Review Article

Advances in Bioengineering & Biomedical Science Research

Importance of Advanced Glycation End Products (AGE) in Human Disease and Diagnosis

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Submitted: 12 Apr 2018; **Accepted**: 18 Apr 2018; **Published**: 08 May 2018

Abstract

Advanced Glycation End (AGE) is a product of non-enzymatic reaction between reducing sugars of carbonyls and proteins. AGE accumulates with age. It may be derived from methylglyoxal (MG), glyoxal, and 3-deoxyglucosone (3DG) groups. AGEs are chemically heterogeneous group of compounds with only 25 AGE structures fully characterized. Among these Nε-carboxymethyl-lysine (CML) is the simplest and best characterized AGE. It is involved in the pathophysiological conditions like diabetes, cardiovascular diseases, atherosclerosis and aging disease like Alzheimer disease. So, it is important to measure the AGE level in human diseases. Skin autofluorescence (AF) is a noninvasive measurement of AGE accumulation. In this review, different methods of determination of AGE level in human will be discussed because of standard method of measurement of AGE have not been established yet. It is suggested that AGE may play an important in assessing diagnosis, prognosis and prevention of some high risk disease in near future.

Introduction

Advanced Glycation End (AGE) a heterogeneous derivative formed by irreversible dehydration, condensation and crosslinking of Amadori compounds which is a chemical linkage between the carbonyl groups and the amino group to form Schiff bases [1]. It was first described by Maillard that the formation of brown-colored substances resulted from nonenzymatic reaction between reducing sugar and proteins [2]. AGE formation is accelerated in diabetes due to hyperglycemia and 25 AGE structures are fully characterized. Nε-carboxymethyl-lysine (CML) is the simplest and best characterized AGE [3]. Formation and destabilization of coronary atherosclerotic plaques can occur reactive oxygen species generation in vascular wall cells by AGE [4,5]. Moreover, AGE is also associated with neurodegenerative diseases like Alzheimers' and other non-communicable disease like cancers. In Alzheimer's disease (AD), Aβ plaques in the AD patient brain contain high concentrations of advanced glycation end-products (AGEs) as well as transition metal ions [6].

It is important to assess the level of AGE accumulation in human diseases. Protein oxidation and glycation adducts can be measured quantitatively by liquid chromatography-tandem mass spectrometry (LC-MS/MS) to know level of exposure to potentially damaging protein modifications, protein inactivation in ageing and disease, metabolic control, protein turnover, renal function and other aspects of body function [7]. Noninvasive method for AGE measurement is skin autofluorescence (SAF) which is a marker for diabetic foot ulcer [8]. It is also a quick method to measure AGE to correlate the cardiovascular risk in dialysis patient. But, it is impossible to measure in patients with highly pigmented skin [9]. One of the highly reactive dicarbonyl compound methylglyoxal (MG) in human blood plasma was measured by high performance liquid chromatography (HPLC) with fluorescence detection [10]. In this review, AGE in human disease and diagnosis were discussed.

AGE

AGE is a brown-colored substance resulted from non-enzymatic reaction between reducing sugar and proteins which was first discovered by Millard. AGE formation and accumulation by increased reactive dicarbonyls production or reduced glyoxalase system detoxification or endogenous scavengers' leads to a state of carbonyl stress [11]. Dietary AGE are absorbed from gastrointestinal tract (~10%), and approximately two-thirds remained in contact with tissues for >72 hr and others are rapidly excreted from the kidneys [12-14]. AGEs are broken down in the body by enzymatic degradation and receptors that binds, internalizes and degrades AGEs. Major degradative enzymes are glyoxalase I and II system [15]. AGE binds to AGE receptor called RAGE which composed of an extracellular region containing one V-type and two C-type immunoglobulin (Ig) domains that belongs to the Ig superfamily of cell surface molecules [16].

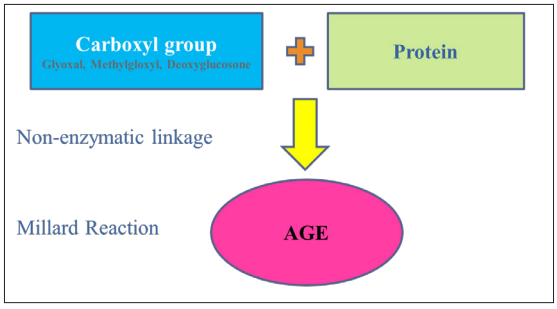

Figure 1: Formation of AGE

AGE and Diabetes

AGEs are risk factors which have great impact on metabolic health in diabetes [17]. Diabetes is a life-threatening disease and its complications such as cardiovascular disease, stroke and microvascular diseases. Extensive intracellular and extracellular formation of advanced glycation end products (AGE) is considered to be a causative factor in sustained hyperglycemia-induced vascular injuries in diabetes [3]. Researchers showed that glucose homeostasis improved in type 2 diabetes patients and in overweight healthy adults when dietary AGE intake reduced [18,19]. AGE may play an important role in the pathogenesis of diabetic vascular complications like diabetic nephropathy, diabetic retinopathy and diabetic neuropathy [3]. It was reported that an interaction between the renin-angiotensin system and the AGE-RAGE axis in podocytes. In diabetic nephropathy, intraglomerular angiotensin II levels are increased and there is an association between development of diabetic nephropathy, podocyte injury and inflammation [20]. The pharmacological blockage of RAGE by soluble RAGE (sRAGE) protected against glomerulosclerosis and other lesions of early diabetic nephropathy in db/db diabetic mice [21].

In nonproliferative stage (NPDR) and proliferative stage (PDR) diabetic retinopathy, there was association between CML accumulation and vascular endothelial growth factor (VEGF) expression [22]. VEGF plays an important growth factor in diabetic retinopathy and oxidative stress causes AGE formation and involved in retinal vascular dysfunction [23]. In one study showed that blood-retinal barrier breakdown and increased leukostasis in endothelial RAGE overexpressing mice which can be improved by sRAGE treatment [24].

Both autonomic and peripheral nerves are affected in diabetic neuropathy. Endothelial injury is the main target that may impair the blood flow which results in peripheral nerves hypoxia and oxidative stress [25]. Researchers explored that RAGE gene deletion protected animals from diabetic injuries though RAGE overexpression enhanced diabetic neuropathy. Furthermore, sRAGE could prevent loss of thermal pain perception in diabetic mice [26-29].

AGE and Neurodegenerative Disease

In aging, there an increase in the formation of advanced glycation end products (AGE). These glycation reactions induce the formation and aggregation of the β-sheet structure results in fibrillar structures that cause Alzheimer's disease, Parkinson's disease and other neuronal disease. Thus, modulation of the AGE-RAGE axis is now considered promising in the prevention of neurodegenerative diseases [30]. Dietary AGE decreased sirtuin 1 expression by increase production of β-amyloid and plaques via a disintegrin and metalloprotease domain–containing protein 10 in a mouse model of Alzheimer disease. It is necessary to explore the role of dietary AGEs or AGE precursors in neurodegeneration but metabolic factors like insulin resistance may involve in neurodegeneration that contributes to strengthening this relation [31,32].

AGE and Atherosclerosis

AGE stimulate reactive oxygen stimulation (ROS) generation in vascular wall cells. This will lead to the formation and destabilization of coronary atherosclerotic plaques by induction of redox-sensitive atherosclerosis related molecular expression such as Monocyte chemoattractant protein 1 (MCP-1), matrix metalloproteinase-9 (MMP-9) and plasminogen activator inhibitor1(PAI-1) [3]. In early stage of atherosclerosis, endothelial dysfunction occurred by AGE secondary to a reduced nitric oxide bioavailability mediated by free radicals which caused endothelium repair by endothelial progenitor cells [33]. Moreover, glycated low density lipoprotein (LDL) and high density lipoprotein (HDL) may also play an important role in atherogenesis. AGE inhibition can reduce the diabetes associated atheroma [34].

AGE and Cancer

AGEs have been observed not only in diseases such as atherosclerosis, rheumatoid arthritis, Alzheimer's disease and diabetes but various forms of cancer [35]. People with diabetes are at a significantly higher risk of many forms of cancer according to epidemiologic evidence. Accumulation of AGEs is especially high in long-living proteins with low biological turnover. AGE binds with receptor of AGE (RAGE) and activation of AGE-RAGE axis produces hallmarks of cancer onset and tumor growth. This RAGE-mediated mechanism causes potential impact of extracellular matrix glycation on tumor progression [36]. Moreover, there is an up-regulation of oncogenic transmembranous receptor (RAGE) in various human cancers. Inhibition of AGE receptor with multiple siRNAs causes apoptosis stimulation, suppression of proliferation and inhibition of cervical squamous cancer cells migration [37]. It was suggested that primary breast cancer cells proliferation, tumorigenicity, invasion and migration were enhanced by AGEs via the extracellular signal-related protein kinases (ERK) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) pathway [38]. In one study shown that AGEs increased prostate cancer cell proliferation directly but inhibition of macrophages for cytokine secretions [39].

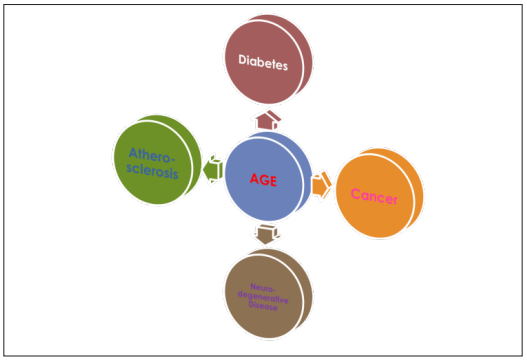

Figure 2: AGE involves in Diseases

Measurement of AGE

AGEs were originally measured according to their fluorescence and browning properties. Each AGE structure in pathological conditions can be demonstrated by high-performance liquid chromatography and gas chromatography mass spectrometry. In modernized techniques, AGE structures involved in diseases can be demonstrated by epitope-identified antibodies against AGEs [40].

Accumulation of AGE can also be measured noninvasively by skin autofluorescence (SAF) which is useful and convenient marker for diabetic vascular diseases in Caucasians [41]. SAF is useful to assess diabetic vascular complications, such as retinopathy, nephropathy in type 2 diabetes patients. In type 2 diabetes with carotid atherosclerosis patients, it may be a beneficial surrogate marker for evaluating carotid atherosclerosis [42]. In elderly people, accumulation of AGEs can be measured by skin autofluorescence (SAF) which may be a marker of metabolic memory [43].

Urinary AGEs can be measured by fluorescence intensity excitation at 370nm and emission at 440nm in a 96-well microplate using spectrophotometer in patients with metabolic syndrome. The results were adjusted according to the urinary creatinine levels [44]. Serum AGEs can be measured at excitation/ emission (370/435nm) to assess its relationship with diabetic chronic kidney disease (CKD) and cardiovascular disease (CVD) [45]. Nonfluorescence AGEs like carboxymethyllysine can be measured by using Enzyme linked immunosorbent assay (ELISA) kit [46].

Conclusion

In conclusion, AGEs are important role in the diabetic complications, atherosclerosis, aging disease and cancer. The accumulation of AGE can be measured by discussed methods and it is very useful for biologic marker to assess the risks and the relationships with diabetic chronic kidney disease (CKD) and cardiovascular disease (CVD). It is suggested that AGEs will be biomarker for inflammatory related disease and cancer for diagnosis, prognosis and prevention of high risk patients.

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