REVIEW ARTICLE
ADVANCED GLYCATED END PRODUCTS (AGES) IN DIABETES AND ITS COMPLICATIONS: AN INSIGHT

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Abstract

Chronic hyperglycemia in diabetes mellitus, glucose forms covalent adducts with the plasma proteins through a non-enzymatic process known as glycation. In the pathogenesis of diabetic complications advanced glycation end products (AGEs) play an important role like retinopathy, nephropathy, neuropathy, cardiomyopathy along with some other diseases such as rheumatoid arthritis, osteoporosis and aging. Proteins glycation interferes with their normal functions by disturbing molecular conformation, shifting enzymatic activity, and intrusive with receptor functioning. AGEs form intra- and extracellular cross linking not only with proteins, but with some other endogenous key molecules including lipids and nucleic acids to contribute in the progress of diabetic complications. Recent studies suggest that AGEs interact with plasma membrane localized receptors for AGEs (RAGE) to alter intracellular signaling, gene expression, release of free radicals and pro-inflammatory molecules. The present review discusses the role of AGEs in the pathogenesis of diabetic complications including retinopathy, cataract, neuropathy, nephropathy and cardiomyopathy.
Keywords : AGE-Receptors, AGER1, Glycation, Oxidation, Inflammation

Introduction

Diabetes mellitus is an endocrine disorder that is also known as 'hyperglycemia' which is caused due to the deficiency of insulin or insulin resistance. The incidence of the diabetes and its complications has been increasing at an unstoppable rate being one of the causes for the increase in mortality and morbidity. Patients suffering from diabetes for a longer period of time and having poor blood glucose control are prone to suffer from various complications such as neuropathy, retinopathy, atherosclerosis, nephropathy, and cataract and impaired wound healing leading to cases such as foot ulcer. Due to these complications, the cell of the organs such as nervous system, kidneys, small blood vessels and heart stops using insulin for glucose uptake. These results in the increase in intracellular concentrations of the glucose in the cells of the organs affected during hyperglycemia. (Forbes *et al.,* 2005)

One of the principal causes of pathogenesis of diabetic complications that has been found is hyperglycemia. It plays a significant role by forming advanced glycation end products (AGEs). AGEs are a heterogeneous sugar derived complex molecules which are formed through a non enzymatic reaction called glycation (Peepa, 2003). Through this reaction, it begins to form covalent bond with the plasma proteins when there is a rise in the glucose levels (Hammes *et al.,* 1999). The formation of the AGE in the normal body begins from the development of early embryo, which is formed at a constant and slow rate and gets accumulated as the time passes. The initial product formed in this reaction is known as Schiff base and depends mostly on the reactants concentration levels. AGE formation is increased rapidly because of the high glucose availability in the body in the diabetic patient but low glucose will not bind with the sugars from amino acids to which they are attached. Furthermore, a series of reactions such as oxidation- reduction, dehydration and other various reactions leads in the formation of AGEs (Pfeffer *et al.,* 2002).

The formation of AGEs can be explained in 3 main stages.

Early stage: In this stage, sugar reacts with a free amino acid to form the base known as Schiff base which forms amadori product, a stable product.

Intermediate stage: The amadori product degrades and forms a dicarbonyl compounds which is reactive in nature.

Last stage: Ages through glycation process is formed, that are irreversible (Singh 2014).

Receptors for Advanced Glycation End Products (RAGE)

AGEs have many receptors to which it can bind with such as RAGE, lactoferrin, oligosaccharyl transferase 48, scavenger type I and II and many others. One of the most important receptor for the pathaogenesis of diabetic complication is the RAGE (Receptors for advanced glycation end products). RAGE can be defined as a signal transduction receptor with a multiligand ability which is found on the smooth muscle cells, endothelial cells, astrocytes, and macrophages. It is a β-sheet fibrils and amyloid beta peptide receptor. Soluble RAGE and polymorphisms in genes coding for this receptor may help in identifying patients who are prone to the diabetic complications and can be used to prevent the injury caused by hyperglycemia (Hudson *et al.,* 2003).

AGE in Diabetic Atherosclerosis

When the atherosclerotic plaques gets deposited on the the inner walls of the artery and occludes the normal flow of the blood, it is defined as atherosclerosis which further leads to various cardiac complications such as angina, myocardial infarctions as well as cerebrovascular diseases such as strokes. It is one of the major complications found as the result of the long term diabetic complications which can

eventually lead to death. As per the studies it has been found that AGEs accelerates the build up and development of the arthesclerotic lesions. The role of AGEs in this formation is that it changes low density lipoprotein (LDL) cholesterol such that it get oxidized and gets deposited in the walls of the vessels, leading to the formation of the atheroma and the LDL glycation also increases in diabetes patient. In diabetic patient, accumulation of AGE and glycation is much higher in the vascular tissue that causes such changes in the walls of the vessels. An AGE breakers helps in reversing the arterial stiffness (Ahmad, 2005).

AGE can also be entered in the body through exogenous sources such as tobacco smoke and food as it gives rise in its formation as well. The AGE serum levels are increased in smokers than in non smokers. Therefore, diabetic patient who smokes are found to have high deposition of AGE in ocular lenses and the arteries. Almost 10 % of AGE that are ingested is absorbed through food. Studies in animals have demonstrated a direct correlation between circulating AGE and those that are taken through food and also the relation between high AGE dietary intake and progression of diabetes related damage of tissue. A study was performed in a diabetic mice, where a group apoE null mice was fed on high and low AGE diet , the formation of atherosclerotic lesions was higher in mice with high AGE diet as compared to the mice on low AGE diet. However, immuno-histochemical studies showed a decrease in tissue AGE, RAGE expression, in diabetic mice fed on a low AGE diet (Cerami *et al.,* 1997).

The inability of the glomerulus to filter normally and decrease in the glomerular filtration rate eventually is known as Diabetic nephropathy (Marshal, 2004). It causes conditions such as proteinuria and retinopathy, which is one of the complications of the diabetes. AGEs plays a significant role in the pathogenesis of diabetic nephropathy (Wolf, 2004). It activates sequence of intracellular signalling pathways by binding with the RAGE. A novel treatment based on dual target drugs has therefore been developed which is useful for diabetic nephropathy therapy. (Jang *et al.,* 2011). ADMA (asymmetric dimethyl arginine) is generated in the tubular cells by the interaction between AGE and RAGE, suggesting the significance of AGEs in the pathogenesis of diabetic nephropathy (Giacchetti *et al.,* 2004).

AGEs in Diabetic Neuropathy

Diabetic neuropathy (DN) is a complication caused in the diabetic patient which is defined as signs and symptoms of peripheral nerve dysfunction such as reduced blood flow and nerve conduction and whose other causes of peripheral nerve dysfunction have been excluded. The most common sign of diabetic neuropathy is numbness and pain in the limbs and impotence in men. The reason for its occurrence is due to the accumulation of AGE as glycation activity increases of myelin in diabetes. These myelins that are glycated are prone to in vitro phagocytosis by the macrophages and these macrophages release proteases which lead to the demyelination in diabetic neuropathy. Moreover, the AGEs present on myelin can lock up the plasma proteins such as IgM, IgG and C3 to enhance immunological activity that may lead in neuronal demyelination. According to the recent studies in animal, the velocity produced in the sensory motor conduction, peripheral nerve blood flow has been decreased

due to AGEs but the role of glycation in still unknown (Brownlee, 2000).

AGEs in Diabetic Ocular disease (Retinopathy)

Diabetic Retinopathy is ocular disease that is affected in the diabetes patient. It is a micro vascular complication which doesn't usually show signs and symptoms at the beginning, but slowly develops a lack in clarity of the vision, resulting in blindness in severe cases. In patient with type II diabetes with retinopathy, AGEs have been found on the site of the retinal blood vessels (Fong *et al.,* 2004). In a study, a non diabetic animals was given AGE albumin, the adducts got accumulated in the pericytes and enhanced the thickness of the basement membrane and lead to the breakdown of the barrier covering inner blood retina (Goh and Cooper, 2008). A potent mitogen expression VEGF is elevated by the AGEs that contribute in the regulation of the ICAM-1 that results in rise in monocyte adhesion to the endothelial cells of retina. These leads to the stimulation of the neo- vascularization and angiogenesis that are the main reason for the occurrence of proliferative retinopathy (Mamptu, 2004).

The AGE-RAGE signaling plays a major role in the diabetic retinopathy as it contributes constant inflammation that causes microvascular dysfunction along with the neurodegeneration with the help of oxidative stress. In retinal muller cells, AGEs are reported in the induction of bFGF (basic fibroblast growth factor). Moreover, in microvascular endothelial cells and pericytes, RAGE expression rises as the AGEs rises (Ciulla, 2003).

AGEs in Diabetic cardiomyopathy

Diabetic cardiomyopathy is defined by the myocardial fibrosis and myocellular hypertrophy that results in diastolic dysfunction. Diabetic patient is more prone to heart failure. Almost 50- 60 % T2DM patients has diastolic dysfunction and is mostly seen in patient with diabetes and microalbuminuria which later develops into systolic dysfunction. Due to the accumulation of AGEs in the myocardium, there is a relation between diastolic dysfunction (Ahmad, 2005). Cardiac RAGE mRNA is regulated by the MG-RAGE which triggers the cardiomyocyte contractile dysfunction. The activation of (PPAR-γ) reduces RAGE as reported by the study. RAGE has therefore been found as a one of the important receptor in diabetic myocardial fibrosis, from the studies in which the effect of rosiglitazone, a PPAR-γ agonist on myocardial expression of RAGE, extent of cardiac fibrosis, and left ventricular (LV) diastolic function in experimental models of diabetes. Figure 1. (IHM, 2010)
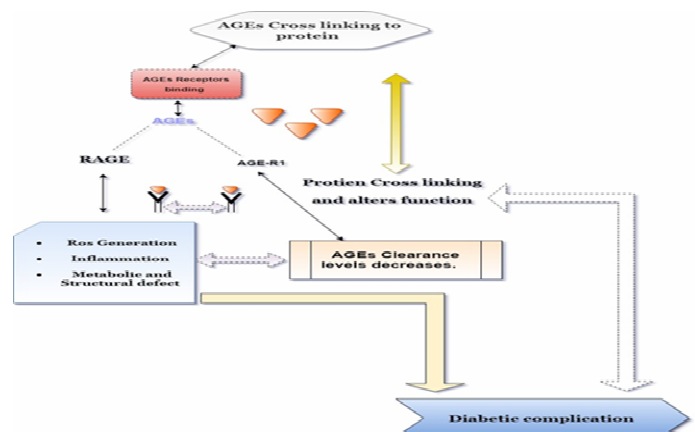

Fig. 1 : Role of AGEs in Diabetic Complications.

Therapeutic modalities

A study on anti-AGE drugs is being studied intensively worldwide in order to inhibit the progression and formation of AGEs to prevent diabetic complications caused by it. The first drug discovered was the Aminoguanidine. It worked by inhibiting glycation activity by inhibiting the early AGE product conversion. As per the study, it has been suggested that in the prevention of arterial stiffening and cardiac hypertrophy, amainoguanide shows effects in experimental diabetic animal models and focuses on the role of AGEs in pathogenesis of diabetic cardiomyopathy (Vasan, 2003). Animal studies proved that aminoguanidine proved to be useful for many other diabetes complications as per the animal studies. The drug therefore needed more testing for confirmation. Other anti AGE drugs that inhibit AGE formation is the AGE breaker which is still under studies. Animals and human studies have been by far most useful and informative for the development of such drugs. With the use of the AGE breaker, a major improvement of severe heart failure, systolic hypertension was observed due to vascular inelasticity reversal. Other additional pharmacological approaches are still in early stages of development (Peepa, 2003). Best explained n Table 1.

Table 1: Concentration of standard 1 ppm for each one.

S. No	Intervention	Comments	References
1.	Pravastatin	Reduces tubular damage and attenuating AGEs-induced apoptosis by inhibiting ADMA generation in tubular cells in diabetic nephropathy.	Moore *et al.*, 2003
2.	GLP-1 Receptor Agonist	Inhibits the generation of AMDA generation in tubular cells to attenuate the development and progression of diabetic neuropathy.	Antonetti *et al.*, 1998
3.	Aminoguanidine	Prevents cardiac hypertrophy and arterial stiffing in diabetic cardiomyopathy.	Oldfield *et al.*, 2001
4.	Rosiglitazone	Reduces the expression of RAGE on myocardium and Attenuates cardiac fibrosis and left ventricle diastolic function in experimental models of diabetic myocardial fibrosis.	Twigg *et al.*, 2002
5.	Grape seed anthocyanidins extracts	Effective against diabetic peripheral neuropathic pain by decreasing AGEs.	Wada *et al.*, 2001
6.	Pyridoxamine	Produces beneficial effect in relation to microalbuminuria and proinflammatory cytokines in experimental diabetic neuropathy	Montagnani 2008
7.	Hesperidin	Prevents retinal and plasma abnormalities in diabetic rats by inhibiting accumulation of AGEs.	Amore *et al.*, 1997
8.	Epalrestat	Supress the deuteration of diabetic peripheral neuropathy, by inhibiting the polyol pathway and supressing production of AGE.	Schmidt *et al.*, 1994
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Conclusions

This review explains that the advance glycated end product formation increases in case of diabetic patient and leads to various complications. Furthermore, the increase in the accumulation of the plasma proteins that are glycated also plays a significant part in the pathogenesis of different diseases. RAGE also has a major role diabetic complication pathogenesis further mechanism of RAGE activation is yet to be studied. Moreover, few anti AGE drugs have been discovered in order to prevent or disrupt the complication caused due to diabetes and few are yet to be studies.

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