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ORIGINAL PAPERS

# The Role of Glycation in Pathology of Diabetic Microvascular Complications

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## Abstract

In diabetes mellitus, glucose forms adducts with the proteins through a non-enzymatic reaction termed as glycation. Glycoprotein conflicts with their normal functions via altering of molecular conformation and enzymatic activity. Subsequently, the glycated proteins are chemically modified to advanced glycation end products (AGEs). AGEs discovered in body fluids and all tissues and could interact with intracellular and extracellular proteins conflicts with their normal functions. AGEs can cross-link with specific cell surface receptors (RAGs) and consequently modify cell intracellular signaling, gene expression, the formation of reactive oxygen species and the energizing of many of the inflammatory pathways. AGEs have a central role in the devolopment of diabetic complications, including macrovascular and microvascular complications. Anti-glycation treatments could block the progress of diabetic complications. Understand the AGEs effects and how can be inhibited is a remarkable approach for controlling the diabetic complications. The present review summarizes the possible mechanisms of AGEs on Pathogenic effects including microvascular complications. Furthermore, the biochemical mechanisms of anti glycation reactions are also summarized.

**Keywords:** diabetes mellitus, advanced glycation end products, microvascular complications.

## Introduction

Glycation scientifically outlined as a reaction between reducing sugars and an amine group of proteins, amino acids, and nucleotides. Because of the main role of glycation within the pathogenesis of multiple chronic diseases like diabetes, the literature search concern and yield many articles about glycation (Steiner et al., 2018). According to WHO (2018), the number of diabetes cases has nearly doubled since 1980. Cho et al. (2018) estimated about 415 million people worldwide had diabetes in 2017 and one case dies from diabetes each six cases everywhere the globe. With current trends continue, Cho et al. (2018) predicted that 693 million people worldwide will have diabetes by 2045. Glycation and

advanced glycation end products (AGEs) formation is a central pathogenic part in cellular malfunction and diabetic complications. Diabetic complications can be classified into Microvascular complications and Macrovascular diseases Microvascular complications are more common than macrovascular complications (Cheema et al., 2018). So, the aim of this review is to summarize the role of glycation and AGEs in the pathogenesis of microvascular complications and possisible machansims to inhipit AGEs formation.

## Diabetes mellitus

Diabetes mellitus (DM) is cluster of metabolic disorders resulting from defects in pancreatic insulin secretion, insulin action or both (Dewanjee et al., 2018). Type 1 and type 2 are the main types of DM. The plurality of type 1 is due to insulitis which results from the loss of insulin secreting cells (pancreatic beta cells) when attacking by T cell mediated autoimmune (Rother, 2007). Type 1 DM affected by genetic component, environmental and immunologic factors that destroy the pancreatic beta cells (Prasad et al., 2012). Type 2 known as additionally adult onset diabetes, non insulin-dependent diabetes starts with insulin opposition, a case during which cells fail to respond to insulin completely. In DM, a glucose form adducts with the plasma proteins and DNA by nonenzymatic glycosylation termed as glycation, subsequently, the glycated proteins are chemically modified to AGEs. AGEs discovered in body fluids and all tissues (Fishman et al., 2018). AGEs may decrease the elasticity, flexibility, and functionality of the proteins followed with initiate harmful inflammatory and autoimmune responses.

## Glycation and AGEs formation

Glycation (Maillard reaction, amino-carbonyl reaction, non-enzymatic glycosylation, or browning reaction) defined as reaction between reactive carbonyl compounds, such as reducing sugars and ε-amino cluster of protein's amino groups, nucleic acids, and phospholipids, in addiontion to sulfhydryl groups (Freund et al., 2018). Glycation included a 3 sequence series of complex nonenzymatic reactions: early, intermediate, and late (Singh et al., 2014). In the first stage (the Shiff base), electrophilic carbonyl groups of the reducing sugars link with free amino groups of amino acids and form unstable aldimine compound called the Shiff. Schiff base rapidly rearrangement to form a more constant early glycation ketoamine (fructosyl-lysine (FL)), and other fructosamine derivatives termed as the Amadori products (Monnier et al., 1996). Within the second stage, the Amadori product degrades to a set of reactive dicarbonyl compounds like glyoxal, methylglyoxal, and deoxyglucosones. pervious products are more reactive than the starter compounds, doing as propagators of the reaction, once more linking with free amino . The last step occurred within the

presence of reactive oxygen species, or redox active transition metals and AGEs (Ahmed, 2005). AGEs are irreversible products formed during early, intermediate and the late stage of glycation, in particular, under conditions enhanced oxidative stress of and/or hyperglycaema (Van Zoelen et al., 2011). The AGEs are insoluble substances characterize as yellow-brown, often fluorescent and cumulate on long-lived proteins. AGEs can be divied into 3 main groups: fluorescent and cross-linking structures (crosslines and pentosidine), non-fluorescent and crosslinking structures (imidazolium dilysine cross-links, alkyl formyl glycosyl pyrrole (AFGP) cross-links and arginine−lysine imidazole (ALI) cross-links) and Non-cross-linking AGEs like pyrraline and N-carboxymethyllysine (CML) (Ahmed, 2005). Simm (2013) classified AGEs depending on their toxicity to non-toxic compounds ( CML and pyrraline) and toxic compounds which derived from glycolaldehyde or glyceraldehydes.

**Pathophysiological of protein glycation**

AGEs are a part of normal metabolism, but it can become glycotoxins when accumulate for a long time in the body and take a part in the diabetic complications due to a high blood sugar level which assist AGE formation (Ulrich et al., 2001). According to Brownlee, (2005) and Fishman et al. (2018), there are 3 possible mechanisms of cells damage, the first is the intracellular proteins change involved, most important proteins included in the gene transcription regulation. Secondly, the cellular dysfunction as a result to AGE precursors diffusion out of the cell and alter molecules of extracellular matrix, which modifies signaling between the matrix and the cell. The last mechanism is that AGE precursors circulate out of the cell and change plasma protein. Glycated blood proteins can then link to AGE receptors (RAGEs) and stimulate them, resulting in inflammatory cytokines and growth factors secretion, which cause vascular pathology. Intracellular aggregation of AGEs within the endoplasmic reticulum ends up in stress, which might reduce normal folding of protein processes then leading to cell apoptosis (Adamopoulos et al., 2014). Extracellular proteins are particularly long-lived, and that they are extremely vulnerable to modification by AGEs (Duran et al., 2009). The function of protein, mainly depends on structural stability and any disorder cause amendment in its purposeful properties resulting in pathologic process of assorted diseases and complications (Siddiqui et al., 2019). Glycation and AGEs modify the plasma proteins, including albumin, fibrinogen and globulins contribute to the pathological effects inclusive change activation of platelet, production of free radicals, failure in the immune system, leading to bone remodeling and skeletal fragility (Singh et al.,2014). Malliard reacting target albumin and collagen due to its concentration and long half-life, contributes to microvascular complications in diabetes (Sternberg et al., 2016). Glycated albumin takes a part in diabetic

retinopathy (Fishman et al., 2018), enhances neo-epitopes generation so demonists immunological complications in diabetes (Raghav et al., 2017).

**Receptors of advanced glycation end products (RAGE)**

AGEs may induce their harmful actions via the biological properties and their engagement with specific receptors called as RGAE (Tobon- Velasco et al., 2014). The binding of AGEs with RAGE of plasma membrane lead to change intracellular signaling, gene expression, free radicals generation, develop oxidative stress and inflammation and AGEs pathologic effects (Singh et al., 2014). RAGE is a member of the immunoglobulin (Ig) super family, that ordinarily found at dim levels within inflammatory cells, podocytes of the kidney, many types of epithelial cell, Müller cells of the retina, neurons and microglial cells, and malignantly transformed cells (Goh and Cooper, 2008). Binding of AGEs with RAGE on endothelial cells lead to diabetic vascular stress via up regulates main adhesion molecules which effect on the adherence of activated inflammatory cells (Schmidt et al., 1992).

**AGEs and complications of diabetes**

It is estimated that prolonged exposure to high levels of glucose certainly contributes to diabetic complications, including conditions that affect the cardiovascular and nervous system, eyes or kidneys. It is noticeable that AGEs play an important pathogenic role in cellular dysfunction and diabetic complications and many age-related disorders. (Freund, et al. 2018 and Koska et al., 2018). Progressive diabetic exposure is a key factor in diabetes-associated complications due to metabolic memory. Rhee and Kim (2018) reported that AGEs are produced and accumulated permanently in the body, so that AGE can be a major cause in the development of metabolic memory in diabetic complications (Koska et al., 2018).

**AGEs and diabetic cataract**

AGEs can play a significant role in the formation of diabetic glaucoma, retinopaty, and cataracts. Stitt and Curtis (2001) concluded that diabetes greatly affects on a lot of tissues and cells of the ocular, AGE accumulation at known eye disease sites and is the major cause of visual dysfunction. Over worldwide, AGEs are responsible to alter in the opacity, color of the eye lens (Franke et al, 2003) and are the most a significant reason for cataract development (Hashim et al., 2012) which the main cause of blindness (Pollreisz and Erfurth, 2010). AGEs significant change in structure of lens proteins and lens fibre membrane this leads to accumulation and covalent cross linking of lens crystallins which scatter light, disturb vision and form cataract (Nagaraj et al., 2012). Cataract formation

mechanisms are primarily increased nonenzymatic glycation / glycooxidation, protein kinase activation C, oxidative nitrosative stress, and polymerase activation (PARP) (Mandal et al., 2013).

**AGEs and diabetic retinopathy**

Diabetic retinopathy (DR) is described as microvascular system damage, including blood vessel proliferation, vascular stenosis, angiogenesis, microaneurysms, haemorrhages, ischemia and retinal infarction due to elongated hyperglycaemia that may result in blindness (Rohilla et al., 2012). Nearly all patients with Type 1 and over sixtieth of patients with type 2 can have some extent of retinopathy once twenty years of diabetes (Elosta et al., 2012). AGEs and RAGEs are found within the vasculature of retinal (Stitt et al., 1999). AGEs accumulation act as a growth inhibitors on pericytes this cause to the loss of pericyte and thus in turn, increase basement membrane thickening which significantly take a part in the collapse of the inner blood-retinal barrier (Elosta et al.,2012). AGE aggregation develops the expression of diabetic retina for glial fibrillary acid protein, stop synthesis of glutamate (Chilelli et al., 2013).

**AGEs and diabetic neuropathy**

Diabetic neuropathy characteristics as a type of nerve damage and its symptoms depending on the affected nerves and vary from pain within the legs and feet to issues with the blood vessels, heart, urinary tract and gastrointestinal system. Peripheral symmetric neuropathy impacts on the feet and hands, It is the main reason for diabetic neuropathy (Prelipcean, 2019). It's estimated that, There are approximately 20-30 million people suffer from diabetic neuropathy, which is expected to double by 2030 (Bayram et al., 2016). Approximately 66% of patients of type 1 and 59% of patients of type 2 are likely to develop neuropathy (Tracy and Dyck, 2008). Jack and Wright (2012) concluded that, diabetic neuropathy could be developed by generation and aggregation of AGEs within the peripheral nerve. Changes in glycated collagen and laminin affect a vasodilation mediator, thereby reducing nerve blood flow and inducing peripheral nerve hypoxia (Singh et al., 2014). Toxic products in neural tissues (3-deoxyglucosone (3-DG) and methylglyoxal (MG) generated during early and intermediate stages of glycation lead to devolp progress of neuropathy within diabetes (Nawroth et al., 2018). In addition to, AGE-RAGE axis has an important role in the diabetic foot-associated with diabetic neuropathy (El-Mesallamy et al., 2011). AGE –RAGE links activated NADPH oxidase and NF-κB to exert proinflammatory reaction (Haslbeck et al., 2005). Physiologically, A precursor of AGEs (glycolaldehyde) stimulates diabetic neuropathy by reduction of the Schwann cells viability (Satoh et al,.2013)

## AGEs and diabetic nephropathy

Diabetic nephropathy is that the most typical cause for hypertensive nephropathy and foremost necessary causes of end-stage renal disease (ESRD) (Ghaderian et al., 2015). The loss of kidney occupation in diabetic patients, related to increasing AGEs levels (Genuth et al., 2005). AGEs modifying in proteins of extracellular matrix and resultig in basement membrane thickening (Thomas et al 2005) and target mesangium in which changes caused by AGEs (devolved apoptosis of the pericyte and expression of the vascular endothelial growth factor) lead to glomerular hyperfiltration, an early dysfunction in diabetes (Wendt et al., 2003).

## Anti glycation Inhibitors and diabetes complications

Suppression of AGE formation may block the development of diabetic complications. Generally, the anti glycation mechanisms involve any mechanism that may retard or block the glycation reaction and according to Wu et al. (2011), These may be one of the following: 1- Anti-glycation action within early stage is scavenging superoxide radicals and hydroxyl radicals to reduce both of oxidative stress and the production dicarbonyl groups. 2- The production of AGE depend on the existence of transition metal ions. So, chelation of metal ion may be blocked AGE productioon .3-Blocking the production of late stage Amadori products. 4-Breaking the crosslinking structures in the formed AGEs. 5- Blocking RAGEs can repress the oxidative stress and inflammation. Both therapeutic products and natural agents have been studied as antiglycation agents, but a lot of therapeutic inhibitors of AGEs formation were withdrawn from clinical studies due to low pharmacokinetics, poor efficacies, and unsafely. So, natural agents with high efficacy and safety in humans consider alternative therapeutic antiglycating. Several trials concluded that, many natural agents; such as plant extract products, food bioactive compounds, vitamins, Probiotic, prebiotic, Zn oxides and acids act as antiglycation agents and therefore development of diabetic complications (Wu et al., 2011; Guilbaud et al., 2016; Ma et al., 2018 and Zhu, et al.,2019).

## Conclusions

Prolonged exposure to high glucose level is estimated to be a main causal contributing to diabetic complications and increase mortality rate associated with diabetes. Diabetes complications are groubed into microvascular (small blood vessels damage ) and macrovascular (larger blood vessels damage). The function of protein, mainly depends on structural stability and any disorder resulting in pathogenesis of many diseases and complications. It is obvious that through many mechanisms, AGEs and RAGE can play a significant pathogenic role in diabetic complications. So understanding these mechanisms help to find approaches to inhibit the AGEs formation in hence depress the progress of diabetes

complications**. Depending on** Clinical studies, many of therapeutic inhibitors of AGE were withdrew due to low pharmacokinetics, poor effectiveness and unsafe. Thus, natural agents with high human effectiveness and safety consider alternative antiglycating therapy. Many studies are required in order to surmount the mortality caused diabetes complications using nature anti glycation products.

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