

Toxicity of advanced glycation end products (Review)

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Abstract. Advanced glycation end-products (AGEs) are proteins or lipids glycated nonenzymatically by glucose, or other reducing sugars and their derivatives, such as glyceraldehyde, glycolaldehyde, methylglyoxal and acetaldehyde. There are three different means of AGE formation: i) Maillard reactions, the polyol pathway and lipid peroxidation. AGEs participate in the pathological mechanisms underlying the development of several diseases, such as diabetes and its complications, retinopathy or neuropathy, neurological disorders (for example, Parkinson's disease and Alzheimer's disease), atherosclerosis, hypertension and several types of cancer. AGE levels are increased in patients with hyperglycaemia, and is likely the result of the high concentration of glycation substrates circulating in the blood. The present review summarises the formation and nomenclature of advanced glycation end-products, with an emphasis on the role of AGEs in the development of diabetes, neurological disorders, as well as in cancer and other pathologies. A particular focus is placed on the functions of toxic AGEs. Additionally, studies which have shown the cytotoxicity of glycated albumin and other AGEs are also discussed. Finally, the diagnostic relevance of AGEs as well as for targeting in therapeutic strategies are highlighted.

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1. Introduction

Advanced glycation end-products (AGEs) represent a broad heterogeneous group of compounds formed by nonenzymatic reactions between reducing sugars or oxidized lipids and the free amino groups of proteins, amino phospholipids or nucleic acids. There are three different methods of AGE formation, which are schematically depicted in Fig. 1 (1-4).

The initial process, known as the Maillard reaction, leads to the formation of glycated molecules termed Amadori products or early glycation products. Further rearrangement, oxidation, reduction, dehydration, condensation, fragmentation and cyclization of an Amadori product results in the formation of relevant irreversible AGEs. Incubation of proteins with lipid peroxidation products is an alternative method of generating AGEs. The polyol pathway leads to the conversion of glucose into fructose, and also promotes glycation; fructose may further be converted to 3-deoxyglucose and fructose-3-phosphate, both of which are very potent nonenzymatic glycation agents (5-7). Detailed information on AGE formation is reviewed elsewhere (8-11).

In studies on AGE, two classifications for the nomenclature regarding AGEs are used, which are either focused on the structure of the AGE or instead focused on the proteins being modified. In the first classification system, the most extensively studied AGEs are *N*-carboxymethyllysine (CML), pentosidine, crossline, pyrraline and hydroimidazolone (2). The second group includes AGE-1 (glucose-derived AGEs), AGE-2 (glyceraldehyde-derived AGEs), AGE-3 (glycolaldehyde-derived AGEs), AGE-4 (MGO/methylglyoxal-derived AGEs), AGE-5 (glyoxal-derived AGEs), AGE-6 (3-deoxyglucosone-derived AGEs) and acetaldehyde-derived AGEs (AA-AGEs) (12,13). Specific modifications of proteins are also considered AGEs; for example, haemoglobin (also referred to as HbA1c, is in fact an Amadori product, not an AGE), albumin, eye crystallin, collagen type IV and others (Fig. 2) (1-3,14).

It has been reported that AGEs adversely affect several processes by two primary mechanisms: Directly through trapping and cross-linking of proteins, and indirectly by binding to specific receptors for AGE on the surface of various cells. Upon binding to receptors, AGEs activate several signalling pathways, including NF- κ B, MAPKs, and Jun N-terminal kinase, which regulate the transcription of proteins, such as cytokines, chemokines, growth factors, adhesion molecules and extracellular matrix proteins. In doing so, AGEs can result alter chemotaxis, angiogenesis, oxidative stress, cell proliferation and programmed cell death (5,7).

AGE molecules (free, peptide-bound and protein-bound) are found in the blood plasma in high concentrations, particularly in diabetic patients. This is explained by their high concentration of the substrates; glucose and its derivatives in blood (5). AGEs are also found in aging patients and those with degenerative diseases, where AGEs accumulate in cells and tissues, such as arteries, neurons and hepatocytes (6).

Glycation may also occur whilst cooking foods, for example during frying, baking, heating food in a microwave oven, and especially during caramelization. The resulting products have a strong taste and aroma. Another source of exogenous AGEs is cigarette smoke (15). Some of the exogenous AGEs are carcinogenic, for example acrylamide or heterocyclic amines, whereas others interfere with cell signal transduction or expression of numerous genes (16-18). Both endogenous and exogenous AGEs bind to specific receptors, and cause oxidative stress and promote inflammatory processes (16,19).

It is postulated that AGEs participate in the pathological mechanism of cardiovascular disease, nephropathy, rheumatoid arthritis, dysfunctions in bone remodelling and neurological diseases (for example, Alzheimer's and Parkinson's disease), cancer growth, metastasis and other degenerative diseases (9,20-22). The list of pathological conditions associated with AGE with a short description of the relationship between glycation and the disease is presented in Table I.

AGEs may also be considered glycotoxins, due to their toxic effects on certain cells and tissues (5). The term 'TAGE' is the abbreviation for toxic advanced glycation end-products, which applies to some (AGE-2, AGE-3 and AA-AGE), but not all AGEs. These molecules induce reactions primarily by interaction with receptors for advanced glycation end-products (RAGEs), and exert their toxic effects in the blood vessels, liver and retinas, and can also promote the development of several types of cancer as well as infertility (12,13,21-23). There is considerable research showing that non-TAGE molecules, such as CML, pentosidine, pyrrolidine and crossline may also be cytotoxic (24-26).

2. Cytotoxicity of AGEs

The viability of various types of cells in the presence of AGEs has been extensively studied. In all reported studies, changes in the survival rate of cells in the presence of most types of AGEs was demonstrated. Below, a brief overview of the studies examining the effects of AGEs on viability of cells is discussed.

The toxicity of CML (the best-defined AGE) was investigated in mice. The estimated LD₅₀ of CML was >5 mg/kg. Administration of 2 or 5 g/kg CML did not induce mortality within 14 days. However, some biochemical and histopathological changes were observed: Markers of aberrant hepatic and renal function were elevated, antioxidant enzyme (SOD and GSH-Px) activities were reduced, the levels of a marker of lipid peroxidation (MDA) were increased and histological changes were observed in the lungs, liver, kidney and spleen (24).

The effect of glycated albumin has been investigated in numerous different cell lines. For example, the impact of BSA-AGE (BSA incubated for 12 weeks with glucose) on cell cultures of amniotic and embryonic origin (WISH and MRC-5

cell lines) and on placental villi explants were determined. The observed effects included: Condensation of chromatin, formation of apoptotic bodies and elevated expression of cytokeratin 18 and Caspase 3. It was concluded that BSA-AGE had a direct toxic effect on the cell viability in a time and dose-dependent manner, and that some pregnancy complications may arise due to the formation of AGEs (5).

The effect of glycated albumin was also analysed on other mammalian cell lines: Peripheral blood mononuclear cells, 293 cells, normal human fibroblasts and Chinese hamster ovary cells. Glycated albumin was significantly more toxic than native human serum albumin (LC₅₀ values between 35.00-48.34 vs. 5.47-9.10 µg/ml, respectively) (2). The addition of rosmarinic acid suppressed the cytotoxic effects and inhibited the activity of elastase and collagenase (2).

The cytotoxicity of BSA-AGE was investigated in BHK 21 hamster fibroblast cells and SH-SY5Y human neuroblastoma cells. It was found that BSA-AGE significantly induced cell death in a dose-dependent manner, which was confirmed by three different methods (Thiazole Blue assay, lactate dehydrogenase assay, Neutral Red assay). Notably, the cytotoxic effects of AGEs were attenuated by antioxidants, such as thiocetic acid and N-acetylcysteine, which lead to the conclusion that the toxic effects of AGEs was associated with the oxidative stress (3). Chowdhury *et al* (27) drew similar conclusions in a study performed using D-galactose-derived AGEs. The experiments were performed using a mouse model; galactose was injected and one group of mice were administered antioxidants, which abolished the toxic effects (27). Similar results were observed when assessing the effects of AGEs generated from ribose. In a study conducted on Chinese hamster ovary cells, the effect was suppressed by glucose-regulated protein 78 kDa (GRP78). Glycation with a ribose is called ribosylation (6). GRP78 acts as a chaperone, and when it is ribosylated, which induces ER stress, it leads to cell death (6).

3. Methylglyoxal (MGO)-AGE

MGO is a by-product of glycolysis. This highly reactive dicarbonyl compound is also a major precursor of AGE-4, a methylglyoxal-derived AGE. MGO is not classified as a TAGE; however, its cytotoxicity has been repeatedly observed.

Sampath *et al* (28) showed the cytotoxic effects of MGO on Human Retinal Pigment Epithelial cells. It was found that MGO-induced cytotoxicity resulted in increased levels of AGEs, such as CML, as well as expression of various RAGEs and glutathione. In the presence of AGE-MGO, the translocation of Nrf2 from the cytosol to the nucleus is inhibited, which results in decreased expression of detoxifying enzymes such as heme oxygenase-1 (28). It is also worth quoting the results of research on the impact of MGOs on bone marrow-derived endothelial progenitor cells (EPC). MGO increased the levels of AGEs, and decreased cell viability and protein expression of vascular endothelial growth factor receptor (VEGFR)-2. The latter is associated with functional impairments of tube formation. Inhibition of RAGEs by FPS-ZM1 significantly reverses the decrease in VEGFR-2 protein expression and angiogenic dysfunction in MGO-treated EPC (29).

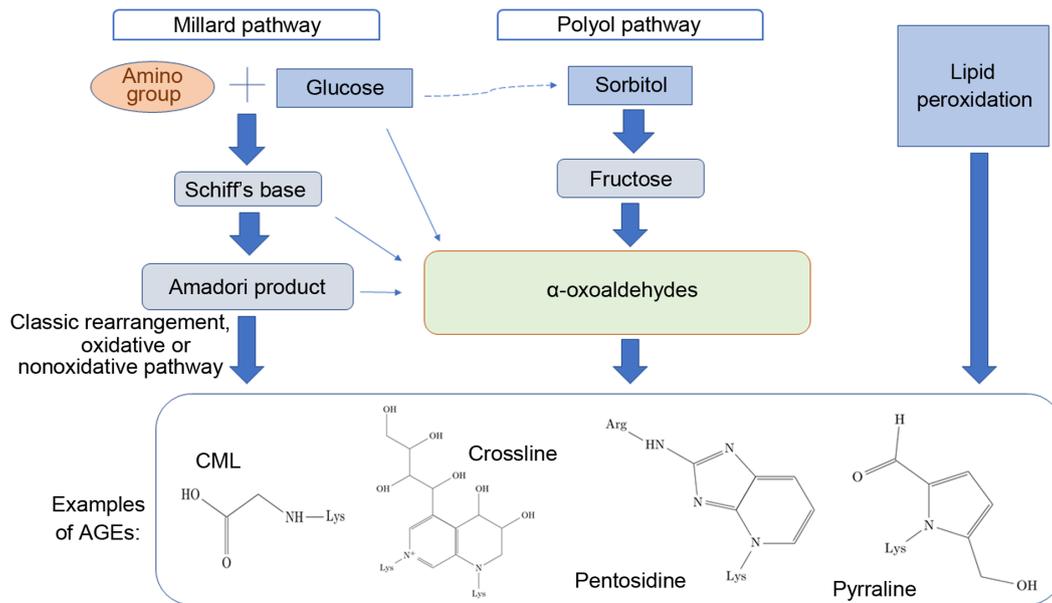


Figure 1. AGE formation pathways, including the Millard pathway, polyol pathway and lipid peroxidation pathway. The structural formulas of the most common types of AGEs are also shown, based on Khan *et al* (9). AGE, advanced glycation end product; CML, carboxymethyllysine.

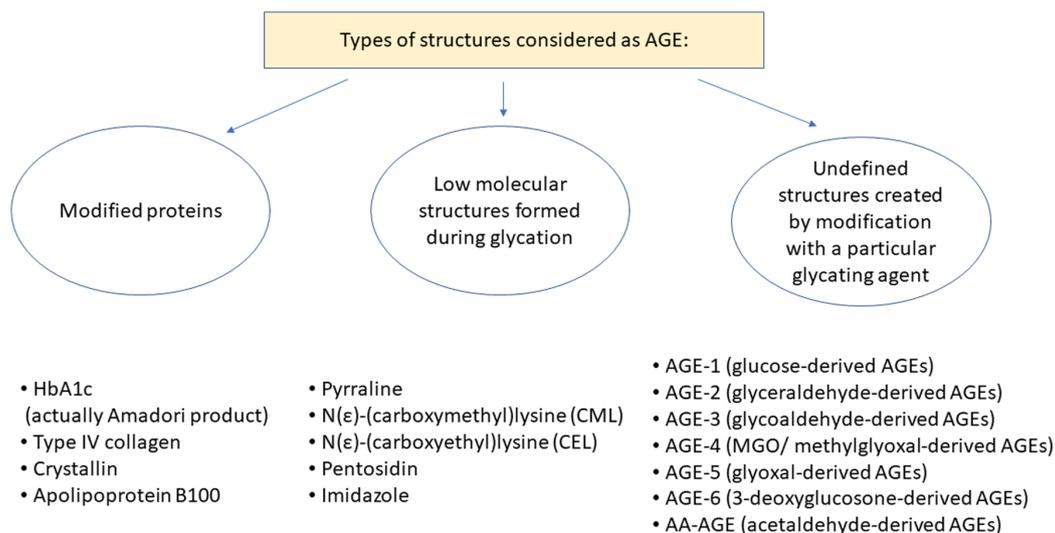


Figure 2. Classification of AGEs based on the type of structure and the origin of the substrates. AGE, advanced glycation end product.

4. TAGEs in diabetes

TAGEs are a subset of AGEs, which include AGE-2, AGE-3 and i AA-AGE. Diabetic hyperglycaemia may be caused by elevated production of TAGEs. Histological analysis of healthy control rats and STZ-induced diabetic rats showed AGE-2 expression in the brain, pancreas and stomach, but not in the adipose tissue, intestine, eye, heart, kidneys, spleen or lungs. However, there seemed to be no difference in the distribution of AGEs between the control group and experimental group (1).

As a common complication of diabetes is retinopathy, it is not surprising to find reports showing the involvement of AGEs in the death of retinal tissue. Takeuchi and Yamagishi (12) reported that in the presence of TAGEs, apoptotic cell death of retinal pericytes was observed, and this was mediated by

TAGE interaction with RAGEs. It was found that AGE-2 and AGE-3 accelerated retinopathy by upregulating vascular endothelial growth factor (VEGF) mRNA levels, as well as stimulating DNA synthesis and tube formation in microvascular endothelial cells via the interactions with RAGEs (12).

Another common complication of diabetes is nephropathy. It has been demonstrated that TAGEs influence nephropathy via two mechanisms: i) They induce apoptotic cell death in human mesangial cells; and ii) cause hyperfiltration and microalbuminuria by stimulating secretion of VEGF and monocyte chemoattractant protein-1 (12).

5. TAGEs in the nervous system

Of all the TAGEs, AGE-2 and AA-AGE appear to be particularly neurotoxic. It was demonstrated that AGE-2 exhibits

Table I. Effects of AGEs in various diseases.

Disease/condition	Types of AGEs implicated in disease	Role of AGEs in disease	(Refs.)
Diabetic retinopathy	AGE-2, AGE-3	Accelerates retinopathy by upregulating VEGF mRNA expression levels, and stimulating DNA synthesis and tube formation in microvascular endothelial cell through interacting with RAGEs	(12)
Diabetic nephropathy	TAGE	Induces apoptotic cell death in human mesangial cells, and causes hyperfiltration and microalbuminuria by stimulating secretion of VEGF and monocyte chemoattractant protein-1	(12)
Diabetic neuropathy	MGO-derived AGEs	Associated with the development of large- and small-fibre dysfunction	(51)
Other neuropathies (including Parkinson's disease)	AGE-albumin	Neurodegeneration associated with upregulation of RAGEs and the MAPK pathway; AGEs also induce protein aggregation and cross-linking between molecules, the formation of Lewy bodies and neuronal apoptosis	(52,53)
Malignant melanoma	AGE-2, AGE-3	Stimulate the growth and migration of human melanoma cells	(12)
Other types of cancer	CML, CEL, and argpyrimidine and other ligands for RAGE	AGEs, via binding to RAGEs, result in sustained inflammation, which leads to metabolic reprogramming, and genomic instability, and may result in oncogenic transformation, telomere elongation and increased angiogenesis	(17,18)
Alzheimer's disease and dementia	AGE-1, MGO-derived AGEs	May affect hippocampal neurons, and increase the percentage of apoptotic neurones in the hippocampus	(22,51,54)
Atherosclerosis	TAGEs and other AGE	AGEs trigger inflammation and cell proliferation, contributing to the development of vascular dysfunction; glycation of apolipoprotein B100 increases the atherogenicity of low-density lipoproteins; AGEs influence platelet activation, thrombosis and hypercoagulability	(45,55)
Other cardiovascular diseases	AGE-3 ^a	Causes fibrosis, hypertrophy, oxidative stress and an exacerbated inflammatory response	(56)
Hypertension	MGO-derived AGEs	Vascular endothelial damage by increasing oxidative stress, reduction of NO-dependent vasorelaxation; increasing arterial stiffness by cross-linking of extracellular matrix proteins	(45,51,57)
Osteoporosis, osteoarthritis, and sarcopenia	Undefined AGE	AGEs accumulate in bones, joints and skeletal muscles, impairing the biomechanical properties of the tissues; AGE-induced chronic inflammation may stimulate osteoblasts, osteoclasts and myocytes, resulting in degradation of bones, cartilage and muscles	(10,58)

^aBased on the assumption that the AGE used from Sigma-Aldrich (Merck KGaA) is a product with the cat. no. 121800, as the authors did not specify. AGE, advanced glycation end product; RAGE, receptor for AGE; TAGE, toxic AGE; VEGF, vascular endothelial growth factor.

potent neurotoxic effects in cortical neuronal cells, and the effect was stronger than that of Glu-AGEs and CML. Additionally, another line of evidence which has shown that GA-AGE is involved in neurodegeneration, is that the neurotoxic effects of serum AGE fractions from diabetic nephropathy

in haemodialysis patients were completely attenuated by the addition of an anti-GA-AGE antibody, but not by antibodies against other types AGEs (30).

On the basis of histological analysis and determination of serum AGE-2 levels, the relationship between the presence of this

antigen and Alzheimer's disease has been suggested. AGE-2 is primarily detected in the cytosol of neurons of the hippocampus and para-hippocampal gyrus, but not in the senile plaques in the brains of AD patients, where CML was present (31).

Acetaldehyde, a product of ethanol metabolism, is a two-carbon carbonyl compound that can react with nucleophiles to form covalent addition products. It has been shown that AA-AGE may participate in the degeneration of neurons as the AA-AGE epitope has been detected in the brains of alcoholic individuals (12).

In the context of neurodegenerative diseases, the proper functioning of both neurons and the glial cells is of paramount importance. The effects of TAGEs (AGE-2 and AGE-3) on cultured Schwann cells has been assessed. Cell viability, proliferation and the production of proinflammatory cytokines were all substantially affected by treatment with TAGEs (12).

6. TAGEs in cancer

AGEs have been known to promote mutagenesis and stimulate proliferation and migration of cancer cells through activation of RAGEs. Stimulation of the receptors upon binding of its ligands, for example with interalial AGE, leads to the activation of several molecular signalling pathways, including the PI3K/AKT, JAK/STAT, NF- κ B, Ras/MAPK, Rac1/cdc42, p44/p42, p38 and SAP/JNK/MAPK pathways, which contribute to the expression of transcription factors, such as NF- κ B, STAT3, HIF-1 α , AP-1 and CREB. AGE-RAGE interactions also result in activation of NADPH oxidases, leading to increased intracellular oxidative stress. These inflammatory mediators induce epigenetic changes in pre-malignant lesions and silence tumour suppressor genes (17).

RAGE expression is upregulated in a vast majority of cancers, but its expression is very low under physiological conditions. Specific examples of types of cancer in which RAGE expression is upregulated include colorectal cancer (32), pancreatic cancer (33), prostate cancer (34), lung cancer (35) and breast cancer, and in breast cancer, it has been reported that the RAGE rs1800624 polymorphism may increase the risk of breast cancer (36).

It has been shown that TAGEs may contribute to the pathogenesis of neoplasia and cancer development. In human pancreatic cancer cells treated with 1-4 mmol/l GA for 24 h, the cell viability and intracellular levels of GA-AGEs, as well as heat shock proteins 90 α , 90 β , 70, 27 were analyzed. Cell viability decreased to almost 0% when cells were treated with 4 mmol/l GA, and the levels of heat shock proteins increased significantly. It was concluded that intracellular GA-AGEs induce pancreatic cancer cell death. Additionally, their secretion may promote the proliferation of other cancer cells (37).

7. Dietary AGEs (dAGEs)

AGEs can also be a toxic component of food. It is estimated that an average human diet consists of ~75 mg AGEs per day (38). It is not clear how much dAGE is absorbed in the digestive system; one study has stated that 10-30% is absorbed (10), whereas another report has stated 30-80% is absorbed (38). Absorbed glycation end-products are biotransformed and excreted, or otherwise accumulate in various tissues. The levels

of accumulated AGEs in tissues can be estimated using the non-invasive skin autofluorescence measurement method (39).

The body's ability to detoxify AGE products is difficult to assess. Glycated proteins, particularly large ones, are resistant to proteolytic enzymes, and this makes it several times more difficult to eliminate them from the body. However, certain AGEs are bound to AGER1 receptors located on macrophages, T-lymphocytes, endothelial cells, mesangial cells, fibroblasts, smooth muscle cells and neuronal cells, which are then excreted by the kidney (10). It is estimated that ~30% of dAGEs are removed in the urine, provided the patient has a healthy kidney, otherwise this percentage will be lower (40).

8. TAGEs for diagnosis and treatment of diseases

It has been suggested that the serum levels of toxic AGEs are correlated with the progression of degenerative diseases, such as atherosclerosis or diabetes. It was also found that higher levels of TAGEs are associated with overeating, a lack of exercise or excessive ingestion of sugars and dAGEs. It is therefore proposed that the serum levels of TAGEs may be a promising novel biomarker for the onset and progression of lifestyle-related diseases (41).

Sato *et al* (13) proposed TAGEs may serve as biomarkers for Alzheimer's disease, and suggested that assessing TAGE levels as a diagnostic tool may improve diagnosis and thus treatment of patients with this disorder.

There are also specific proposals to apply knowledge regarding AGEs and TAGEs for therapeutic purposes. It was suggested that inhibition of the interactions between a TAGE and its RAGE, using an anti-RAGE antibody, was a suitable candidate for treatment of patients with malignant melanoma (12). FPS-ZM1 or other specific antagonists for RAGEs may also be useful in inhibiting RAGEs, and may thus also serve as a potential therapeutic option for management of diabetic vascular complications (29).

Other approaches to reduce the detrimental effects of AGEs may be to inhibit their formation, or the use of compounds that can break the cross-linked bonds, such as aminoguanidine and pyridoxamine, phenylthiazole, 4,5-dimethyl-3-phenyl-acyl-thiazole chloride and ALT-711 (42). These are synthetic substances, and, unfortunately, no endogenous analogues have been identified as of yet. The downside of these compounds is that they may exert a certain degree of cytotoxicity, and this has complicated the development of a clinically suitable anti-AGE treatment. It has not been clearly established whether these compounds affects both TAGE and non-TAGE metabolism; however, it is worth exploring the therapeutic value of such strategies, and possibly applying them in clinical practice.

9. Methodology for determining AGEs in biological materials

Determination of AGEs in tissues is problematic. It is important to pay particular attention to the diversity of compounds that should be analysed (4,11). Additionally, a multitude of conditions that can influence the glycation of AGEs (such as pH, presence and the amount of free radicals and metal ions, amongst others), and the type and concentration of substrates

need to be taken into consideration (4). Moreover, AGEs are typically present in small amounts *in vivo* (14,43). Their isolation from tissues can cause undesirable chemical modifications and the formation of artefacts (44). Nevertheless, research on the content of AGEs in serum, in tissues and in food is very desirable, particularly for diagnostic and therapeutic purposes (14,21,38,41,45,46).

A number of methods for determining AGEs in samples are available. Amongst the most frequently used are chromatographic methods coupled with mass spectroscopy (11,14,44,46). Equally popular are immunoenzymatic methods using antibodies (1,4,44,47); however, the specificity of the antibodies (11,14) or the low quantities of antigens in the sample can cause difficulties (1). The natural properties of AGEs associated with fluorescence can also be exploited in fluorometric methods (43,45,47); unfortunately, the fluorescence of other components in the sample often obfuscates the results (11). Thus, at present, there is no one specific and sensitive method to measure AGE content in samples (11).

10. Summary and conclusions

Despite the fact that methods for determination of the entire range of possible AGEs in biological samples is limited and challenging, it is still recommended to attempt measurement to reduce errors. Numerous studies have shown the association between AGEs and their negative effects, such as oxidative stress, inflammatory processes, and the formation of cross-links, which can alter the biochemical properties of proteins (12,48).

AGEs can be classified as toxic or non-toxic AGEs, however it seems that the effect of each type of AGE may vary based on the specific conditions. A significant challenge in the study of AGEs is that the structures of AGE-1 through AGE-4 and AA-AGE are not defined. Additionally, the epitopes recognized by the antibodies in the study of TAGEs have not been determined. Another problem faced by researchers examining AGEs is the impact of albumin-AGE. The formation of AGE is complex, and is partially dependent on non-enzymatic glycation, and it is difficult to control the course of this process to obtain a homogeneous reaction product. The levels of AGEs or TAGEs in serum or tissues is also very small, hence the difficulty in accurately determining their concentration in biological samples. Thus, there is an urgent need to improve our understanding of the effects of glycated agents, as it may improve our understanding of diabetic complications, and other processes associated with oxidative stress caused by glycation.

It is also important to educate individuals on the risk of AGE toxicity, instilling the importance of a healthy diet, and encouraging them to choose food products that are not processed in high temperature conditions. It is also worth raising patients' awareness on preventing the effects of glycation, used to protect food supplies. Natural anti-glycation agents include anthocyanins and ellagic acid, which are derived from vegetables and fruits, and are also active ingredients contained in green tea; garlic; resveratrol; red wine; curcumin; cinnamic acid derivatives, such as ferulic acid; quercetin, which is found in several plants, caffeic acid from *Ilex paraguariensis* and numerous other food stuffs (49,50). Lowering the intake of

dAGEs can reduce the risk of diabetes, cardiovascular complications and other glycation-related diseases.

Due to the ability of AGEs to increase the risk of diseases and promote neoplastic changes, AGEs are becoming an increasingly popular subject of study in the field of toxicology. However, it is extremely difficult to define the strict toxicological parameters of the various types of AGEs in the literature. At present the following parameters are used: No-Observed-Effect-Level, No-Observed-Adverse-Effect-Level, Permissible Exposure Limit and Time-Weighted Average. An increasing interest in the field of AGEs may emphasize the importance of the role of AGEs in the pathological mechanisms of various diseases, and improve public awareness of the risks associated with ingestion of food-derived AGEs.

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