A REVIEW ON ADVANCED GLYCATION END-PRODUCTS (AGE) AND THEIR ROLE IN DIABETES MELLITUS

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ABSTRACT

A complex and heterogeneous group of compounds known as "Advanced Glycation End-products (AGE)" have been associated with diabetes related complications. Till date it is not known if they are the cause or consequence of the complications observed. The chemistry of AGE formation and their patho-biochemistry particularly related to the diabetic microvascular complications of nephropathy, retinopathy and neuropathy also their role in the accelerated vasculopathy observed in diabetes are discussed. Also, the concept of carbonyl stress as a cause of AGE toxicity and the alterations in the concentrations of AGE in the body, particularly in relation to diabetes and its complications such as nephropathy are also mentioned and also along with age. We have also highlighted the problems relating to current methods of AGE detection and measurement which include the lack of a universally established method of detection or unit of measurement. A review of the agents used for the treatment of advanced glycation end-products accumulation is also mentioned.

KEYWORDS: Advanced glycated end-products(AGE), Diabetes mellitus, carbonyl stress, Maillard reaction, Amadori rearrangement.

INTRODUCTION

The food that we consume, containing carbohydrates is broken down to glucose in the stomach, with the help of the respective enzymes. The glucose then enters the blood stream and the glucose level is detected by the body. Now, the pancreas releases insulin hormones that help the glucose to enter the cells for energy production and thus the body glucose level decreases. But, then the liver also releases some extra stored glucose and again the pancreas release insulin to help the glucose enter the cells. Insulin and glucose both travel thru the blood stream, and thus, the body detects the glucose. It is the food that we intake, liver and pancreas that lead to and maintain the optimum balance of glucose in the body.

Diabetes (medically known as diabetes mellitus (DM**)**) is the name given to disorders in which the body has trouble regulating its blood sugar, or blood glucose levels. Diabetes is due to either the cells of the body not responding properly to the insulin produced or the pancreas not producing enough insulin.

Diabetes is the most common metabolic disorder affecting populations in all geographical regions of the world. The prevalence of diabetes is increasing in epidemic proportions especially in developing countries are projected by the World Health Organisation (WHO). India has the highest number of people with Diabetes in the World.

AGEs (Advanced Glycation End-products) affect nearly every type of cell and molecule in the body and are thought to be one factor in aging and some age-related chronic diseases. They are also believed to play a contributory role in the vascular complications of diabetes mellitus. All forms of diabetes increase the risk of long-term complications. These complications typically develop after many years (10–20), but may be the first symptom in those who have otherwise not received a diagnosis before that time. Under certain pathologic conditions, as hyperlipidemia and oxidative stress due to hyperglycemia in patients with diabetes; AGE formation increases beyond normal levels.

Thus, inhibiting the progress of AGE will in turn prevent the diabetic complications related to it.

ADVANCED GLYCATION END-PRODUCTS (AGE)

Formation and Structure of AGE

Glucose and other such reducing sugars, react with amino groups non-enzymatically in proteins, lipids and nucleic acids through a series of reactions. They form Schiff bases and Amadori products as intermediates which further produce AGE. This process is also known as Maillard reaction. It was described in the early

1900s, when it was noted that amino acids heated in the presence of reducing sugars developed a characteristic yellow-brown colour[15, 25].

The process of advanced glycation occurs over a period of weeks, and thus affects the long-lived proteins. The prime targets are structural components of the connective tissue matrix or basement membrane, such as collagen, but also can include myelin, complement C3, tubulin, plasminogen activator and fibrinogen[3, 32]. In cases such as uraemia, even shorter lived compounds such as lipid constituents and nucleic acids are affected[33].

The early stages of the Maillard reaction are concentration-dependent rather than the later stages for the glycation process and hence it is enhanced in Diabetes[11, 20]. The AGE formation is catalysed by transition metals and is inhibited by reducing compounds such as ascorbate[8]. Glucose has the slowest glycation rate, whereas intracellular sugars, such as glucose-6-phosphate and fructose, form AGE at a faster rate[2]. If oxidation accompanies glycation then the products formed are also known as glycoxidation products. The AGE pentosidine and N-[carboxymethyl]-lysine (CML) are such examples[2, 22].

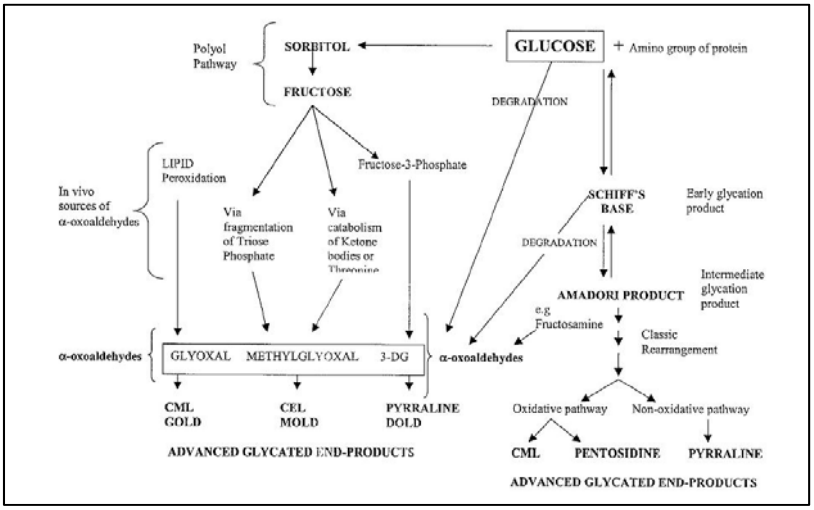
The most important step in the Maillard reaction is the formation of reactive intermediate products during Amadori rearrangement. These compounds are known as alpha-dicarbonyls or oxoaldehydes and include products such as 3-deoxyglucosone (3-DG) and methylglyoxal (MGO)[1, 29]. The 3-DG is formed by non-oxidative rearrangement and hydrolysis of Amadori adducts[1] and from fructose-3-phosphate which is a product of the polyol pathway[21, 27]. The latter has been implicated as one of the mechanisms that leads to Hyperglycemia induced damage in diabetes[23, 27]. Methylglyoxal is also formed from non-oxidative mechanisms in anaerobic glycolysis[30] and from oxidative decomposition of polyunsaturated fatty acids[31]. In addition, MGO can be derived from fructose by fragmentation of triphosphate or the catabolism of ketone bodies and threonine. Although such products have been derived principally by non-oxidative stress and cellular apoptosis.

Methylglyoxal, 3-DG and glyoxal have recently been proposed to be formed from all stages of the glycation process from Amadori products such as fructosamine in the intermediate stages of glycation or by degradation of glucose of Schiff's base in early glycation,. Thus alpha-oxoaldahydes could be considered as important focal points of how glucose can go on to form AGE by the classical Maillard reaction, the polyol pathway, as well as from in vivo factors such as the catabolism of ketone bodies and threomine, and lipid peroxidation.

The accumulation of reactive di-carbonyl precursors or of glycoxidation or both and the lipoxidation products is termed as carbonyl stress. That is, the accumulation of carbonyl precursors whether they go on to form oxidative AGE such as CML and pentosidine or non-oxidative AGE derived from 3-DG or MGO[9]. This recently described phenomenon of carbonyl stress has been observed in both diabetes and uraemia and has been implicated in the accelerated vascular damage observed in both conditions[25].

The structure of some AGE have been identified including CML, pentosidine and pyraline. Furoyl-furanyl imidazole (FFI) was considered an AGE but has subsequently been shown to be an artefact of sample preparation[35]. The known AGE are immunologically distinct and coexist on different carrier proteins such as albumin, haemoglobin, lens crystalline and LDL cholesterol[8]. In blood 90% of pentosidine and CML are protein bound to albumin with 10% being free.

Pentosidine and CML are the best characterised as AGE and are referred to as glycoxidation products. Evidence for this comes from in vivo experiments in which antoxidants resulted in a reduction in CML formation. Metal catalysed oxidation of polyunsaturated fatty acids in the presence of proteins can also lead to CML formation suggesting that lipid oxidation has a role in AGE formation. Therefore, CML should serve as a general biomarker of oxidative stress resulting from carbohydrate and lipid oxidative reactions[10].

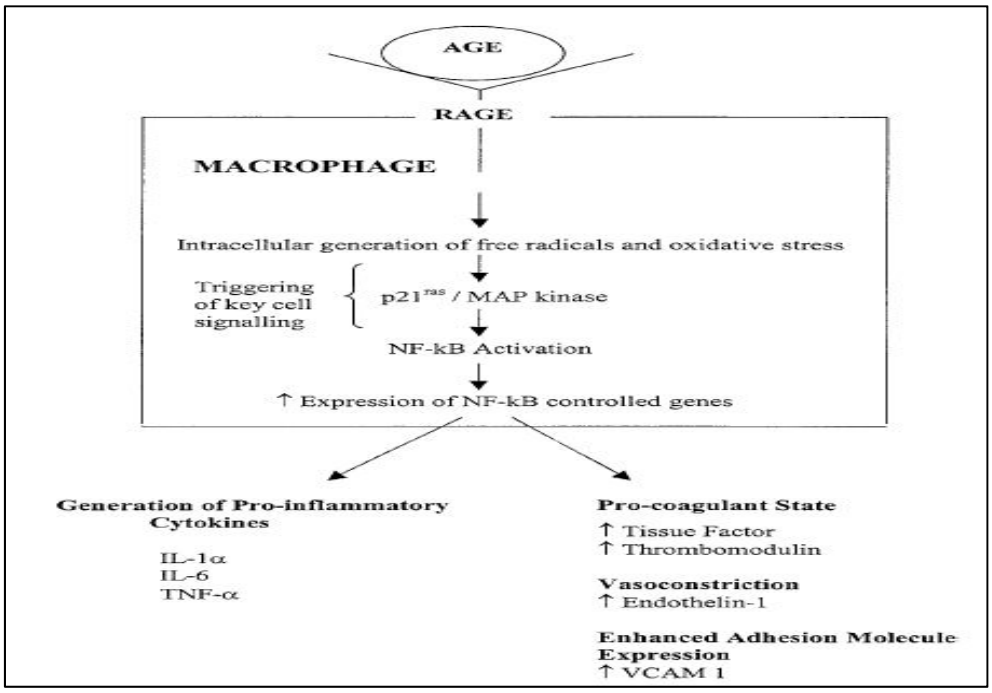


AGE receptors and Binding proteins

Nearly a decade ago, it was observed that a distinct macrophage AGE-receptor system recognized the AGEs formed both those in vivo and those synthesized in vitro. The two AGE-binding proteins, a 60kDa and a 90kDa of apparently unique amino acid sequence, that were isolated from rat liver membranes, and were initially identified on rat monocyte/macrophage surfaces, recently reported to be highly homologous to two independently cloned proteins, oligosaccaharyl transferase-48 (OST-48) and 80 K-H phosphoprotein. OST-48 was originally described in canine rough endoplasmic reticulum membranes, is now found on cell-surface membrane, exhibiting AGE-binding activity whereas the 80K-H phosphoprotein was described as a substrate for protein kinase C, raised the possibility of a role in intracellular signalling leading to activation and cytokine and growth factor secretion associated with AGEs[36].

Additional cell-surface binding proteins for AGE determinants have been identified and cloned from other tissues and cells of interest. RAGE a 35-kDa member of the immunoglobulin superfamily of receptors, consisting of endothelium, and an 80-kDa protein homologous to lactoferrin has been identified. The presence of RAGE on monocytes and in a variety of tissues, including neural tissues and skeletal and smooth muscle was confirmed using immunohistochemical and in situ hybridization techniques[4].

In vitro studies have shown that AGE-RAGE binding on macrophages and microglia leads to oxidant stress and activation of the transcription factor NF-xB[17]. This process involves the activation of the (p21)^ras/MAP kinase signalling cascade, which then activates NF-xB. Evidence for this comes from inhibition of (p21)^ras which blocks NF-xB activation[17]. The NF-xB is a free radical sensitive transcription factor that modulates gene transcription for endothelin-1, VCAM-1, tissue factor and thrombodulin[2]. It has also been linked to states of antioxidant depletion induced by AGE, with a reduction in glutathione, vitamin C and nitric oxide. Further evidence of an interaction between AGE and the NF-xB pathway can be shown from in-vitro studies using hyaluronic acid, which is a glycosaminoglycan polymer that inhibits age-induced activation of NF-xB and NF-xB regulated release of TNF α , IL-1α and IL-6.



Another molecule has recently been added to the AGE-recognizing proteins. A 32-kDa protein, now referred to as Galectin-3, but previously known as Mac-2 or carbohydrate binding protein-35 (CBP-35), is expressed on macrophages and other cells and exhibits high-affinity binding for AGE ligands *(K(l* 3.5 X 10' M"1) compared with that of other carbohydrates *(Ka* 1 X 104 *Mr1)*[34]. Binding of AGE to Galectin-3 occurs within the 18-kDa COOH-terminal peptide and promotes high molecular- weight complex formation with the AGE ligand and with other membrane-associated receptor molecules on the cell surface. This complex formation involves the attack on a thiol ester of Galectin-3 by nucleophilic groups present on AGE proteins[18].

Measurement of AGE

Although there is no universally established unit of measurement, it has recently been proposed to adopt a universal unit of measurement for different laboratories to compare results. The lack of internal standards leaves assay open to error which require a high degree of accuracy and reproducibility for each sample run.

Currently the most common methods used for detection are:

- HPLC(High-performance liquid chromatography)
- ELISA(Enzyme-linked immunosorbent assay)
- Immunohistochemistry

Recently a monoclonal antibody which recognises CML, called 6D12, has become commercially available[14].

AGE Concentrations in Diabetes

Diabetic animal models have shown that AGE concentrations increase within a few weeks after the animal is rendered diabetic and that this increase is systemic, occurring in the kidneys, skin and vascular tissue[1].

Using HPLC methods, the concentrations of AGE such as CML and pentosidine rise with age and are approximately doubled in diabetes, correlating with the severity of diabetic microvascular disease[24].

The AGE concentrations have been compared in diabetic subjects with or without ESRD. Some of the earlier studies using ELISA methods found that diabetic subjects with ESRD had up to a 100-fold increase in serum AGE, compared with those with normal renal function[19].

CONSEQUENCES OF AGE FORMATION IN DIABETES

Microvascular complications such as retinopathy, neuropathy, nephropathy and microvascular disease are manifested by accelerated vascular damage associated with diabetes. Although the mechanisms leading to such complications are not fully understood, three pathways have been proposed:

- Activation of protein kinase C isoforms
- The aldose reductase pathway
- AGE formation

Hyperglycaemia that is associated with diabetes, increases production of reactive oxygen species and leads to a state of oxidative stress[7]. Superoxide anion, hydrogen peroxide, lipid peroxides and other such oxidants cause damage by oxidation, fragmentation and cross-linking[3].

Free-radical production as well as depleting nitric oxide concentrations is induced by formation of AGE that leads to oxidative stress[7]. AGE accumulation results in vascular thickening with loss of elasticity, endothelial dysfunction and hypertension as nitric oxide is vasodilatory and has antiproliferative effects on vascular smooth muscle[3].

Diabetic Retinopathy:

It is characterised by abnormal vessel development leading to haemorrhages, ischaemia and infarctions. Specific morphological and functional changes include basement membrane thickening, loss of pericytes and increased permeability[8]. Accumulation of AGE contributes to this state of vaculopathy by increasing retinal endothelial cell permeability resulting in vascular leakage. Vessel wall thickening and coagulation, leads to occlusion and ischemia.Structural changes in Lens crystalline result in increase in opacity and blindness. Immunohistochemistry has been used to examine the spatial and temporal distribution of AGE in diabetic and non-diabetic rat retinas.The CML immunoreactivity was greater in diabetic rats than in control rats and was mostly present in neurological elements of the retina[13].

Diabetic Neuropathy:

It is both common and complex in its aetiology and manifestations. All the major nervous systems in the body can be affected including the central, autonomic and peripheral nervous systems. As with retinopathy, diabetic neuropathy manifests according to the concentration of diabetic control and duration. A number of complex interactions are involved in producing diabetic neuropathy including:

- Metabolic abnormalities
- Functional abnormalities
- Structural abnormalities

Evidence of vascular dysfunction includes accumulation of AGE in the vasa nervorum leading to wall thickening, ischaemia, occlusion and myelin damage with segmental demyelination.

In-vitro studies show that glycation of axonal cytoskeletal proteins such as tubulin, actin and nuerofilament results in slowed axonal transport, atrophy and degeneration[27].

In addition, glycation of laminin, an important constituent of Schwann cell basal laminae, impairs its ability to promote nerve fibre regeneration.

Advanced glycation has also been reported to affect growth factors such as fibrin and nerve growth factors such as fibrin and nerve growth factors, causing a loss of function[2].

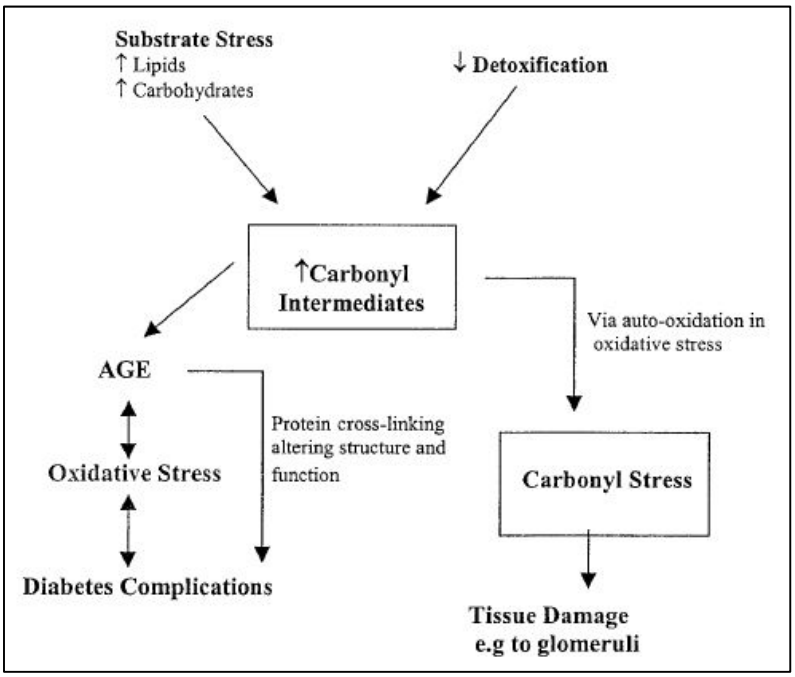
To compare peripheral nerves from both human diabetic and control subjects Immunoperoxidase staining methods for CML have been used. The CML was detected in the perineurium, endothelial cells, pericytes of

endoneurial microvessels as well as in myelinated and unmyelinated fibres of diabetic subjects compared with control subjects. Thus a correlation between the intensity of CML accumulation and myelinated fibre loss suggesting the role for advanced glycation in Diabetic neuropathy was noticed[12].

Diabetic Nephropathy:

Diabetic nephropathy can lead to basement membrane thickening, vascular leakage and glomerulosclerosis by its histological feature of expansion of the extracellular matrix is one of the dominant histological features of diabetic nephropathy[8]. In-vitro studies using rat mesangial cells have recently shown that mesangial oxidative stress and activation of protein kinase C-β is a result of exposure to AGE-rich protein. These results show that activation of protein kinase C isoforms have been associated in the mechanism of cause of diabetic complications in diabetic animal models[26].

A number of AGE such as CML, pyrraline and pentosidine have been identified in the renal tissue of diabetic patients with or without ESRD, with AGE accumulation increasing the severity of diabetic nephropathy. Immunochemistry using diabetic rat models has shown AGE concentrations rising with age and more rapidly with diabetes and accumulates in the glomerular extracellular matrix[5].



AGE, Lipids and Diabetic Atherosclerotic disease:

A dyslipidemia characterized by increased levels of LDL, VLDL, and intermediate-density lipoprotein is not only common in diabetic patients but also increases the likelihood that these patients will suffer from the atherosclerotic complications of heart attack and stroke. LDL is the major lipoprotein component responsible for transferring both exogenously absorbed and endogenously synthesized lipids to peripheral tissues. Biochemical modifications that affect the structural and functional integrity of LDL are believed to be central to atherogenesis.

Advanced glycation has shown that it results in a new class of chemical modifications that can render it more atherogenic, in addition to the oxidative modification that has been shown to affect the clearance of LDL[6].

AGE have been observed in atherosclerotic lesions from diabetic subjects using ELISA and immunohistochemistry. A correlation has also been shown between tissue AGE concentrations and the severity of atherosclerotic lesions. Susceptibility to atherosclerotic lesion formation by AGE has been shown by in-vitro studies indicating endothelial dysfunction manifesting as changes in vascular permeability, coagulation and increased adherence or migration of macrophages and T-lymphocytes into the intima, with the initiation of a prolonged sub-inflammatory reponse[35]. Endothelial migration of monocytes, considered to be the first step in atherogensis, is dependent on the upregulation of vascular cell adhesion molecule-1 (VCAM-1) expression. AGE have been shown to increase the VCAM-1 expression[16].

AGE INHIBITON

Progression to protein cross-links requires slow rearrangement reactions to create reactive intermediates that then react directly with additional amino groups, thus the formation of Amadori products represent an important branch-point in advanced glycation chemistry. This suggested a possible pharmacological tactic for interfering

in advanced glycation before progression to irreversible cross-linking occurs. In 1986, the small nucleophilic compound aminoguanidine was shown to be a potent and specific inhibitor of glucose-mediated cross-linking and tissue damage in vivo[6].

By virtue of its low pKa, the terminal amino group of aminoguanidine reacts specifically with glucose-derived reactive intermediates and prevents protein-protein or protein-lipid cross-links from forming. This mechanism of action of aminoguanidine have been avowed by recently performed experimental studies. A number of studies have demonstrated an efficacious role for aminoguanidine in preventing either AGE formation or diabetes-related complications in-vivo.

Drugs that reported to show inhibition of AGE[28]:

SR. NO.	DRUG OR AGENT	CHEMICAL TYPE	METHOD OF ACTION
1.	Aminoguanidine	Hydrazine	Traps reactive di-carbonyls impeding conversion to AGE Prevents cross-link formation Inhibits free radical formation, lipid peroxidation and oxidant induced apoptosis
2.	Vitamin C & E, Nicarnitine	Antioxidants	Inhibits oxidative conversion involved in di-carbonyl and AGE formation
3.	A717	Monoclonal antibody	Acts on Amadori adducts containing albumin
4.	Pyrodorin(Pyridoxamine)	Amadorin	Inhibitor of the conversion of Amadori intermediates to AGE
5.	Phenacyl Thiazolium Bromide	Thiazolium compound	A coss link breaker that could cleave di-ketone brodges between 2 adjacent carbonyl groups which could form intermolecular cross-links
6.	2Isopropyldenehydrazone-4-oxo-thiazolidin-5-ylacetanalide	Synthetic Thiazolidine Derivative	Reduced Age accumulation in glomeruli Thought to work by suppressing TGF-beta ab\nd VEGF expressuion
7.	Pyruvate	Alpha-keto acid	Hypothesised to prevent glycation of protein competitively by forming a Schiff base Also inhibits oxidative conversion of the initial glycation product to an AGE

CONCLUSION

Thus, we can conclude that there is increasing evidence of the presence of AGE in diabetes and its complications. AGE affects cellular signalling, activation of transcription factors and subsequent gene expression has been shown through animal and in-vitro studies. A number of receptors for AGE have been identified but their physiological roles need to be determined. The role of AGE and specifically which particular AGE is involved in the cause or set of causes of diabetic micro and macrovascular complications is, however, yet to be established. In the face of these concerns the drugs that reduce AGE accumulation could benefit subjects with Type I diabetes. Further trials are required in Type II diabetic subjects and patients with ESRD with or without diabetes. The importance of detecting AGE and advancements in measuring AGE using reliable methods will help determine the role they have in the pathogenesis of many diseases, especially Diabetes and its complications.

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