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Non-Enzymatic Glycation: A Link between Chemistry and Biology

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Review Article

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Abstract

The role of nonenzymatic glycation and advanced glycation end products (AGEs) in the progression of complications in diabetes patients has been explored to add knowledge in present spectrum. However, the association between highly reactive carbonyl adducts and diabetic complications are still unclear. The Maillard chemical reaction between carbohydrates and reactive amino groups of proteins is the key link between chemistry and biology. The chemistry of the glycation alters and impairs the RAGE expression via formation of carbonyl adducts. Excessive generation of non-enzymatic glycosylated products appears to be the connecting link between chronic hyperglycemia and pathophysiology of micro- and macro-vascular complications in diabetes mellitus.

Keywords: Glycation; Diabetes mellitus; Maillard reaction; Receptor advanced glycation end products

Introduction

Glycation, also known as non-enzymatic browning or the Maillard reactions, has centered the mind of a worldwide scientist nearly a century before. By initiating the non-enzymatic condensation and addition of reducing sugars with protein and being considered to be one of the severe forms of protein damage in the field of medicine and food science. Named after the pioneering biologist, the Maillard reaction was stated in 1912. The transformations occurring due to Maillard reaction are diverse and complex, despite thorough research, still poorly understood. The early research of Louis Camille Maillard states the theoretical background of the reactions which showed the interest of various food scientists in this pioneer era. Further reaction was described in detail by John E. Hodge proposing three-stage mechanism (1) reaction of carbonyl group of sugar with amino residues of protein to form an unstable Schiff base (2) the Schiff base undergoes rearrangement and condensation via Amadori mediated reaction creating a first stable product, ketamine [1,2,] and (3) ketamine undergoes further rearrangements, polymerization, and condensations leading to the formation of advanced glycation end products (AGEs) [3].

Advanced glycation end products (AGEs) are synthesized endogenously upon the reaction of carbonyl groups of reducing sugars with free amino groups of proteins. AGEs are generated in-vivo as normal consequences of metabolism but accelerate under adverse conditions of hyperglycemia, hyperlipidemia, and oxidative stress. Reducing sugars such as glucose actively react non-enzymatically with amino groups in proteins, lipids, and nucleic acids via Schiff base Amadori rearrangement to form AGEs. AGE formation involves a

diverse and complex sequential biochemical reaction, whose mechanism is still debated even though the pathways of AGE generation are well established. Advanced glycation end products formed and occur over a period of weeks, thereby affecting biomolecules adversely. The structural composition of connective tissues, basement membrane, such as collagen, albumin, other biomolecules is also the target of AGEs [3,4]. Glucose has reported the slowest glycation rate compared to intracellular sugars such as glucose-6-phosphate and fructose [5]. Pentosidine and N-carboxymethyl-lysine (CML) are oxidation products formed via glycoxidation mechanism [5]. Amadori rearrangement in Maillard reaction includes the formation of reactive intermediate known as α-dicarbonyls or oxoaldehydes such as 3-deoxygluosone (3-DG) and methylglyoxal (MGO) [5-7]. Non-oxidative rearrangement and hydrolysis of Amadori adduct forms 3-DG along with fructose-3-phosphate via polyol pathway [8,9]. Methylglyoxal is also formed from the oxidative decomposition of polyunsaturated fatty acids [10] and non-oxidative anaerobic glycolysis [11]. The accumulation and deposition of reactive di-carbonyl precursors of glycoxidation are termed as carbonyl stress [12,13]. The carbonyl comes from the accumulation of carbonyl precursors whether they enter into the formation of oxidative AGE such as CML and pentosidine or non -oxidative AGE via 3-DG {deoxyglucasone-lysine dimmer (DOLD)} or MGO [methyl glyoxal lysine dimmer (MOLD)] [14]. The structure of some AGE has been identified and characterized including CML, pentosidine, and praline. The well characterized AGE is immunologically distinct and coexists with several essential proteins such as albumin, hemoglobin, lens crystalline along with cholesterol [15]. It has been reported that 90 % of pentosidine and CML are albumin-bound AGE and only 10 % are in free form in circulation [16].

Apart from endogenous AGEs formed inside the body, AGEs, and their respective precursors are also taken from outside source known as exogenous AGEs. The exogenous AGEs sources include cigarette smoking and high heat cooked foods. Browning and excessive heating of cooked foods enhance its flavor, color, and aroma, but it also accelerates the generation of AGEs via Maillard reaction [17]. However, excessive AGEs are generated in foods exposed to dry heat (grilling, frying, roasting, baking and barbecuing) for a period of a long time [18]. The process of curing tobacco leaves readily enhances in-vivo AGEs formation. A literature reported glycotoxins by cigarette smoking transmit into alveoli, transported into the blood stream where they interact with circulating glycation product to enhance the AGEs formation [19]. Heat treatment improves food safety, bioavailability, and taste, but in addition to these useful effects, overheating of foods also provokes degradation of proteins and essential nutrients and gave birth to deteriorative reactions [20]. The growing evidence reflects that average Western diet pattern is plentiful of exogenous AGEs supply. The content of AGEs depends on the nutrient composition and way of food processing [21,22]. Previous findings were demonstrated with AGE-specific ELISA and estimated that around 10% of ingested exogenous immunoreactive AGEs are persisting in the circulation, among them, two-third remain in the body incorporated covalently into tissues, while only one-third is excreted via the kidneys [23].

However, a controversy is there about the deterioration effect of dietary AGEs to human health due to lack of characterization of heterogeneous AGEs class. In food science, the product of the last reaction is known as melanoidin [24]. As previously reported that regardless of AGEs diversity, carboxymethyl lysine (CML) has been reported as major in-vivo and also one of the AGEs characterized in foods (milk and milk products) therefore CML is chosen as an Ages marker in various studies related to foods and in-vivo [25]. Studies on the adverse effects of AGEs from food are not only restricted to CML, but melanoidins are also the main culprit in the bakery and coffee industry. A literature describes that melanoidins increased anaerobes, clostridia, and bifidobacteria [26]. Supplementation of malt and bread crust to the rats' diet increased the glutathione-S-transferase (GST) activity by 18% and UDP-GT by 27%, thus concluding that diet malt and dietary bread crust show chemopreventive enzyme activity in rats [27]. Besides the formation of endogenous AGEs, dietary AGEs have also represented RAGE ligand activity and initiate major signal transduction pathways in vitro [28,29]. Endogenous in combination with dietary AGEs promote a glycoxidant burden, oxidant stress and cell activation [30,31].

Previously published literatures have focussed on explaining the absorption, metabolism, and excretion of dietary exogenous AGEs. The phenomenon of intestinal absorption of AGEs is not yet well explained. A recent literature reported that proline is absorbed by peptide transporter known as hPEPT1 [32]. The level of serum AGEs depends on their endogenous production, an exogenous source of intake and renal enzymatic clearance, which plays an important role in the existence and removal of serum AGEs levels. Enzymes like glyoxalase I, II and carbonyl reductase, receptor (AGER1) have been found in detoxification and counter-regulation mechanism against president adverse effects of glycation [33,34]. Renal excretion effectively eliminates the excess of endogenous and exogenous AGEs.

Advanced glycation end products and complications of Diabetes Mellitus

The pathogenesis of diabetes-associated complications is the prime issue in current diabetes research [35]. One of the most prevalent metabolic syndromes worldwide is diabetes mellitus, proving an endemic to the global population. It is characterized by persistent hypoglycemia resulting in an alteration in metabolic pathways and homeostasis of lipids, proteins, and nucleic acids. These changes have widely contributed to the progression of diabetes-associated macro and micro-vascular complications in diabetes mellitus. The prolonged hyperglycemia initiates a devastating change in protein modifications that termed as glycation resulting in the formation of advanced glycation end products (AGEs) via Amadori mediated Maillard reaction. AGEs are a heterogeneous class of diverse and complex structures often unstable, highly reactive formed excessively during diabetes mellitus [36]. As stated by glaciation hypothesis deposition of AGEs alters the structural and functional characteristics of tissues proteins and homeostasis [37,38]. It has been reported that AGE formation is accelerated by hyperglycemia [39]. Some protein modifications observed in diabetes mellitus patients resemble those with older non-diabetic patients [40]. High quantity of pentosidine has been reported in patients with diabetes mellitus [41]. Inhibition of AGE-mediated cell injury has been proposed as a key element in the prevention of diabetes associated complication onsets [42]. With the time span, wide research was performed to understand the mechanism of AGEs related studies.

AGEs formation and protein glycation induced the combinatorial effect in the foster free radical generation mechanism that majorly contributes to Biomolecular damage in diabetes mellitus [37,43,44]. The literatures reflect that AGEs contribute to chemical and physical changes in human skin collagen in diabetes patients [45]. AGEs Crosslink's formation in collagen contributes to diabetic circulatory complications like stiffening of blood vessels and myocardial dysfunction [46]. Although the unifying mechanism of development of diabetes complications via AGEs mediated is not well established, the only culprit is the hyperglycemia that plays important role in progression of retinopathy, nephropathy, neuropathy and stiffness in joints [47,48]. Literature reported that reduced clearance rate enhances the level of serum and tissues AGEs in end-stage renal disease [37]. In-vitro and In-vivo studies also reported that AGEs results in irreversible cross-links formation in type IV collagen, laminin, and fibronectin [37].

The biochemistry of AGEs is implicated in the pathogenesis of diabetes mellitus associated long-term complications [49,50]. Hyperglycemia-induced tissue damage leads to irreversible changes. Intracellular hyperglycemia results in increased flux via diverse metabolic pathways enable impairment in glomerular basement membrane. Polyol pathway activation results in a decrease in NADPH, glutathione, and myoinositol level [51]. A prime consequence of hyperglycemia is enhanced non-enzymatic glycosylation of proteins leading to structural and functional impairments [52]. An elevated level of glycation adducts such as praline, pentosidine, and CML found to be increased in diabetic patients [52].

The pathogenesis of progression of diabetes-induced complications initiates with the binding of AGEs with their receptors. Several receptors of AGEs have been found, one of which known as RAGE that is well characterized and initiate the intracellular signaling disrupting cellular functions. RAGE is a member of the immunoglobulin super family of receptors [53,54]. Chromosome 6 of major histocompatibility complex located between class II and class III is responsible for human RAGE expression [55]. RAGE promoter sequences comprise of nuclear factor-β (NF-κ β), an interferon response element and IL-6 DNA binding motifs [56]. RAGE has 332 amino acid residues comprising of 2 "C" type domains preceded by 1 "V" type domains similarly like immunoglobulin followed by single transmembrane domain with 43-amino acid highly charged cytosolic tail [57]. The variable "V" domain N-terminus is the site for ligand binding whilst the cytosolic tail initiates the critical RAGE intracellular signaling [58].

RAGE may be complexed with other polypeptides like lactoferrin-L (LF-L) that shows noncovalent binding with AGEs to the extracellular domain [58]. RAGE upregulation occurs on binding with AGE initiating positive feedback activation on endothelial cells, smooth muscle cells along with mononuclear phagocytes in diabetes vasculature [57,59]. In diabetes complications RAGE binds to CML adduct and hydroimidazolones [60]. Other receptors like AGE-R1 (oligosaccharyl transferase-48) ,AGE-R2 (80K-H phosphoprotein) and AGE-R3 (galectin-3) along with macrophage scavenger receptor type I and II of class A have the ability to recognize and bind with AGE legends to transducer intracellular signaling cascade. The RAGE is widely distributed over the tissues that show adverse response over AGEs binding (Table 1).

Tissues	No. of RAGE	Tissues	No. of RAGE
Adipose Tissue	0	Liver	0
Adrenal Gland	0	Lung	144
Ascites	0	Lymph	0
Bladder	0	Lymph node	32
Blood	0	Mammary Gland	12
Bone	0	Mouth	0
Bone marrow	0	Muscles	0
Brain	0	Nerve	0
Cervix	0	Oesophagus	0
Connective tissue	26	Ovary	9
Ear	61	Pancreas	9
Embryonic tissue	4	Parathyroid	0
Heart	33	Pharnyx	0
Intestine	4	Pituitary gland	0
Larynx	0	Placenta	0
Prostate	10	Spleen	0
Salivary gland	0	Stomach	12
Skin	0	Testis	6
Thymus	12	Tonsil	0
Thyroid	0	Umbilical Cord	0

Table 1: Tissue distribution of RAGE expression.

The AGE-R1 receptor is type 1 single transmembrane protein with a small extracellular N-terminal domain along with cytoplasmic C-terminal domain [61]. AGE-R2, a tyrosine phosphorylated domain, with a size of 80-90 code located in the plasma membrane of cell severely involves in intracellular signaling of fibroblast growth factor receptor [62]. AGE-R3, C-terminus, highly binds to AGE ligands to initiate intracellular signaling [63]. CD36, class B type I along with two class B scavenger receptors have been also reported to bind with AGEs. A literature supported the expression of LOX-1 (lectin-like oxidized LDL receptor-1), a class E receptors upon binding with AGEs in diabetic rats [64,65]. The General phenomenon of AGEs induced diabetic complications includes (1) generation of cross-links among basement membrane of extracellular matrix (2) association of AGEs with RAGE on the cell surface. AGEs can impair characteristics of collagen, vitronectin, and laminin [66]. Non-enzymatic glycation initiates the synthesis of collagen type III, IV, V, VI, laminin and fibronectin in the extracellular matrix through upregulation of TGF [67-69]. Modification of laminin and type I, IV collagens upon glycation restrict the adhesion to endothelial cells for glycoproteins and matrix too [70]. Circulating AGEs in association with endothelial RAGEs leads to upregulation of transcription factor NF-κβ thereby inducing various cytokines and proinflammatory cytokines expression along with various endothelial factors [71]. Binding of AGEs to RAGE upregulate the expression of NAD (P) H oxidase, MAPKs, p21 ras along with kinase 1, p38, GTPases Cdc42 and Rac activating NF-κβ thereby initiating a cascade of complications [72-75]. Endogenously AGEs-albumin complex interact with vessel via the RAGE-mediated pathway, triggers the activation of NF-κβ [76], TNF-α, IL-1 [76] and IL-6 mRNA expression [76]. Some AGEs have been reported to alter the basement structure and functions [76]. In human kidney, podocytes were expressed for RAGE and cause several complications along with tubular epithelia. Literature has reported that increase in AGE fluorescence was found in hypoglycemic and hyperlipidemic mice. In diabetic retinopathy, RAGE-ligand complex was amplified within the retina along with a vitreoretinal interface [76].

Falsely elevated glycated adduct in diabetes patients

Sometimes the patients' encounters falsely elevated HbA1c levels. Several factors that affect the life span of erythrocyte may falsely give the glycation status in diabetes patients. Studies have done describing that iron deficiency may lower the levels of glycated HbA1c [77]. Similarly other factors including Asplenia, Uremia, Severe hypertriglyceridemia, Severe hyperbilirubinemia, Chronic alcohol consumption, Chronic salicylate ingestion, Chronic opioid ingestio, Lead poisoning, Anemia from acute or chronic blood loss, Splenomegaly, Pregnancy, Vitamin E ingestion, Ribavirin and interferon-alpha, Red blood cell transfusion, Hemoglobin variants, Vitamin C ingestion [78]. The all mentioned factors severely affect the level of glycated HbA1c and give false readings in patients with diabetes mellitus.

Conclusion

In conclusion, there is well and published evidence of the existence of AGEs in diabetes and its associated complications. Animal and several In-vitro studies have demonstrated that AGEs adversely affect the cellular signaling via RAGE-mediated mechanisms. A number of RAGEs need to be characterized to precisely describe the indulgement in the progression of complications of diabetes mellitus. The present review proves to be

connecting link between the chemistry of the Maillard reaction and biology of RAGE expression.

Conflict of Interest

The authors declare no conflict of interest.

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