with an AGE inhibitor, namely through aminoguanidine, lends support to the role of AGEs in the development of the pathophysiological framework for diabetic retinopathy. An increase in vascular permeability was associated in vitro with endothelial endocytosis. An increase in endocytosis in vascular endothelial cells of the retina has been observed with elevated concentrations of glucose, and this could be reduced by aminoguanidine, suggesting also that this alteration is mediated by the AGEs [125].

Diabetic nephropathy Diabetic nephropathy is predominantly characterised by the abnormal depositing of proteins in the glomerular mesangial space, such as type IV and type V collagen, laminin and fibronectin, leading to its expansion and, consequently, to the progressive occlusion of capillaries with consequent renal dysfunction. Two predominant mechanisms should be considered in this process, namely the enlargement of cells and the expansion of the mesangial matrix; the latter is apparently a determinant factor in the progression of renal disease associated with diabetes [123]. Various authors have described a direct relationship between levels of hyperglycaemia and the lesions observed in diabetic nephropathy, principally in the expansion of the mesangial matrix (e.g., [12, 13]). On the other hand, a close relationship has also been shown between serum and tissue levels of AGEs and the occurrence of functional renal alterations [130], with an increased amount of these products in the mesangium and in the glomerular basal membranes of diabetic patients. CML seems to be the most abundant AGE type in the mesangium (96%), in the glomerular basal membranes (42%), in the tubular basal membranes (85%) and in the vein walls (96%). Pentosidine appears to be preferentially localised in the interstitial collagen (90%) and, in comparison to CML, presents a less consistent concentration in the mesangium (77%), in the glomerular basal membranes (4%) and in the tubular basal membranes (31%) [131]. The presence of these compounds in renal structures may contribute to the tissue lesions described in diabetes, thus altering the architecture of the extra-cellular matrix through glycation reactions with the formation of protein cross links [28, 123]. Another mechanism that appears to participate in the pathogenesis of nephropathy is also mediated by the AGEs through their interaction with the RAGEs [148], as well as by the deregulation of these receptors, particularly at the podocytes [57]. Indeed, a direct relationship between serum levels of circulating RAGEs and AGEs and the severity of the nephropathy in DM2 patients has been established [130]. In another longitudinal study performed with type 1 diabetic patients followed up over 2.5 years, the predictive value of AGE serum levels for the development of morphological alterations in the kidneys was highlighted [18].

Diabetic neuropathy Peripheral and autonomic neuropathies are the most frequent manifestations of diabetic neuropathy, both as independent predictors of ulcerations and amputations of the lower limb, and they are related to the mortality associated with diabetes [49]. Diabetic neuropathy increases with age and with the evolution of the disease and is present in more than 50% of DM2 patients older than 60 years of age [149]. An increased skin auto-fluorescence has been described in diabetes, which is directly correlated with the severity of peripheral and autonomic nervous dysfunction, with the patient's age, with the time period of the disease, with average HbA1c levels over the preceding years and with the occurrence of

ulcerations of the lower limbs [84]. These observations suggest that the determination of AGEs in the skin by autofluorescence may constitute an important tool for the early diagnosis of diabetic neuropathy. From the several chronic complications of diabetes, neuropathic physiopathology has been the most difficult to be associated with AGEs.

Various studies suggest that the irreversible glycation of the cytoskeletal proteins in axons of peripheral nerves is responsible for the formation of cross-links and for the occurrence of functional alterations in neurons, especially axonal degeneration [86, 112, 113]. Other authors also propose the contribution of peripheral arterial occlusion to this process, and this link is supported by the similar pattern distribution between the areas showing ischaemia and neuropathic alterations [26, 146]. Irreversible links between AGEs and the myelin proteins have also been described, which appear to contribute to the process of segmental demyelination observed in the peripheral nerves of diabetic patients and of aged subjects [141]. The phagocytosis of glycated myelin by macrophages was described in vitro, leading to the assumption that these cells are also able to secrete proteases to the extra-cellular medium, which may further contribute to the nerve demyelination observed in diabetic neuropathy [142]. This demyelination and axonal degeneration should explain the diminution in the speed of sensible and motor nervous conduction in the peripheral nerves associated with diabetes and aging [70]. In fact, diabetic patients followed up over 8 years showed a reduction of 1.3 m/s in the speed of nervous impulse conduction in the peroneal, posterior tibial and sural nerves when the HbA1 levels increased by 1% [9]. Additionally, the interaction between AGEs and RAGEs seems to activate the transcription factor NF-κB in the micro-vascular environment [21], which plays a central role in sensorial neural dysfunction and, therefore, might contribute to the physiopathology of diabetic neuropathy [20].

AGEs and regular physical activity

Several publications report the beneficial effects of lifestyle intervention programmes on DM2 prevention [77, 133], as well as on the improvement of glycaemic control, with a consequent delay of chronic complications in diabetic patients [23, 75]. In these patients, the simple diminution of 1% in HbA1c has reduced the overall risk of death by 21%, of fatal and non-fatal myocardial infarction events by 14%, of fatal and non-fatal cardiac arrests by 12%, of micro-vascular complications by 37%, of required cataract surgeries by 19%, of the number of amputations by 43% and of cardiac insufficiency incidents by 16% [128].

The practice of regular physical activity has displayed a positive relationship with the improvement of glycaemic control in patients with DM2 through the diminution of fasting glycaemia [41, 72, 132] and HbA1c [22, 31, 41, 45, 72, 82, 132, 139]. However, some authors were unable to observe this association [117], which could be explained by the different methodology used (questionnaires) to determine physical activity levels.

In spite of the number of works analysing the control of glycaemia through regular physical activity [23, 24, 29, 31, 32, 45–47, 60, 72, 73, 78, 79, 82, 119, 132, 152], very few have focused on the effects of physical activity on the formation of AGEs in diabetic patients and/or during aging [96, 98]. It can nevertheless be assumed that regular physical activity, as an integrated part of an active lifestyle, may influence the accumulation of AGEs in the organism because the amount of these compounds is conditioned by glycaemia levels [58]. Therefore, the improvements of glycaemic control in DM2 due to physical exercise, usually linked with the reduction of the peripheral resistance to insulin [37, 72, 132], could attenuate the formation and accumulation of AGEs in the tissue.

However, because of its irreversible character, a significant diminution of AGEs affecting tissue proteins of low turnover, such as collagen [11, 122], elastin [69, 122] and myelin [66, 112], cannot be predicted. Regarding oxidative stress, it is assumed that regular physical activity contributes to an augmentation of the antioxidant capacity, facilitating a more efficient combat against the formation of ROS [39, 71, 72, 104]. However, when a subject is unaccustomed to exercise or when it is practised too intensively, it can induce considerable oxidative stress and damage to the exercised muscles, affecting capillaries, muscle fibres and connective tissue [44].

In a recent study, a reduction in the antioxidant enzyme capacity was observed in red blood cells of diabetic mice, showing a negative correlation with hyperglycaemia, and was attenuated by the administration of aminoguanidine [126]. Some authors argue that AGE formation may contribute to the antioxidant diminution observed in uncompensated diabetes, where the loss of glucose homeostasis, with the consequent glycation of antioxidant enzymes such as catalase, glutathione peroxidase, glutathione reductase and reduced glutathione, may attenuate their activity [1, 114]. The hyper-production of free radicals during unbalanced diabetes also appears to interfere at the level of endothelial dysfunction by the reduction of nitric oxide production, leading to impairment in vasodilatation by smooth muscle cells [144]. On the other hand, the AGEs can also increase the susceptibility to LDL oxidation, which will diminish the production of endothelial nitric oxide [28]. Therefore, the association between oxidative stress and AGEs may explain, at least in part, the close relationship between hyper-

glycaemia, endothelial dysfunction, and tissue damage, namely through the observation of correlations between microvascular lesions and the accumulation of AGEs in diabetic patients with retinopathy and nephropathy [145]. It has also been observed that the formation of AGEs can be retarded or attenuated, but not completely abolished, through an efficient glycaemic control [134]. In this sense, the option of the regular practice of physical activity could be one interesting approach to controlling glycaemia through the reduction of peripheral resistance to insulin, attenuating the formation of AGEs, as well as associated oxidative stress [24, 45]. Moreover, the enhancement of the antioxidant enzymatic capacity [63], the improvement of vasodilatation capacity of blood vessels [38] and the favourable modifications of lipoprotein blood profile [6, 32] and the increment of LDL oxidation resistance [150] have also been described as favourable adaptations of diabetic patients taking part in physical exercise programmes. All these advantages may also be complemented by the improvement in the profile of inflammatory markers induced by physical exercise in diabetic patients, namely a diminution of the C-reactive protein [54, 67, 103], IL-1 [54], IL-6 [40, 54, 67], IL-8 [93], IL-18 [67], tumour necrosis factor-α [67], interferon γ [54] and ICAM-1 [151] and an increase in IL-10 [54].

There appears to be a scarcity of studies which have looked at the effects of regular physical exercise on AGE formation, analysing not only the regularity and intensity of this exercise but also the aspects related to its interaction with exogenous sources of those compounds. However, the existing body of literature on this topic allows speculation that the implementation of structured and controlled programmes designed to increase the levels of regular physical activity among DM2 patients, in conjunction with a hypo-calorific diet poor in AGEs, would be fundamental for diminishing the risk of early triggering of chronic diabetic complications and for increasing their physical, psychological and social well being. It is, however, necessary to consider the real impact of the implementation of physical exercise programmes, especially among the population of advanced age with inherent physical limitations where these programmes may exaggerate the acute stress normally induced by physical exercise. Indeed, some evidence [1] has reinforced the concept of the lower capacity of diabetic patients to tolerate elevated levels of physical activity, partially due to their greater vulnerability to the oxidative stress and damage.

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