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Review Article

Advance Glycated End Products in Type 2 Diabetes Mellitus and Role of Dietary Supplement in their Management

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Abstract

Advance glycated end products are a heterogeneous group of molecules formed from the non-enzymatic reaction of reducing sugars with free amino groups of proteins, lipids and nucleic acids. Advance glycation is an irreversible process, its physiological roles are to identify senescent proteins and hence there is an accumulation of advanced glycation end products. Diabetes is currently recognized as an oxidative stress disorder and hyperglycemia is a condition has an important role in the pathogenesis of diabetic complication. Diabetes has an overload of reducing sugars which accelerate advance glycated end products formation in body tissues. Interventions that can reduce advance glycated end products accumulation are also helpful in preventing the development of diabetic complications. Antioxidants can protect the formation of advanced glycated end products by blocking the free amino groups on proteins and also trap the carbonyl group. However, the efficiency of these dietary supplements against advance glycated end products in vivo is unknown. The antioxidants are now used as add on to pharmacotherapy in diabetic patients to reduce hyperglycemia and prevent advance glycated end products formation.

1. INTRODUCTION

Diabetes mellitus is a metabolic disorder characterized by increased glucose level i.e. persistent hyperglycemia. It is a chronic disease associated with diabetic complications such as microvascular and macrovascular complications[1]. Persistent hyperglycemia leads to abnormal changes i.e. formation of advanced glycated end products, oxidative stress and increase of polyol pathway flux. AGEs are implicated in the pathogenesis of diabetic complications[2]. AGEs accumulation is not just a measure of hyperglycemia, but represents metabolic burden of both hyperglycemia and hyperlipidemia[3]. Although there have been important advances in the control of diabetes by means of glycemic drugs,insulin,the insulin pump, the dietary compounds are now also in use as an adjuvant that can reduce glycation and are promoting the health of diabetics[4].

2. ADVANCE GLYCATED END PRODUCTS

Advance glycated end products are heterogeneous end products of non-enzymatic glycation, sequential glycation and oxidation of sugars with free amino groups on proteins, peptides. This sequence of events is known as the Maillard reaction. These are implicated in the pathogenesis of microvascular and macrovascular complications of diabetes. AGEs are generally divided into two types on the basis of chemical structure; one type is fluorescent properties and another one iscross linking structures AGEs[5].

2.1 Advance Glycated End Products Formation

In early-stage glycation, the amino group of the body proteins (specifically lysine residues in protein) produces a labile covalent bond with aldehyde group of the physiological sugars to form a schiff base. This Schiff base, in turn, undergoes molecular re-arrangement to form one ketoamine known as Amadori product[6].Covalent cross linking of these Amadori products once again with the sugar group in other glycated protein lead to development of irreversibly modified molecules, termed as advanced glycation end products (AGEs) (Figure 1).

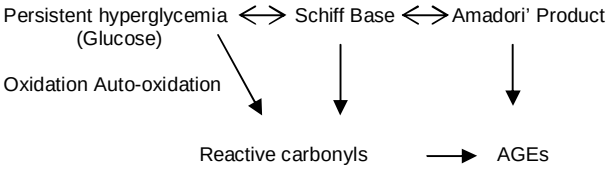

Figure 1: Pathways for the formation of advanced glycated end products

Other pathway which may lead to AGEs formation is through auto-oxidation of glucose by reactive oxygen species, and through carbonyl compounds. In particular methylglyoxal, a reactive carbonyl is the most reactive AGE precursor[7].

The level of these early advance glycated end products change in response to blood glucose and are reflected in the analysis of HbA_{1c} and glycated albumin to monitor average blood glucose control. However,the irreversibly formed AGEs level does not return to normal when glucose level is normal and accumulates over the lifetime of the proteins[8].

In addition to endogenous formation, AGEs are alsoderived from exogenous sources i.e. diet and tobacco smoke. When sugars are cooked with proteins or fats exogenous glycation and advance glycated endproducts (AGEs) are formed. Temperatures over 120°C (~248°F) greatly accelerate the reactions, however lower temperatures with longer cooking times also promote their

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formation. A significant proportion of ingested AGEs are absorbed from foods exposed to high temperatures. AGE levels are seen higher in smokers and individuals on high-AGE diets [9].

3. INHIBITION OF ADVANCE GLYCATION

Attempts have been made to pharmacologically influence the process of synthesis of AGEs in order to prevent or slow down the formation of AGEs. Different types of AGEs inhibitors have been classified (Table 1).

Table 1: Types of AGEs inhibitors

S. No.	TYPE A	TYPE B	TYPE C	TYPE D	TYPE E	TYPE F
1.	Aspirin	Guanidine	EDTA	Guanidine	Guanidine	ALT-711
2.	Pyridoxal-5 phosphate	Aminoguanidine	Penicillamine	Aminoguanidine	Aminoguanidine	-
3.	Pyridoxamine	Metformin	Carnosine	Carnosine	Metformin	-
4.	-	Thiamine	Vitamin C	L-Arginine	Carnosine	-
5.	-	-	Vitamin E	Metformin	-	-

Type A- Prevent sugar attachment
Type B- Block formation of cross-links
Type C- Chelating agents and antioxidants
Type D- Trap reactive carbonyls
Type E- Prevent formation of AGEs from amadori products
Type F- Cross-linkage and AGE breakers that can break cross-links after they form

3.1 Dietary Antioxidants

A dietary antioxidant can be defined as ''a substance in food that significantly decrease the adverse effects of reactive species, such as reactive oxygen species (ROS) and nitrogen species on normal physiological function in humans''[10].Studies show that antioxidant compounds such as vitamin C, vitamin E prevents or reverse nerve conduction velocity deficits in experimental model. They have also shown to reduce *in vitro* and *in vivo* protein glycation[11]. Vitamin C works in conjuction with vitamin E to maintain its potency.

Carnosine, a natural dipeptide, is a major brain and muscle antioxidant which can compete with proteins for binding with sugars with effects on AGEs[12].

Essential trace elements, selenium works with vitamin E to protect cell membrane and tissues. In-vitro studies suggest that AGEs-inhibitory activities of antioxidants have been achieved by preventing autoxidative pathways of AGEs formation[13].

3.2 Synthetic and Natural Advance Glycation End Products-Inhibitors

A pharmacologic approach for the prevention of AGEsformation is the use of carbonyl traps. Promising substances are pyridoxamine, aminoguanidine and the well known metformin. Pyridoxamine, also known as vitamin B6, scavenges α-dialdehydes as well as lipid peroxidation intermediates. The first compound which has been extensively studied in vitro and in vivo to be a powerful inhibitor of AGEs formation is aminoguanidine, which prevents diabetic complications. Aminoguanidine inhibit the formation of CML or CEL, traps reactive carbonyls and a potent inhibitor of nitric oxide synthase [14]. The use of aminoguanidine hindered reduction in glomerular filtration rate reduced 24-h urinaryproteinuria and prevented the deterioration of retinopathy[15]. Ligation of advanced glycation end products (AGEs) with their receptor (RAGE) plays an important role in the development of various secondary complications of diabetes, including atherosclerosis. Monocyte activation, adhesion, and migration are key events in the pathogenesis of atherosclerosis.LR-90has novel anti-inflammatory properties and might thereforehave additional protective effects against diabeticvascular complications[16]. OPB-9195 is a thiazoline derivative, has a property to reduce AGEs level and reported to be more efficient thanaminoguanidine[17]. OPB-9195 more efficiently blocks CML and pentosidine than aminoguanidine[18].

Most recently, ALT-946, N-(2-acetamidoethyl) hydrazinecarboximidamide hydrochloride, a new inhibitor of AGE, was found to have minimal inhibitory effects on nitric oxide synthase as compared with aminoguanidine in experimental diabetic nephropathy [19].

AGEs-crosslink breaking drugs have been introduced which cleaves the preformed AGEs-crosslink i.e. ALT-711 (Alagebrium) is the most promising for therapeutical use. Treatment with ALT-711 reduced stiffness of arteries and myocardium which is associated with diabetes and ageing [20-22].

Metformin also inhibit AGEs with the mechanism of trapping methylglyoxal and dicarbonyls[23].Benfotiamine, a lipid soluble compound, was found to be a potent inhibitor of glycation[24]. This drug was recently shown to block the three major pathways of hyperglycemic damage and was successful in preventing diabetic retinopathy in rats [24].Benfotiamine prevented both microvascular and macrovascular endothelial dysfunction and oxidative stress induced AGEs rich meal and also the use of lipoic acid with benfotiamine normalizes the level of AGEs[25].The natural compounds curcumin, a constituent of turmeric, also have an anti-AGEs and anti-inflammatory property. Resveratrol prevents the impairment of AGE on macrophage lipid homeostasis partially by suppressing RAGE via PPARÁ activation, which might provide new insight into the protective role of resveratrol against diabetic atherosclerosis[25]. Resveratrol has been shown to inhibit AGE-induced proliferation and collagen synthesis activity in vascular smooth muscle [26]. Other natural compounds are garlic extract and green tea also prevents formation of AGEs [27].

4. ADVANCE GLYCATED END PRODUCTS (AGEs) AND DISEASES

The presence of AGEs is correlated with several important diseases. The rate of AGEs formation is accelerated in diabetics as it is often accompanied with hyperglycemia and oxidative stress(Figure 2). This glycation reaction contributes to morbidity of diabetes, end-stage kidney and heart diseases, and it is also involved in the pathophysiology of Alzheimer´s disease, arthritis and ageing.AGEs causes intermolecular collagen cross-linking which leads to vascular stiffness, phenomena that are considered to explain partly the increase in diastolic dysfunctionand systolic hypertension seen in diabetic[28]. AGEs accumulate in most sites of diabetes complications i.e. the kidney, retina, and atherosclerotic plaques[29, 30].

4.1 Advance Glycated End Products and Diabetes

It has long been recognized that increased $HbA_{1c\%}$ (a precursor of AGEs) levels are associated with a higher incidence of vascular complications and reduced life expectancy in diabetes patients. In addition, the intervention studies to reduce $HbA_{1c\%}$ lead to lower microvascular and macrovascular lesions and a reduced death rate over several years.Serum levels of AGEs in patients with type 2 diabetes appear higher than those without diabetes.Preliminary studies in diabetic patients have shown that aminoguanidine therapy for 28 days reduces hemoglobin derived AGEs thus providing evidence that aminoguanidine can reduce AGEs in vivo. However, the same study showed that aminoguanidine inhibited only AGEs but had no effect on levels of Amadori products [29].

4.2 Diabetic Nephropathy

Diabetic nephropathy is the major cause of end-stage renal disease. Pathophysiologically, it is characterized by abnormal

deposits of matrix material in the glomerular mesangium, leading to glomerulosclerosis. This is accompanied by increased AGEs deposition in these structures. Interestingly, not only endogenous AGEs contribute to renal disease but also exogenous AGEs cause thickening of glomerular basement membrane[31].

AGEs result in the expression and activation of a number of transcription factors implicated in the development of diabetic nephropathy, including nuclear factor κB (NF-κB) and protein kinase C (PKC)[32, 33].This effect may be both direct (through AGE receptors) and indirect through generation of free oxygen radicals leading to the production of cytokines, adhesion molecules, and chemokines and extracellular matrix may also be substantially altered[34].The expression of extracellular proteins such as fibronectin and types I and IV collagen is increased by AGE in a dose- and time-dependent manner, in the presence or absence of hyperglycemia[35].This has been considered to be a direct effect via AGE-specific receptors involving activation of the JAK/STAT signal transcriptionpathway, leading to the induction of profibrotic cytokines and growth factors, including TGF-β1, PDGF-B and CTGF. CTGF (also known as IGF-binding protein-related protein-2) is a potent profibrotic agent and is increased in diabetic nephropathy [35].

Animal studies have shown that glomerular hypertrophy is associated with an over expression of type IV collagen, TGF-β and platelet derived growth factor, all of which can be ameliorated by aminoguanidine treatment [36].

Methylene bis4, 4'-(-2 chlorophenylureidophenoxyisobutyric acid) (LR-90) has been investigated in number of animal studies [37]. LR-90 inhibited albuminuria and reduced serum creatinine concentration and circulating AGE levels in diabetic rats without any effect on glycemic control. It also inhibits glomerular AGEs accumulation. LR-90 is also currently being tested on macrovascular complications in a range of animal studies and has recently inhibited S100b-induced expression of RAGE and other proinflammatory genes in human monocytes [38].In animal studies, the high-dose therapy of thiamine and benfotiamine increased transketolase expression in renal glomeruli, and prevent microalbuminuria and diabetes-induced hyperfiltration[39].Phenacylthiazolium in *in vitro* experiments was shown to cleave crosslinks. Subsequently, it was shown in diabetic rat models to decrease tissue AGE accumulation[40] but was not shown to decrease proteinuria[41].ALT-711 or alagebrium in studies on various models of diabetic complications has shown to confer end organ benefits. Alagebrium attenuate the development of albuminuria in diabetic rats in association with modest effects on blood pressure [42].

4.3 Diabetic Neuropathy

Diabetic neuropathy is complex in its etiology and manifestations and is produced by metabolic abnormalities (polyol pathway, AGEs, oxidative stress), functional abnormalities (reduced nerve conduction) and structural abnormalities such as glycation of axonal cytoskeletal protein i.e. tubulin, actin and neurofilament results in slow axonal transport and degeneration. AGEs also affects growth factors such as fibrin and nerve growth factors contributes to loss of function [43].

Hyperglycemia induced AGEs on peripheral nerve myelin contribute to segmental demyelination by increasing itssusceptibility to phagocytosis by macrophages. AGEs by increasing macrophage recognition and uptake, stimulates macrophage – derived growth factor. This results in proliferation of smooth muscle and atherogenesis and glycation of extracellular matrix protein laminin leads to impaired regenerative activity in diabetic neuropathy[44].

In diabetic neuropathy AGEs and interaction of AGEs with its receptor induce oxidative stress, result in upregulation of nuclear factor (NF)-kappaB and various NF-kappaB-mediated proinflammatory genes, and exaggerate neurological dysfunction, including altered pain sensation.

AGE – RAGE interaction producing reactive oxygen species, ROS accelerating AGE generation, and AGE quenching nitric oxide. The quenching action of AGE binding on NO is relevant to nerve ischemia. The reduction of NO is one of the most important mechanisms of ischaemic nerve injury [45].

Benfotiamine has beneficial effects on nerve conduction velocity in the peroneal Nerve [46] in diabetic patients, and a short 3-week clinical study showed alleviation of painful neuropathy [47], but long-term human data are still lacking.Capsaicin alleviate peripheral neuropathy symptoms, works on pain by binding to the VR 1 receptors and stripping nerves of substance P, a pain-signaling neurotransmitter. In a clinical study topical capsaicin was applied to the feet of patients with symptomatic diabetic neuropathy which results in improvement of symptoms, including pain perception threshold. Researchers concluded that capsaicin cream was effective in diabetic neuropathy, without causing adverse effects on nerve fiber function[48]. Six-week trial of10 diabetic patients to evaluate the effect of25 mg of oral vitamin B6 on diabetic peripheral neuropathy revealed symptomatic improvement in all patients[48]. Type 2 diabetic patients showed improvement of some clinical featuresof neuropathy after 3-week treatment of lipoic acid. Alpha-lipoic acid treatment improves nerveblood flow and distal nerve conductionand increases endoneurial glucose uptake and energy metabolism in animals[49].

4.4 Diabetic Retinopathy

Retinopathy is the most common microvascular complication of diabetes and is a common condition affecting 90% of diabetic patientswith background retinopathy and 8-26% with proliferative retinopathy after 25 years of diabetes. The retinal microvasculature dysfunction occurs in response to variable hyperglycemia and in this progressive disease there is widespread loss of retinal pericytes and failure of endothelial cells, leading to capillary closure and retinal ischaemia[50].

AGEs are not only localized to vascular basement membranes (BMs), but also appear to accumulate in the retinal pericytes[51] and co-localize with AGE receptors, induce basement thickening, and cause breakdown of the inner blood-retinal barrier[52]. Retinal vascular endothelial cells show abnormal endothelial nitric oxide synthase expression, which may account for some of the vaso-regulatory abnormalities observed in the diabetic vasculature[53]which can be modulated by AGE receptors. In addition, VEGF at high levels is important for vascular incompetence and proliferationcan be up regulated in many retinal cell types afterexposure to AGEs[54].

It has been found that in rats AGEs deposits in the basement membrane and the retinal pericytes and optic nerve head and these glycation proteins causes dysfunction of retinal pericytes[55].Scientists found that rats given vitamin C for 36 weeks experienced increases in blood flow and reductions in pro-inflammatory leukocytes in the retina. As this study was conducted on rats, researchers also believe to achieve similar results in humans[56].In rats LR-90 prevents diabetic retinopathy atdoses that are several-fold less than the doses of pyridoxamine[57].Diabetic rats fed a diet of antioxidants, including vitamin E, showed an inhibition of diabetes-induced NF-kB activation, whichis an early marker of diabetic retinopathy and is sustained throughthe development of the disease[58].

Aminoguanidine was one of the first inhibitors of AGE formation studied, and in type 2 diabetes patients decreases the progression of retinopathy[59]. Pyridoxamine also prevents diabetes-induced retinal vascular lesions. Some of the preliminary clinical trials with this agent have been performed[59]. Diabetic retinopathy patients have abnormal blood vessels inside the retina which causes vision loss. Researchers found that resveratrol was effective at destroying abnormal blood vessels and preventing the development of new blood vessels in the retina[59].Pine bark, or pycnogenol is used for treating blood circulation problems, allergies, asthma, high blood pressure, muscle soreness, pain, osteoarthritis, diabetes. Patients with diabetic retinopathy for two months received either pycnogenol or a placebo. Scientists observed that the group received pycnogenol experienced improvements in clearness of vision compared to those administered a placebo[60].

4.5 Advance Glycated End Products and Cardiovascular Disease

Diabetes by itself is regarded as the strongest risk factor for cardiovascular disease, but it is not just high blood glucose levels, but a variety of mechanisms that interact. The blood vessels in patients with diabetes are more susceptible to well-established risk factors such as smoking, high cholesterol and high blood pressure. In fact, cardiovascular disease is by far the most frequent cause of death in both men and women with diabetes. Another major component of cardiovascular disease is poor circulation in the legs, which contributes to a greatly increased risk of foot ulcers and

amputations[61]. Diabetes also affects the heart muscle and causes both systolic and diastolic heart failure. The etiology of this excess cardiovascular morbidity and mortality is not completely clear. Evidence suggests that although hyperglycemia contributes to myocardial damage, it is clearly not the only factor, because both pre-diabetes and the presence of the metabolic syndrome, even in normoglycemic patients, increase the risk of most types of cardiovascular diseases[62-64].Heart failure is characterized by a structural or functional cardiac disorder that results in an inability of the heart to fill with or pump out blood combined with dyspnoea or fatigue. AGEs may contribute to the development of heart failure through two pathways, firstly, AGEs affect the physiological properties of proteins in the extracellular matrix by creating cross-links and secondly, advanced glycated end products cause multiple vascular and myocardial changes via the interaction with AGE receptors. AGEs can cause diastolic,systolic and vascular dysfunction through these pathways. Later, these abnormalities may result in the development and progression of heart failure [65].

- AGEs and diastolic dysfunction: Cross-linking of extracellular matrix proteins is essentially a physiological phenomenon. It results instrengthening tissues ensuring tissue integrity without compromising flexibility. AGEs, however, can bind covalently with other AGEs and form additional cross-links between matrix proteins like collagen, laminin and elastin. Excessive cross-linking caused by AGE accumulation undermines the flexibility of matrix proteins and will induce diastolic dysfunction in the heart. Another pathway by which AGEs could contribute to the development of diastolic dysfunction is via the activation of AGE receptors. Receptor for AGE (RAGE) over-expression was found to reduce the systolic and diastolic intra-cellular calcium concentration [65].
- AGEs and systolic dysfunction: AGEs accumulation may be involved in the development of systolic dysfunction by accelerating the progression of coronary artery disease. AGE-RAGE interaction results in atherosclerosis, thrombosis, and vasoconstriction. By negatively influencing LDL-metabolism, AGEs could further increase the risk of developing atherosclerosis and subsequent myocardial infarction[66, 67, 68].
- AGEs and vascular dysfunction: Endothelial dysfunction is a very important predictor of adverse cardiac events, hospitalization of patients with heart failure, and death[69]. Together with vascular compliance, endothelial dysfunction relates closely with the functional capacity of chronic heart failure patients [70]. AGEs impair vascular function by influencing both endothelial function and vascular compliance. AGEs may induce endothelial dysfunction by reducing the availability of the vasodilator nitric oxide (NO) [71, 72]. Furthermore, AGEs can enhance the production of endothelin-1, a potent vasoconstrictor [71, 72]. Vascular compliance is influenced by AGE cross-linking in asimilar fashion as in myocardial tissue. In humans the level of circulating AGEs correlates with arterial compliance [73].

Hyperglycemia contributes to cardiovascular risk and patients with diabetes have increased risk of cardiovascular morbidity and mortality.AGEs accumulate at a much higher rate in diabetics and contribute in the development and progression of cardiovascular disease in diabetes. Serum AGEs level are elevated in diabetic patients with coronary heart disease compared to patients without coronary heart disease[74]. AGEs levels are further related to other features of cardiovascular disease, such as carotid stenosis and peripheral artery occlusive disease [75, 76].

In a study of type 2 diabetic mice with cardiac dysfunction benfotiamine protects diabetes mellitus-induced cardiac dysfunction through pleiotropic mechanisms, culminating in the activation of prosurvival signaling pathway. Thus, benfotiamine merits attention for application in clinical studies[77].In randomized clinical trials (RCTs), patients with coronary heart disease were administered omega-3 fatty acid supplements and the result shows significant reduction in CV events. Omega-3 supplements can also slow down the progression of atherosclerosis in these patients[78].Research concerning nutritional regimens has shown that persons who consume large amounts of fruit and vegetables have lower incidences of cardiovascular diseases although the precise mechanisms for this protective effect are elusive. Possible explanations include (a) increased consumption of dietary fiber (b) reduced consumption of dietary cholesterol and other lipids, and (c) increased intake of the antioxidant vitamins (A, C, and E)[79].

5. CONCLUSION

AGEs can act as pro-oxidants and pro-inflammatory agents that mediate the development of diabetes-related complications. Hyperglycemia, in combination with high-serum AGE levels, may further accelerate the progression of the complications. The effective dietary supplements are used for their antiglycation activity and also are beneficial to prevent AGEs associated chronic diseases. This review examined the use of supplements for their putative AGE-lowering properties, and effects on complications in diabetic patients. In conclusion, dietary supplements are intended to be used as a therapeutic option in specifically type 2 diabetes patients and also act as add-ons to the pharmacotherapy for a healthy lifestyle; therefore supplements can be used to promote overall good health and prevent disease.

REFERENCES

1. Huang KH, Pai MH et al. Supplemental dietary arginine reduces renal RAGE expression and oxidative damage in rats with streptozotocin-induced type 2 diabetes, Euro e-J of ClinNutrMetab, 2010, 5:77–84
2. Ardestani A, Yazdanparast R. Cyperusrotundus suppresses AGE formation and protein oxidation in a model of fructose-mediated protein glycoxidation, Int J of Biol Macro, 2007, 41:572-578.
3. MeerwaldtR, links T et al. The clinical relevance of assessing advanced glycation end products accumjulation in diabetes, Cardiovascular Diabetology,2008, 7:29-35.
4. Vinson JA, Howard TB.Inhibition of protein glycation and advanced glycation end products by ascorbic acid and other vitamins and nutrients, J NutrBiochem,1996, 7:659-663.
5. Ho SC, Wu SP et al. Comparasion of antiglycation capacities of several herbal infusions with that of green tea, Food chemistry, 2010, 122:768-774.
6. Wu Q, Chen H et al. Oligomeric procyanidins of lotus seedpod inhibits the formation of advanced glycation end-products by scavenging reactive carbonyls,Food Chemistry,2013, 138:1493-1502.
7. Thorpe SR, Baynes JW. Maillard reaction products in tissue proteins: new products and new perspectives, Amino Acids,2003, 25:275-281.
8. Wolff SP, Jiang XY et al. Protein glycation and oxidative stress in diabetes mellitus and ageing, Free Rad Biol Med,1991, 10:339-352.
9. Muhlestein JB, Anderson JL et al. Effect of fasting glucose levels on mortality rate in patients with and without diabetes mellitus and coronary artery disease undergoing percutaneous coronary intervention, Am Heart J,2003, 146:351–358.
10. SamuelR, Figarola JL. Novel inhibitors of advanced glycation endproducts,Archives of Biochemistry and Biophysics,2003, 419:63–79.
11. Sima AA, Sugimoto K.Experimental diabetic neuropathy: an update, Diabetologia, 1999, 42:773-788.
12. Goh SY, Cooper ME. A Review: The role of advanced glycation end products in progression and complications of diabetes, J Clin Endocrinol Metab, 2008.
13. Miyata T, Ueda Y et al. Mechanism of the inhibitory effect of OPB-9195 on advanced glycation end products and advanced lipoxidation end product formation, J Am Soc Nephrol, 2000, 11:1719-25.
14. Brownlee M, Vlassara H et al. Aminoguanidine prevents diabetes-induced arterial wall protein cross-linking, Science, 1986, 232:1629–1632.
15. James LF, Narkunaraja S et al. Anti-Inflammatory Effects of the Advanced Glycation EndProduct Inhibitor LR-90 in Human Monocytes, Diabetes,2007, 56:647–655.
16. Hegab Z, Gibbons Set al.Role of advanced glycation end products in cardiovascular disease, World J Cardiol, 2012, 4:90-102.
17. Tsuchida K, Makita Z et al. Suppression of transforming growth factor beta and vascular endothelial growth factor in diabetic nephropathy in rats by a novel advanced glycation

end product inhibitor, OPB-9195,Diabetologia,1999, 42:579-88.
18. Figarola JL, Scott S et al. LR-90 a new advanced glycation end product inhibitor prevents progression of diabetic nephropathy in streptozotocin-diabetic rats, Diabetologia, 2003, 46:1140-1152.
19. Forbes JM, Soulis T et al. Renoprotective effects of a novel inhibitor of advanced glycation, Diabetologia, 2001, 44:108–114.
20. Asif M, Egan J et al. An advanced glycationendproduct cross-link breaker can reverse age-related increases in myocardial stiffness, Proc Natl Acad Sci, 2000, 97:2809–2813.
21. Kass DA, Shapiro EP et al. Improved arterial compliance by a novel advanced glycation end-product crosslink breaker, Circulation, 2001, 104:1464–1470.
22. Wolffenbuttel BH, Boulanger CM et al. Breakers of advanced glycation end products restore large artery properties in experimental diabetes,Proc Natl Acad Sci,1998, 95:4630–4634.
23. Rahbar S, Natarajan R et al. Evidence that pioglitazone, metformin and pentoxifylline are inhibitors ofglycation,Clin Chim Acta, 2000, 301:65–77.
24. Hammes HP, Du X et al. Benfotiamine blocks three major pathways of hyperglycemicdamage and prevents experimental diabetic retinopathy, Nat Med, 2003, 9:294–299.
25. Uribarri J, Peppa M et al. Restriction of dietary glycotoxins reduces excessive advanced glycation end products in renal failure patients, J Am SocNephrol, 2003, 14:728-31.
26. Babu PV, Sabitha KE et al. Therapeutic effect of green tea extract on advanced glycation and cross-linking of collagen in the aorta of streptozotocin diabetic rats, Clin Exp Pharmacol Physiol, 2006, 33:351–357.
27. Yihua Z, Zhidan L et al. Resveratrol prevents the impairment of advanced glycosylationend products (AGE) on macrophage lipid homeostasis by suppressing the receptor for AGE via peroxisome proliferator-activated receptor Á activation, Int J of molecular medicine, 2010, 25: 729-734.
28. Hammes HP, Alt A et al. Differential accumulation of advanced glycation end products in the course of diabetic retinopathy, Diabetologia, 1999, 42:728–736.
29. Smit AJ, Lutgers HL. The clinical relevance of advanced glycationen dproducts (AGE) and recent developments in pharmaceutics to reduce AGE accumulation, Curr Med Chem, 2004, 11:2767–84.
30. Goh SY, Cooper ME. The Role of Advanced Glycation End Products in Progression and Complications of Diabetes, Clin Endocrinol Metab, 2008, 93:1143–1152.
31. Halat KM, Dennehy CE. Botanicals and dietary supplements in diabetic peripheralneuropathy, J AM Board Fam Pract, 2003, 16:47.
32. Inoguchi T, Sonta Tet al. PKC-dependent increase in reactive oxygen species (ROS) production in vascular tissues of diabetes: role of vascular NADPH oxidase, J Am SocNephrol, 2003, 14:227–232.
33. Tan Al, Forbes JM et al. AGE, RAGE and ROS in diabetic nephropathy, SeminNephrol, 2007, 27:130–143.
34. Chappey O, Dosquet C et al. Advanced glycation end products, oxidative stress and vascular lesion,Eur J Clin Invest,1997, 27:97-108.
35. Archer D. Diabetic retinopathy: some cellular, molecular and therapeutic considerations, Eye, 1999, 13:497–523.
36. Thirunavukkarasu V, AnithaNandhini AT. Lipoic acid improves glucose utilisation and prevents protein glycation and AGE formation, Pharmazie, 2005, 60:772-5.
37. Figarola JL, Shanmugam N et al. Anti-inflammatory effects of the advanced glycation end product inhibitor LR-90 in human monocytes, Diabetes, 2007, 56:647-655.
38. Babaei-Jadidi R, Karachalias N et al**.** Prevention of incipient diabetic nephropathy by high-dose thiamine and benfotiamine, Diabetes, 2003, 52:2110–2120.
39. Ohgami N, Nagai R et al. Scavenger receptor class B type I-mediated reverse cholesterol transport is inhibited by advanced glycation end products, J Biol Chem, 2001, 276:13348–55.
40. Bucala R, Makita Z et al.Modification of lowdensity lipoprotein by advanced glycation end products contributes to the dyslipidemia of diabetes and renal insufficiency, Proc Natl Acad Sci, 1994, 91: 9441–5.
41. 41.Witztum JL, Steinberg D. Role of oxidized low density lipoprotein inatherogenesis, J Clin Invest, 1991, 88:1785–92.
42. Fischer D, Rossa S et al. Endothelial dysfunction in patients with chronic heart failure is independently associated with increased incidence of hospitalization, cardiac transplantation, or death, Eur Heart J, 2005, 26:65–9.
43. Borlaug BA, Melenovsky V et al. Impaired chronotropic and vasodilator reserves limit exercise capacity in patients with heart failure and a preserved ejection fraction, Circulation,2006, 114: 2138–47.
44. Quehenberger P, Bierhaus A et al. Endothelin 1 transcription is controlled by nuclear factor-kappaB in AGE-stimulated cultured endothelial cells, Diabetes, 2000, 49:1561–70.
45. Sanders DB, Kelley T et al. The role of nitric oxide synthase/ nitric oxide in vascular smooth muscle control, Perfusion, 2000, 15:97–104.
46. Yoshida N, Okumura K et al. High serum pentosidine concentrations are associated with increased arterial stiffness and thickness in patients with type 2 diabetes, Metabolism,2005, 54:345–50.
47. Archer DB. Diabetic retinopathy: some cellular, molecular and therapeutic considerations, Eye, 1999, 13:497–523.
48. Chakravarthy U, Hayes RG et al. Constitutive nitric oxide synthase expression in retinal vascular endothelial cells is suppressed by high glucose and advanced glycation end products, Diabetes, 1998, 47:945– 52.
49. Yamagishi S, Fujimori H et al. Advanced glycation endproducts accelerate calcification in microvascular pericytes, Biochem Biophys Res Comm, 1999, 258:353–7.
50. Ruggiero-Lopez D, Rellier N. Growth modulation of retinal microvascular cells by early and advanced glycation products, Diabetes Res Clin Pract,1997, 34:135–42.
51. Li J, Gobe G. Protein kinase C activation and its role in kidney disease, Nephrology,2006, 11:428–434.
52. Boulton AJM, Malik RA. Diabetes Mellitus: Neuropathy, Endocrinol- Adult & paediatric, 2010, 1:984-98.
53. Forbes JM, Cooper ME et al. Role of Advanced Glycation End Products in Diabetic Nephropathy, J Am Soc Nephrol, 2003, 14:S254–S258.
54. Schonlav F, Rchdewald P. Pycnogenol for diabetic retinopathy, Int Opthalmol, 2001, 24:161-71.
55. Bierhaus A, Humpert PM et al. Understanding RAGE, the receptor for advanced glycation end products, J Mol Med, 2005, 83:876–886.
56. Quinn PJ, Boldyrev AA. Carnosine: its properties, functions and potential therapeutic applications, Mol Aspects Med,1992, 13:379-444.
57. Kowluru RA, Koppolu P et al. Diabetes-induced activation of nuclear transcriptional factor in the retina, and its inhibition by antioxidants, Free Radic. Res, 2003, 37: 1169–1180.
58. Dronavalli S, Duka I et al. The pathogenesis of diabetic ephropathy, Nat ClinPractEndocrinolMetab, 2008, 4:444–452.
59. BhatwadekarA, Glenn JV et al. A new advancedglycation inhibitor, LR-90, prevents experimental diabetic retinopathyin rats, Br J Ophthalmol, 2008, 92:545–547.
60. Jariyaponqskul A, Runqiaroen T et al. Long-term effect of vitamin C supplementation on the endothelial dysfunction in the iris microvessels of diabetic rats,Microvasc Res,2007, 74:32-8.
61. Cooper ME, Bonnet F et al. Mechanisms of diabetic vasculopathy, Am J Hypertens, 2001, 14:475–486.
62. Thrainsdottir IS, Aspelund T et al. The association between glucose abnormalities and heart failure in the population-based Reykjavík Study, Diabetes Care,2005, 28:612–616.
63. Nielson C, Lange T. Blood glucose and heart failure in nondiabetic patients,Diabetes Care,2005, 28:607–611.

64. Ganda OP. Diabetes and Cardiovascular disease, Joslin Diabetes,2013.
65. Cooper ME, Thallas V et al. The cross-link breaker, N-phenacylthiazolium bromide preventsvascular advanced glycation end-product accumulation, Diabetologia, 2000, 43:660–664.
66. Schwedler SB, Verbeke P et al. N-phenacylthiazolium bromidedecreases renal and increases urinary advanced glycation end products excretionwithout ameliorating diabetic nephropathy in C57BL/6 mice, Diabetes Obes Metab, 2001, 3:230–239.
67. Peppa M, Brem H et al. Prevention and reversal of diabetic nephropathy in db/db mice treatedwith alagebrium (ALT-711), Am J Nephrol, 2006, 26:430–436.
68. Stracke H, Lindemann A et al. A benfotiamine-vitamin B combination in treatment of diabetic polyneuropathy, Exp Clin Endocrinol Diabetes, 1996, 104:311–316.
69. Ceriello A, Giugliano D et al. Vitamin E reduction of protein glycosylation in diabetes. New prospect for prevention of diabetic complications, Diabetes Care,1991, 14:68-72.
70. Karmakar PS, Goswami RP**.** Advanced Glycation End Products (AGEs):It's Role in the Pathogenesis of Diabetic Complications, Diabetology, 2012, 22:277-82.
71. Ahmed N. Advanced glycation end products-role in pathology of diabetic complications, Diabetes Res and Clin Practice,2005, 67:3-21.
72. Haupt E, Ledermann H et al. Benfotiamine in the treatment ofdiabetic polyneuropathy–a three-week randomized, controlled pilot study (BEDIP study),Int J ClinPharmacolTher, 2005, 43:71–77.
73. Bucala R, Vlassara H. Advanced glycosylation end products in diabetic renal and vascular disease, Am J Kidney Dis, 1995, 26:875-888.
74. Cooper ME. Importance of Advanced Glycation End Products in Diabetes-Associated Cardiovascular and Renal Disease, AJH, 2004, 17:31–38.
75. Yoshida N, Okumura K et al.High serum pentosidine concentrations are associated with increased arterial stiffness and thickness in patients with type 2 diabetes, Metabo-lism, 2005, 54:345-350.
76. Lapolla A, Piarulli F et al. Advanced glycation end products and antioxidant status intype 2 diabetic patients with and without peripheral arterydisease, Diabetes Care,2007, 30:670-676.
77. Katare RG, Caporali A et al. Vitamin B1 Analog Benfotiamine Prevents Diabetes-Induced Diastolic Dysfunction and Heart Failure Through Akt/Pim-1–Mediated Survival Pathway, Circ Heart Failure,2010, 10:294-305.
78. Bolton WK, Cattran DC et al. Randomized trial of an inhibitor of formation of advanced glycation end productsin diabetic nephropathy, Am J Nephrol, 2004, 24:32-40.
79. Kris-Etherton PM, Harris WS et al. Omega-3 Fatty Acids and Cardiovascular Disease, Arteriosclerosis, Thrombosis and Vasc Biol, 2003, 23:151-152.