Journal of Alcoholism & Drug Dependence

Parwani and Mandal, J Alcohol Drug Depend 2017, 5:6
DOI: 10.4172/2329-6488.1000290

Review Article Open Access

Association of Advanced Glycation End Products (AGEs) with Diabetic Nephropathy and Alcohol Consumption

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Received date: Nov 30, 2017; **Accepted date:** Dec 06, 2017; **Published date:** Dec 08, 2017

Abstract

The occurrence of diabetes is accelerating worldwide, with consequent increase in the secondary complication like diabetic nephropathy (DN). Diabetic nephropathy refers to a set of structural and functional abnormalities of kidney in patients with diabetes. Detrimental changes like glomerular hypertrophy, glomerulosclerosis, hyperfiltration, proteinuria, etc. occur in DN. One of the major pathways suggested for the pathogenesis is formation of Advanced Glycation End Products (AGEs) via non enzymatic glycation (NEG). NEG is the process in which reducing sugars irreversibly modify free amino groups of proteins, by various events leading to the formation of a Schiff base resulting in Amadori products, culminating into AGEs. AGEs activate several cascades of intracellular signaling via interaction with Receptor for AGEs (RAGE) that results in responses like release of pro-inflammatory cytokines resulting in inflammation, autophagy and programmed cell death. AGEs can also come into circulation from baked food and processed food items. AGEs can also be formed through various oxidative reactions, including the chronic use of alcohol. Alcohol in excess could result in accumulation of acetaldehyde that would lead to insulin resistance. Many risk factors like race, genetic susceptibility, hypertension, hyperglycemia, hyper filtration, smoking, advanced age, male sex, and high-protein diet account for development of DN. Therapeutic interventions include glycemic control, control of blood pressure. This review focuses on the formation of AGEs via non enzymatic glycation, its implications in pathogenesis of DN and therapies designed to break AGEs so as to prevent the development of DN.

Keywords: Non-enzymatic glycation; Alcohol; Insulin resistance; AGEs; AA-AGEs; RAGE; Diabetic nephropathy

Introduction

Diabetes Mellitus is a metabolic disorder characterized by hyperglycemia owing to either lack of insulin release, lack of insulin action termed as insulin resistance or a in few instances, both. Non-Insulin Dependent Diabetes Mellitus (NIDDM) also called as Type 2 Diabetes Mellitus (T2DM) results due to acquisition of insulin resistance by the endothelial cells, resulting in failure to respond to insulin being produced by beta cells of the pancreas.

Secondary complications in diabetes

Insulin resistance and impaired beta cell mass and function are the hallmarks of T2DM, resulting in a compromised glucose regulation. The persistent hyperglycemia is one of the major factors leading to the development of secondary complications in diabetes; macrovascular and microvascular. Oxidative stress resulted due to hyperglycemia is incriminated as a factor for diabetes associated tissue complications. Macrovascular complications include atherosclerosis that affects arteries supplying blood to the heart, brain and lower extremities imparting a higher risk of developing myocardial infarction, stroke and limb amputation in diabetic patients. Microvascular complications damage the blood capillaries leading to complications like neuropathy, retinopathy and nephropathy associated with peripheral nerves, retina and renal glomerulus respectively. Many researchers have shown positive correlation between glycaemia and microvascular complications in both type 1 and type 2 diabetes [1,2].

There are four major hypotheses about hyperglycemia induced diabetes complications which are (i) accelerated glucose flux through polyol pathway [3]; (ii) activation of protein kinase C (PKC) isoforms through *de novo* synthesis of the lipid second messenger diacylglycerol induced by hyperglycemia [4]; (iii) formation of Advanced Glycation End Products (AGEs) [5] and (iv) increased oxidative stress [6].

Diabetes Nephropathy

Diabetes nephropathy (DN) broadly can be termed as a disease caused due to damage in the capillaries that supply blood to the kidneys. It is also a leading cause of End Stage Renal Disease (ESRD) in the world. It can be characterized by glomerular hypertrophy, thickening of basement membrane, mesangial expansion, tubular atrophy, interstitial fibrosis and arteriolar thickening [7,8]. Also, there occurs the accumulation of extracellular matrix (ECM) protein in the glomeruli, which results in an imbalance in the synthesis and degradation of the ECM components. Studies done over the last few years to facilitate differentiation of stages of renal modification (Figure 1).

Advanced glycation end products

Non-enzymatic glycation (NEG) is the process in which amino groups in the protein are irreversibly modified by reducing sugars by various events like Schiff's base formation resulting into formation of Amadori products, which yields AGEs. This process of reaction between free amino acids and reducing sugar is called as Maillard reaction. AGEs are yellowish brown, mostly fluorescent and insoluble adducts that modify a protein to lose its physiological functions [9]. AGEs and Advanced lipoxidation end products (ALEs) are complex,

heterogeneous compounds implicated in the pathogenesis of various diseases like diabetic complications [5,10], atherosclerosis [11], Alzheimer's disease [12], and in the process of normal ageing [5,13].

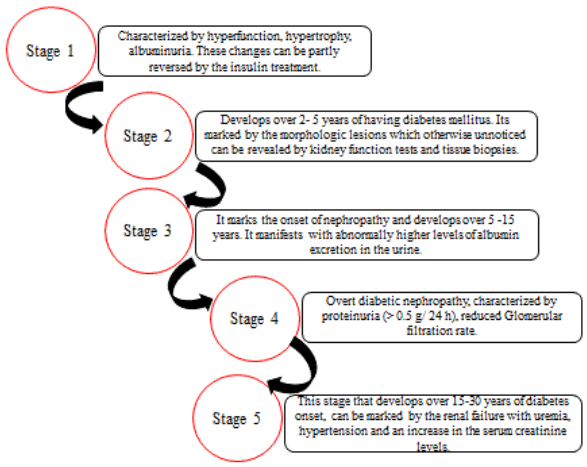

Figure 1: Studies done over the last few years to facilitate differentiation of stages of renal modification.

The formation of AGEs can be a one-step reaction or a series of complex reactions that leads to formation of crosslinks. Apart from this, Amadori products breakdown via oxidation to form reactive carbonyls such as glyoxal, methylglyoxal, which form intermediate glycation products by reacting with free amino groups of proteins. After a series of reactions like condensation, dehydration, Amadori products and intermediate glycation products, form irreversible intra- or inter-protein crosslinks AGEs. Carboxymethyllysine (CML), pentosidine, argypyrimidine, pyrraline, glyoxal-lysine dimer (GOLD), methylglyoxal-lysine dimer (MOLD), 3-deoxyglucosonelysine dimer (DOLD), carboxyethyl-lysine, fructose-lysine, methylglyoxal-derived hydroimidazolones are very well studied AGEs.

AGE and ALE, both are formed by reaction between reactive carbonyl species (RCS) and protein residues [14]. These RCS are products of metabolism of carbohydrates, lipids and amino acids in the body [15,16]. Oxidative stress also is implicated as a causative factor for diabetes associated secondary complications. Oxidative stress is reported to be increased in patients with diabetes, especially in those with poor glycemic control [10]. ROS, in excess, results in the formation of AGE/ALE, which accelerates oxidative stress both *in vitro* and *in vivo* [17,18]. Along with oxidative stress, AGEs are also most prevalent during hyperglycemic state as observed in diabetes. They accumulate in the vessel wall, where they affect the functioning and the structure of cells and have been thus reported to be involved in secondary complications of diabetes [19]. The formation of glycated products, although is accelerated during diabetic conditions, owing to hyperglycemia, does not negate the phenomenon of formation of AGEs at lower rates during normal metabolic processes. But however this can be defensed by cellular anti-AGE machinery of the host. It also is illustrious that apart from the endogenous formation of AGEs, they also are ingested through food items, baked and processed food in particular [20,21]. Environmental factors like diet, smoking, alcohol consumption, etc. can also exert impact on the rate with which AGEs accumulate endogenously. Table 1 describes the carbohydrate sources which form these AGEs [22]. Alcohol could exert formation of AGEs via oxidative stress.

Carbohydrate Source	Formed AGEs	Reference
Ribose	Pentosidine	[22]
Glucose, Threose	CML	
Methylglyoxal when reacts with Arginine	Argypyrimidine	
Methylglyoxal when reacts with lysine	Carboxyethyl lysine, and MOLD	
3-Deoxyglucosone when reacts with Arginine	Imidazolone	
3-Deoxyglucosone when reacts with Lysine	DOLD	
Glyoxal	GOLD	

Table 1: Carbohydrate sources which form these AGEs.

Plausible link between alcohol and AGEs

Detoxification and elimination of alcohol happen predominately in the liver via a series of oxidative reactions [23-25]. Metabolism of alcohol takes place in three stages: (a) Oxidation of ethanol to acetaldehyde by alcohol dehydrogenase (ALD), (b) acetaldehyde to acetate by aldehyde dehydrogenase (ALDH) and (c) acetate breaks down to water and carbon dioxide. The resulting acetate formed in step (b) being unstable gets readily converted to water and carbon dioxide. Acetaldehyde accumulated in excess turns toxic and forms adducts with DNA, lipids and proteins [26-29]. This could result in the formation of acetaldehyde derived- AGEs termed as AA-AGEs via Maillard reaction [30]. It was previously reported that ALDH2, a gene coding for aldehyde dehydrogenase is cardioprotective against ischemic heart disease [31]. This was concomitant with the reports suggesting an association of genetic polymorphism of ALDH2 that result in reduced enzymatic activity with higher risk of diabetes mellitus in Chinese women [32]. Reduced ALDH activity may result in the accumulation of acetaldehyde, resulting in the production of AA-AGEs, which in turn would result in the formation of DNA, protein and lipid adducts These findings were also supported by a group of researchers showing amelioration in myocardial hypertrophy, insulin/Akt signaling and therefore insulin resistance, by overexpressing ALDH2 in transgenic mice [33,34]. This could be hence hypothesized that acetaldehyde if not metabolized by ALDH, can result in insulin resistance and hence secondary complications in diabetes.

Studies with human subjects have shown higher levels of AGEs with subtly higher levels of CML in subjects with chronic alcohol misuse [35]. It is also reported that alcohol diminishes the antioxidants that could protect the liver by scavenging ROS [36]. Reports also state association of reduced antioxidants like Vitamins A, C, E with increased levels of AGEs in alcoholic patients [37]. The possible mechanism of how alcohol and hyperglycemia induced AGEs could have a common pathway to precipitate in diabetic secondary complications is explained in Figure 2. Alcohol tends to accelerate oxidative stress, which leads to formation of AGEs, which results in cell death, tissue damage and changes in biological structures.

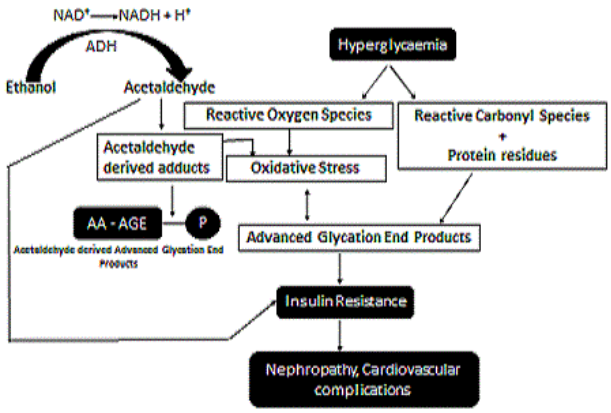

Figure 2: The possible mechanism of how alcohol and hyperglycemia induced AGEs could have a common pathway to precipitate in diabetic secondary complications.

Role of Rage-age Axis in Diabetes Nephropathy

AGEs are found to be present in both forms; free and protein bound at several places which include plasma, eye lens, glomerulus basement membrane, and mesangium of the kidney. They interact with different classes of receptors, which either would felicitate the activation of pro-inflammatory events and cellular damage, or would eventualize self-endocytosis and clearance. RAGE belongs to the immunoglobulin superfamily of receptors, and is expressed by various cells, podocytes i.e. glomerular epithelial cells, macrophages, endothelial cells, neuronal cells to name few [22]. Expression of RAGE depends on physiological conditions, which otherwise low can be overexpressed under stress and inflammation. Reports suggest an increase in RAGE expression during DN [38,39].

Full length RAGE protein forms cleaved RAGE via proteolytic cleavage by metalloproteinase and alternative splicing of RAGE mRNA leads to formation of endogenous secretory RAGE. They both together are termed as soluble RAGE (sRAGE). sRAGE provides protection against the inflammatory signaling events normally triggered by full length RAGE upon interacting with AGEs [40-42]. Induction of proteinuria and degenerative changes in renal tissue upon administration of AGEs in non-diabetic rats proved the crucial role played by AGEs in the development of DN [43]. Studies with RAGE-transgenic mice showed development of features of advanced DN such as kidney enlargement, glomerular hypertrophy, mesangial expansion, glomerulosclerosis, and proteinuria [44].

AGEs accumulate in the kidney and contribute to the alteration in the renal construction and disrupting the renal functioning. Interaction of AGEs with full-length RAGE activates NF-κB and its nuclear translocation, which in turn results in binding to RAGE promoter leads to increased RAGE expression [45]. AGEs stimulate the production of ECM along with inhibition of its degradation. Accumulation of ECM in the glomerular mesangium and tubulointerstitium is one of the key characteristics of DN. AGEs remarkably alter the composition of ECM which disrupts cell-matrix interactions, causing changes in cellular adhesion [46]. Also extracellular proteins such as fibronectin and collagen are found to have elevated expression triggered by AGEs independent of hyperglycemia [47,48].

Type 2 diabetic patients are found to have significantly elevated levels of AGEs, CML- and hydroimidazolone-AGEs in particular [49]. Researchers have shown positive correlation between renal impairment and serum CML levels in patients with proteinuria [50]. Modification of proteins by AGEs renders them resistant to degradation by metalloproteinases resulting in mesangial expansion and thickening of the basement membrane of the kidney [51]. AGEs augment the expression of proinflammatory cytokines like TGF-β, which accelerates the production of laminins, collagen, fibronectin. AGEs altogether alter glomerular expression of various ECM proteins via JAK/STAT signal transduction [52] which results in expression of various growth factors like TGF-β and platelet-derived growth factor (PDGF) [53].

Crosstalk between AGEs and Renin Angiotensin System (RAS)

The kidney produces components of RAS namely renin, angiotensin I, angiotensin converting enzyme (ACE), angiotensin II. RAS is primarily known to play a role in the regulation of fluid balance and therefore blood pressure. Hyperactivation of RAS is strongly found to be associated with the pathogenesis of diabetic nephropathy [54]. RAS hyperactivation results in augmented angiotensin II activity in DN. Inhibition of ACE decreases renal hyperfilteration thereby rescuing glomerular injury. This was supported by studies on prevention of *in vitro* AGE formation upon cotreatment of ACE inhibitors with glucose and protein [55]. Expression of NADPH oxidase along with its activity may hint renal origin of oxidative stress in diabetes [56].

Age inhibition: prevention of diabetes nephropathy

A large number of natural and synthetic AGE inhibitors have been discovered [57]. AGE inhibitors should stop the formation of AGEs, stop interaction of AGEs with RAGE, or should recognize and break the Amadori products. Our body has developed a natural anti-AGE system which either catalyse the conversion of carbonyl species like glyoxal and methylglyoxal to lactic acid [58] or destabilizing the Amadori products which renders their breakdown [59]. Statin like atorvastatin has been shown to prevent AGE induced RAGE expression in healthy rats [60], while pravastatin prevented AGE induced tubular damage and cell death in DN [61]. Aminoguanidine was the first synthetic compound to inhibit AGE formation *in vitro* and *in vivo*. However, it is withdrawn back after clinical trials due to its side effects. As the interaction between AGE-RAGE induces oxidative stress, antioxidants could play role in ameliorating AGE induced damage. Vitamin C and E along with combination of N-acetylcysteine with taurine and oxerutin were shown to be potential anti-glycative agent [62,63].

Conclusion

DN remains one of the important factors leading to End Stage Renal Disease (ESRD). DN results due to many factors, one of them being the interaction between AGE-RAGE. Formation of AGEs due to hyperglycemia is one of the hallmarks of type 2 diabetes which results in oxidative stress. Oxidative stress, thus formed can lead to activation of various pathways which further deteriorate conditions persistent in the cells. There is a plausible link between alcohol and AGEs as

consumption of excessive alcohol leads to the formation of ROS which give rise to AGEs. Also, it has been noted that acetaldehyde if gets accumulated in excess due to reduced activity of ALDH could result in the formation of adducts with DNA, protein and lipids. They also can form acetaldehyde derived AGEs that could result in insulin resistance, which culminates into cardiovascular complications and nephropathy. Therefore, there arises a need for developing new strategies and new molecules to curb the pathophysiological effects of AGEs in DN. Although there are various molecules available for inhibiting the formation of AGEs, there remains a need for a therapy or a molecule that targets multiple pathways that could prevent the precipitation of AGEs mediated DN.

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