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ADVANCED GLYCATED END PRODUCTS: A REVIEW

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ABSTRACT

Chronic diabetes leads to the development of complications. One of the major mechanisms of development of these complications is the formation of advanced glycation end products (AGEs). The free amino groups of proteins, lipids and guanyl nucleotides in DNA react with reducing sugars to form AGEs endogenously. These AGEs accumulate in longlived proteins of tissues causes cross linking and develops inflammation and thickening of basement membranes. This leads to the development of complications like retinopathy, neuropathy, nephropathy and atherosclerosis. The present review describes about the endogenous and exogenous source of AGEs, metabolism of AGEs, receptors for AGEs (RAGEs) and complications of AGEs and their measurement.

Keywords: Diabetic complications, Advanced Glycation End Products (AGEs), RAGEs

Advanced glycation end products (AGEs):

Advanced glycation end products (AGEs) are defined as the amine containing molecules which are formed through the nonenzymatic reaction between the reducing sugars and free amino groups of proteins, lipids and guanyl nucleotides in DNA. This process is known as Millard reaction.

In AGE mediated diabetes, the cells are unable to utilize the excess glucose (Dominiczak MH et al., 2003; Brownlee M et al., 2005; Gugliucci A et al., 2000).So, excess amount of NADH and $FADH^+$ will be formed which increases the function of mitochondria i.e., electron transport chain. Thereby, there is an excess buildup of proton gradient across the transport chain at which complex-III stops this electron transport chain (Topol et al., 2006). Then, reactive oxygen species will be produced by mitochondria, which activates PARP1 by damaging DNA. PARP1 inactivates a protein involved in glucose metabolism i.e. GAPDH through ADP ribosylation which results in accumulation of previously formed metabolites in the metabolic pathway. Thus these accumulated metabolites activate production of AGE through one of the multiple pathogenic mechanisms.

Sources of AGEs:

The natural sources for the production of AGEs are sugars, lipids (Bucala R et al., 1995) and nucleic acids (Brownlee M et al., 2011). The naturally occurring sugars like glucose, fructose, fructose-6 phosphate, glyceraldehyde-3 phosphate and threose form AGEs. Of these glucose shows slowest glycation rate when compared to the later ones (Suarez G et al., 1989).

The entry of AGEs in to the circulation of human body exogenously by means of nutrients (Koschinsky T et al., 1997) or tobacco smoking (Cerami C et al., 1997) at the time or before diabetes. Food processing methods like heating (boiling, searing or frying) and dehydration will significantly accelerate the formation of protein and lipid-AGE contents of food. Most of the exogenously ingested AGE is involved in the related pathology of diabetes (O'Brien Jet al., 1989; Cai W et al., 2002).

Normally AGEs will form during ageing via both milliard reaction and lipid peroxidation. But AGE production accelerates during diabetes when compared to ageing (Koschinsky T et al., 1997; Cai W et al., 2004).

Recent investigations revealed that modern diet contains AGE and related precursors which are mainly occurred due to processing of food to impart safety, conservation and improving its taste, flavor and appearance (Uribarri J et al., 2011; Goldberg T et al., 2004). This leads to the generation of different unstable a-β-dicarbonyl derivatives of glycoxidation and lipoxidation reactions. Among these CML and MG derivatives are found in most foods where CML is used as a marker to estimate the AGEs generation in over 200 common foods. The formation of AGEs depends on content and type of nutrients present in food (Brownlee M., 2001). The order for the rate of formation of AGE is fats, proteins, and carbohydrates respectively (Vlassara H et al., 2002; Peppa M et al., 2004).

Biology of advanced glycation:

AGEs are the rearrangement products of the Schiff base adducts which were formed by the reaction between sugar and free amino group. This rearrangement is known as Amadori rearrangement. The levels of

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Amadori products are higher in diabetic patients when compared to normal individuals (Monnier et al., 1986). This is mainly due to the reversible nature of Amadori products. Because of the highly basic nature of lysine and arginine they preferably undergo glycation modifications although they can present on lipids and DNA. Further they spontaneously undergo a series of reactions and rearrangements to form reactive products with different crosslinking, pigmentation and fluorescence properties (Baynes et al., 1989). The precursor molecules required for the formation of AGE products have different structure which indicates the heterogencity of AGE structure. For example, In Metal catalyzed reactions, the Amadori intermediate lead to "glycoxidation" irreversible products such as *N* Carboxy Methylated Lysine (CML) or *N*-(Carboxyethyl) lysine (CEL) (Ahmed et al., 1986; WellsKnecht et al., 1995).These adducts give rise to the formation of dicarbonyl products which are highly reactive and they accumulate on the substrate with the help of attachment. Because of their natural fluorescent property CML and pentosidine are readily detectable as markers for AGE accumulation in various tissues like eyes, kidney, nerves etc. In hyperglycemia, up regulation of highly reactive intermediate dicarbonyls are formed. e.g.: 1-, 3-, or 4-deoxyglucosones, glyoxal, and methylglyoxal and these intermediate molecules combine with proteins and leads to AGE (Thornalley et al., 1999; Thornalley et al., 1990) which is a rearranged product by either intramolecular or intermolecularly. Most of these adducts of AGEs are accumulated excessively in diabetic tissues and cells (Baynes JW et al., 2000). Apart from these reactions advanced lipoxidation end products plays a vital role in the emergence of diabetic complications. Accumulation of these end products in various blood vessels that underlying different organs will lead to both micro vascular and macro vascular complications in diabetes. Normally these AGEs are constantly removed by receptor systems to minimize their harmful effects (Vlassara H et al., 2001;Schmidt AM et al., 2000). The adverse effects caused by binding of advanced glycation are mediated by the AGE-receptors (RAGE) (Schmidt AM et al.,1994). Structurally, AGE receptor comprises three components (AGE-RC: AGE-R1, -R2, -R3) (Stitt AW et al., 1999; Stitt AWet al., 2000) together forms an AGE receptor complex and the type I and II scavenger receptor (Horiuchi S et al., 1996). These receptors either promote or limit AGE mediated cell and tissue dysfunction.

Metabolism of AGEs:

Normally AGEs are at steady state concentration in our body. Catabolically AGE is dependent on a protein source i.e. from tissue degradation and renal elimination. Therefore equilibrium is maintained between the circulating AGEs and oral intake, endogenous formation, and its catabolism including tissue degradation and renal elimination.

AGEs thus far activates various cells and causes tissue injury by increasing reactive oxygen species. All these processes acts through receptors for AGEs, although they have different ligands, RAGEs have specific actions mediated by AGEs. Another type of receptors is present normally to protect cells from oxidant injury acts by degrading AGEs. There are different kinds of AGE receptors are present, of these the most prominent one that has most promising anti-oxidant and anti-inflammatory properties is Advanced Glycated End-Product Receptor 1 (AGER1) (Vlassara H et al., 2009; Cai W et al., 2010). So, in order to maintain homeostasis of oxidants the balance between these two receptors is very crucial. Sirtuin (silent mating type information regulation 2 homolog) 1 (SIRT1), is a deacetylase enzyme, which is essential for the regulation of inflammation and actions of insulin. AGER1 protects sirtuin. But eventually both AGER1 and SIRT1 actions are suppressed in chronic diabetes. Good thing is that it can be reversible after lowering external oxidant burden by AGE restriction. In contrast to other peptides AGE peptides can cross the glomerular membrane and undergo reabsorption and further catabolism by renal proximal tubule, the remaining is excreted through urine. AGEs undergo proteolysis and produces AGE peptides and "AGE free adducts" (AGE adducts bound to single amino acids), which are easily excretable through urine. In chronic diabetes resistance will develop to the extracellular matrix proteins towards proteolysis. Therefore, it is difficult to eliminate the un-metabolized AGEs. Some of the AGE free adducts are reabsorbed through lumen of nephron. Some of the AGEs gets degraded to AGE peptides through endolysosomal system present in the epithelial cells of proximal tubule, which are further lysed to AGE free adducts (Gugliucci A et al., 1996) as single amino acids. This is so far another way to eliminate the excess AGEs as its simplest forms i.e. amino acids through urine. But in diabetes the above mentioned process fails to eliminate AGE (Gugliucci A et al., 1996) which results in its accumulation in plasma of patients with chronic renal failure. Peripheral macrophages, (Gugliucci A et al., 1996) liver sinusoidal endothelial cells and kuppfer's cells (Smedsrod B et al., 1997) are involved in the degradation of extracellular AGE proteins (which are much larger than usual) to AGE peptides and AGE free adducts (Svistounov D et al., 2004).

The same process occurs in the conversion of tissue level AGE in to low molecular weight AGE peptides. Therefore, it is essential to keep the renal function normal to eliminate these AGEs. (Vlassara H et al., 2001; Makita Z et al.,1991). There are some protective systems which limits the harmful accumulation of AGEs and its derivatives at the cellular level. AGEs damages various tissues by either crosslinking with structural proteins and lipids which further disrupts the membrane or by interacting with both specific and non-specific for AGE cell surface receptors. Altogether leading to intracellular events that induce oxidative stress and inflammation.

Receptors of AGEs:

Structurally RAGE is a 3kd transmembrane receptor which belongs to immunoglobulin super family(Neeper M et al., 1992). These receptors are able to bind AGE especially glycoprotein glycan. So they are also named as AGER. They are also considered as pattern

recognition receptors since they are able to recognize a class of ligands through a common motif. These receptors contain at least one agonistic ligand; HMGB1 (DNA binding protein) which is playing a key role in remodeling of chromatin which can be released by necrotic cells passively and active secretion from macrophage, NK cells and dendritic cells. Proinflammation reactions are initiated due to the interaction of RAGE(Bierhaus A et al., 2001) with their ligands. In diabetes and other chronic disorders AGEs formation is increased thereby much more interaction is there between RAGE and AGEs results in hypothesized RAGE to cause inflammatory diseases such as diabetic complications, Alzheimer's and some tumors.

Most of the receptors have the transmembrane and signaling domain to elicit the ligands action on various organ systems of our body. But these are absent in certain isoforms of the RAGE protein. Thus RAGE is hypothesized to reverse the default action of a complete receptor and is believed to provide a way to provide a cure for RAGE mediated diseases and complications. Most of the receptors play a key role in signal transduction but these receptors mostly participate in the elimination of AGE. There are several AGE receptors are present. They are

- SR-A (Macrophage scavenger receptor Type I and II)
- OST-48 (Oligosaccharyl transferase-4) (AGE-R1)
- 80 K-H phosphoprotein (Protein Kinase C substrate) (AGE-R2)
- Galectin-3 (AGE-R3)
- LOX-1 (Lectin-like oxidized low density lipoprotein receptor-1)

Antagonists for AGEs:

The most possible mechanisms to antagonize the AGEs and its formation are

1) By inhibiting the post Amadori advanced glycation reactions or
2) By trapping carbonyl intermediates (glyoxal, MG, and 3-deoxyglucosone)

e.g. aminoguanidine-hydrochloride form, benfotiamine (Pomero F et al; 2001) and pyridoxamine (Thornalley PJ, 2005) Williams ME et al; 2007).

Most of the investigations revealed that various antioxidants also acts as anti-AGE agents which includes vitamin E, N-acetylcysteine(Nakayama Met al., 1999), taurine(Trachtman H et al., 1994), alpha lipoic acid, (Kunt T et al., 1999) penicillamine, (Jakus V et al., 1999) nicarnitine (Hammes HP et al., 1997) etc. but the effectiveness of antioxidants as antiAGE agents are yet to be established.

Another mechanism is to breakdown the pre accumulated AGE or existing crosslinks, into AGE peptides and then AGE adducts which are simpler forms of AGE that can be easily passes through urinee.g. PTB (N-phenylthiazolium bromide)131 and ALT-711(Forbes JM et al., 2003). Recent studies revealed that some of the antihypertensive agents like losartan, olmesartan and hydralazine, seem to inhibit AGE formation. These AGEs were leading to the various complications like

Retinopathy:

In chronic diabetes, due to hyperglycemia excess amount AGEs are formed and crosslinks with certain proteins which leads to damage of tissues. So, accumulation of AGEs in retinal blood vessels damages eye ultimately causes permanent blindness. According to diabetes statistics, 80% of the patients suffering with diabetes are prone to retinopathy (Kertes PJ et al., 2007). Fortunately, initial treatment itself reduces 90% of the retinopathy cases (Tapp RJ et al., 2007). Scientific causes of retinopathy are as follows.

1) Accumulation of glucose and its metabolites due to hyperglycemia causes micro vascular retinal changes which leads to intramural pericyte death and thickening of basement membrane of retina.
2) Increase in permeability of retinal blood vessels by the damage of blood retinal barrier (Pardianto G et al., 2005). This leads to micro vascular complications.

Hyperglycemia activates protein kinase C-□ and p38 MAPK which further increases the expression of PKC-□ signal. This signaling causes the initiation of apoptotic death of intramural pericytes. SHP-1(protein tyrosine phosphatase) causes PDGF receptor de-phosphorylation and reduction in downstream signaling also leads to pericyte apoptosis (Geraldes et al., 2009). Small blood vessels in eye are unable to tolerate high glucose levels in blood which damages tiny blood vessels in retina. The initial stage itself considered as non-proliferative diabetic retinopathy, since there are no signs of change in eye sight.

Due to increase in permeability of damaged blood vessels most of the fluid and lipids will accumulate in macula and finally leads to swelling of macular tissue. This causes blurred vision which is known as macular edema.

AGEs alter the small wall integrity and structure by inducing cytokines, growth factors and increased oxidative stress (Yamagishi Set al., 2002; Stitt AW et al., 2001). Degree of retinopathy can be assessed by measuring the levels of CML and AGEs in retinal blood vessels. This phenomenon can be studied in rodents by inducing AGE albumin. Thereby AGE adducts accumulate in and around pericytes co-localize with RAGEs which thickens the basement membrane and finally causes retinal damage by break down of blood retinal barrier (Stitt AW et al., 1997; Stitt AW et al., 2000). AGEs abnormalizes the endothelial nitric oxide production which creates problems in retinal microcirculation especially in diabetes (Chakravarthy U et al., 1998).

AGEs potentially promoting the retinal neovascularization when they exposed to VEGF in retinal cells by inducing oxidative stress (LuM,KurokiM et al;1998), PKC pathway and abnormal eNOS expression which increase permeability to proteins across the retinal barrier (Mamputu JC et al., 2002) (Chakravarthy U et al., 1998).

In diabetes induced rats of 8 months old due to persistent hyperglycemia AGEs accumulated in vascular membrane and also in pericytes (Stitt AW et al., 1997).

Even, it was proved by administration of AGE albumin to non-diabetic animals shows the same effect of accumulation around and within the pericytes, colocalized with AGE receptors inducing retinal vessel wall thickening and loss of retinal pericytes. (Clements RS Jr et al., 1998) (Xu X et al., 2003)

In humans, due to increased accumulation of glycated vitreous collagen (Koga K., 2002) and glycosylation products in retinal vessels of diabetic patients, increasing with severity of retinopathy (Sulochana KN et al., 2003). In diabetic retinopathy cataract (Hammes HP et al., 1991) (Swamy-Mruthinti S et al., 1999) formation is very common which shows the glycation of Na-K-ATPase pump alters the integrity and function of lens membrane (Matsumoto K et al., 1997) (Zhao W et al., 2000). This can be recovered by pyruvate administration (Matsumoto K et al., 1997). Similarly, diabetic keratopathy is seen with glycation of corneal epithelial cells which reduces their cell adhesion and spreading.In diabetes, vitreous liquefaction and posterior vitreous detachment occurs due to glycation of vitreal collagen fibrils results in dissociation from hyaluronan and further destabilization of gel structure (Stitt AW et al., 1997) (Sebag J et al., 1992).

Neuropathy:

A group of neuropathic disorders associated with diabetes mellitus is known as diabetic neuropathy. Diabetic neuropathy is mainly due to injury to the small blood vessels supplies neurons i.e. micro vascular injury and some of the macro vascular condition. Disorders associated with neuropathy are as follows:

- Third nerve plasy
- Mono neuropathy
- Mono neuropathy multiplex
- Diabetic amyotrophy
- Painful poly neuropathy
- Autonomic neuropathy
- Thoraco abdominal neuropathy

In diabetic neuropathy hyperglycemia causes glycation of nerve proteins which alters neuron structure and function. This slowdowns the sensory motor conduction velocity and blood flow to peripheral neurons. The mechanism linking with micro-angiopathy and neuropathy is AGE-RAGE axis which is proved by co-localization of CML, RAGE, NF-kB and IL-6 to epineurial vessels, perineurium and endoneurial vessels. When AGE binds to RAGE it doubles the effect of hyperglycemia by increasing the expression of NF-kB and IL-6 in sciatic nerve studies. This is proved by measuring the AGE markers CML in dorsal root ganglia. Pretreatment with AGE inhibitors prevents the slowing sensory motor conduction velocities and nerve action potentials in peripheral nerve blood flow of diabetic rats.
In humans, increase in AGE by excessive glycation of cytoskeletal and myelin proteins (Dyck PJ et al., 1997) (Boel E et al., 1995) of the sural and peroneal nerves results in loss of integrity and function of the basement membranes of perineurium cells of both myelinated and non-myelinated nerve fibers correlated with the myelinated fiber loss. This segmental demyelination bycausing vascular abnormalities.

Nephropathy:

Diabetic nephropathy is a progressive kidney disease which is caused by “angiopathy of capillaries” in kidney glomeruli. Nephropathy is also known as kimmelsteil-wilson syndrome, nodular diabetic glomerulosclerosisand inter capillary glomerulonephritis. Earliest detectable change in nephropathy is thickening in glomerulus which allows more serum albumin reported as albuminuria. This complication is known as microalbiminuria. Albumin content in urine is act as a marker for the severity of nephropathy. Kidney biopsy at this stage clearly shows nephropathy.

The Armani-Ebstein cells contains deposits of glycogen in the pars straight of proximal convoluted tubule and loop of Henle. This change happens when glycaemia superior to 500mg/dL and severe glycosuria which is reversible alteration without functional manifestations. This leads to unspecific chronic changes in interstitium. End stage renal disease (Ritz E et al; 1999) also occurs due to diabetic nephropathy.

Since the kidney is the major site for clearance of AGEs, where due to cross linking of proteins the structural integrity and function of nephron impairs progressively (Miyata T et al; 1991). AGE receptors are found in renal mesangial cells. The ligand receptor interaction of AGE and RAGE stimulates the overproduction of matrix proteins and change in the expression of matrix metallo proteinases and proteinase inhibitors (Doi T et al., 1992) (Yamagishi S et al., 2002), whereas induction of mesangial oxidative stress leads to activation of protein kinase C-β (Scivittaro V et al., 2002). This causes secretion and apoptosis of VEGF and MCP-1. Anti-AGE agent which prevents the above process is N-acetyl cysteine(Yamagishi S et al., 2002).

In vivo, animal studies have clearly describes the pathogenic role for AGEs and RAGE in diabetic nephropathy. Diabetic animals have significant increases in renal AGEs (Soulis-Liparota T et al.,1995), and these abnormalities have been linked to various structural aspects of diabetic nephropathy, including glomerular basement membrane thickening, mesangial expansion, glomerulosclerosis, and tubulointerstitial fibrosis (Oldfield MD et al., 2001). Administration of AGE albumin in murine models has resulted in changes similar to that observed in diabetic nephropathy, including glomerular basement membrane thickening, mesangial matrix expansion, and increased collagen IV and TGF-β expression (Vlassara H et al., 1994). The strongest evidence of a role for AGEs in the development of diabetic nephropathy has come from studies targeting the AGE-RAGE pathway. Specifically, renal pathological changes are reduced by AGE formation inhibitors such as amino guanidine. (Soulis-Liparota T et al., 1995), (±)-2-isopropylidenehydrazono-4-oxo-thiazolidin-5 ylacetanidilide (OPB-9195) (Tsuchida Ket al., 1999) , and ALT-946 (Forbes JM et al., 2001), as well as with agents that are postulated to reduceAGEaccumulation such as the putative cross-link breaker ALT-711, also known as alagebrium (Forbes JM et al., 2003). Treatments

targeting RAGE such as sRAGE, which acts as an endogenous antagonist to the full-length receptor (Wendt TM et al., 2003) and a RAGE-specific neutralizing antibody (Flyvbjerg A et al., 2004), have also been shown to attenuate nephropathy.

AGE interact with the renin-angiotensin system, another potential mechanism for initiating renal disease. In addition, AGE induce cytokines, adhesion molecules, chemokines, growth factors and oxidant stress production which are involved in the pathogenesis of diabetic nephropathy. Human studies, have shown increased CML, pyralline and pentosidine deposition in the renal tissue of diabetic subjects with or without end-stage renal disease, increasing in parallel with the severity of nephropathy, as well as a significant reduction of nephrin, an important regulator of the glomerular filter integrity (Sugiyama S et al., 1996)(Doublier S et al., 2003).

Atherosclerotic disease:

The accumulation of fatty materials like cholesterol in artery walls results thickening of arterial blood vessels which is known as atherosclerotic disease. It is a syndrome affecting arterial blood vessels, a chronic inflammatory response in the walls of arteries, caused largely by the accumulation of macrophagewhite blood cells and promoted by low-density lipoproteins (plasma proteins that carry cholesterol and triglycerides) without adequate removal of fats and cholesterol from the macrophages by functional high density lipoproteins (HDL). It is commonly referred to as a hardening or furring of the arteries. It is caused by the formation of multiple plaques within the arteries.

Atherogenesis is the developmental process of athermanous plaques. It is characterized by a remodeling of arteries leading to sub endothelial accumulation of fatty substances called plaques. The buildup of an athermanous plaque is a slow process, developed over a period of several years through a complex series of cellular events occurring within the arterial wall, and in response to a variety of local vascular circulating factors. One recent theory suggests that, for unknown reasons, leukocytes, such as monocytes or basophils, begin to attack the endothelium of the artery lumen in cardiac muscle. The ensuing inflammation leads to formation of athermanous plaques in the arterial tunica intima, a region of the vessel wall located between the endothelium and the tunica media. The bulk of these lesions is made of excess fat, collagen, and elastin. At first, as the plaques grow, only wall thickening occurs without any narrowing. Stenosis is a late event, which may never occur and is often the result of repeated plaque rupture and healing responses, not just the atherosclerotic process by itself.

AGEs are likely to be linked to atherosclerosis in multiple ways, including enhancing endothelial dysfunction, elevating vascular low-density lipoprotein (LDL) levels by reducing LD uptake, promoting plaque destabilization via effects on matrix metalloproteinase, inducing neointimal proliferation, and inhibiting vascular repair in response to injury. Serum levels of AGEs have increased in patients with type 2 diabetes and coronary heart disease (Kilhovd BK et al; 1999). Furthermore, AGEs have been localized to atherosclerotic lesions, fatty streaks, lipid-containing smooth muscle cells, and macrophages in individuals with diabetes (Friedman EA 1999) (Stitt AW et al; 1997). A correlation between tissue AGE concentration and the severity of atherosclerotic lesions has also been demonstrated. There appear to be multiple potential mechanisms whereby AGEs may enhance atherosclerosis. AGEs quench nitric oxide and impair LDL removal by trapping LDL in the sub endothelium and decreasing LDL receptor recognition of AGE-modified LDL (Bucala R et al., 1994). AGE binding to apo lipoprotein (apo) B impairs its hepatic clearance, and induces increased retention of LDL in the aortic wall and increased recognition by macrophages at this site. Consequently, there is increased localization of AGE-LDL in vessels and increased production of foam cells, accelerating atheroma formation (Sobenin IA et al., 1993). Endothelial migration of monocytes, one of the first steps in atherogenesis, is dependent upon up-regulation of vascular cell adhesion molecule (VCAM)-1 expression, and AGEs have increased VCAM-1 expression via activation of the key nuclear transcription factor NF- κB (Kunt T et al., 1999). Have shown that attenuation of the plaque area can be achieved in a murine model of diabetes-associated atherosclerosis with the AGE inhibitor amino guanidine as well as with the putative AGE crosslink breaker alagebrium. These two disparate pharmacological interventions resulted in reduced accumulation of AGEs within the aortas, reduced expression of RAGE, and diminished expression of prosclerotic growth factors and various collagens. Animal studies using sRAGE, either as a preventative strategy or delayed intervention (Bucciarelli LG et al., 2002), resulted in suppressed vascular lesion formation.

The term macro vascular disease in diabetes includes atherosclerosis and increased stiffness of the arterial wall mediated by the interplay of various factors including AGE (Vlassara H et al., 2002) (Peppa M et al., 2004). In vitro studies have shown that AGE form intra- and intermolecular cross-links with matrix proteins in the vascular wall increasing vessel rigidity, trapping lipoproteins within the arterial wall and disrupting its clearance.

In vivo, an increased AGE deposition has been described in aortic atherosclerotic lesions, correlated with the degree of atheroma, (Wautier MP et al., 2001) events which were restored by using anti-AGE agents. (Brownlee M et al., 1986) (Park I et al., 1998)

In humans, an increased AGE deposition has also been found in the atherosclerotic plaque in vessels from diabetic patients (Nakamura Y et al., 1993) (Schleicher ED et al., 1997) and in the radial artery wall of chronic renal failure patients with or without diabetes. (Yamada K et al., 1994) (Sakata N et al., 1999)In addition, an increased tissue AGE accumulation and AGE receptors with a similar distribution pattern associated with an increased aortic stiffness have been found in human aortas obtained from post-portem examination of diabetic subjects. (Sims TJ et al., 1996) (Stitt AW et al., 1997)

Furthermore, increased circulating AGE levels and increased vascular tissue AGE deposition associated

with impaired endothelium dependent and endothelium-independent vasodilatation and increased arterial stiffness have been found in diabetic patients, restored by the administration of anti-AGE agents (Tan KC et al., 2002) (Winer N et al., 2003).

Measurement of AGEs:

Despite intensive investigation, the elucidation of the structure of specific AGE remains a problem. The different methods used in the various studies lead to no consistent and conflicting results. Till now, there is no ideal way to measure various AGE moieties. The currently used methods are HPLC, chromatography, fluorescence and Elisa.

Clinical studies have demonstrated that the level of circulating AGEs may be linked to various diabetes complications. However, until recently the sophisticated and expensive laboratory techniques required such as mass spectrometry, gas and/or liquid chromatography, for measurement of specific AGEs have retardedany attempts at widespread use of such measurements in the clinic. Furthermore, there is no universally accepted method to detect or measure AGEs, with no internal standards or an internationally recognized standard unit of measurement, thus making comparison of results between different laboratories very difficult. Blood is more accessible for repeated measurements of AGEs than tissue-requiring biopsies, but plasma AGE assays have not yet been shown to be directly related to tissue AGE content (Dorrian CA et al., 1998).A noninvasive tool has been developed using skin auto fluorescence, which has been correlated with tissue levels of pentosidine, CML, measures of long-term glycemic control, and the presence of diabetic complications (Hartog JW et al., 2005). Recentpublications have suggested that skin auto fluorescence serves as a marker of vascular damage(Lutgers HL et al., 2006), as well as a predictor of cardiac mortality in patients with type 1 and 2 diabetes (Meerwaldt R et al.,2007). However, long-term studies validating both the specificity and sensitivity of this investigation, and its link to certain AGEs, remain to be confirmed. Thus, currently there is no evidence that the measurement of AGEs has any clinical use, and importantly, AGE measurements should not be considered a replacement for HbA1c as a marker of overall glycemic control.

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