International Journal of Applied and Natural Sciences (IJANS)
ISSN(P): 2319-4014; ISSN(E): 2319-4022
Vol. 7, Issue 4, Jun - Jul 2018; 55-66

International Academy of Science, Engineering and Technology
Connecting Researchers; Nurturing Innovations

STUDYING THE EFFECT OF DIETARY ADVANCED GLYCATION END PRODUCTS ON TYPE II DIABETES AND RELATED COMPLICATIONS RISK

Amenah Alhajri[1], Rima Mashal[2] & Salma Tukan[3]

[1]*Research Scholar, University of Jordan, School of Graduate Studies, Amman, Jordan*

[2]*Assistant Professor, Department of Food and Nutrition, Agriculture College, University of Jordan, Amman, Jordan*

[3]*Professor, Department of Food and Nutrition, Agriculture college, Amman, Jordan*

ABSTRACT

Advanced glycation end products (AGEs), also known as glycotoxins, are extremely reactive compounds produced during glycation processes from endogenous or exogenous sources. They include the generation of the various group of compounds that are formed when reducing sugar, reacts in a non-enzymatic way with amino acids in proteins and other macromolecules. Those produce could play an important role in health, especially in diabetic complications, cardiovascular diseases, as well as delayed wound healing. Dietary AGEs intake contributes to the body AGE pool further prompting oxidative stress and progression inflammation. Furthermore, dietary AGEs are now considered as pathogenic disease precursors that employ multiple molecular mechanisms to influence cell and tissue physiology. The purpose of this review is to investigate the role of dietary AGEs in Type II diabetes and related complication risk.

KEYWORDS: *AGEs, Diabetes, Diabetic Complications, Inflammation*

Article History

Received: *24 May 2018* | ***Revised:*** *01 Jun 2018* | ***Accepted:*** *19 May 2018*

INTRODUCTION

Advanced glycation end products (AGEs) are a complex group of extremely oxidant and biologically reactive compounds formed via a series of chemical chain reactions, which form through oxidation of sugars, lipids, and amino acids to create aldehydes that bind covalently to proteins [1,2]. The formation of AGEs is a normal part occurs during the aging process. However, most immediate and extreme accumulation occurs in patients with constant hyperglycemia and persistent oxidative stress [3]. Elevated blood glucose, a common consequence of uncontrolled diabetes, may lead to the development of macro- and microvascular problems [4]. It has been suggested that there is a linear relationship between hyperglycemia, increased oxidative stress, pro-inflammatory effects and excessive formation of AGEs [5]. Recently, Dietary AGEs intake considered as pathogenic disease precursors that employ and promoting oxidative stress, and progression inflammation reactions [6]. Pentosidine and ε-N carboxymethyl-l-lysine (CML) has been well considered as biomarkers for the creation and accumulation of AGEs [7] and are recognized to play a crucial role in the path physiology of diabetes chronic complications [5].

AGEs Sources

AGEs sources are endogenous exogenous. Endogenously, AGEs are formed as by-products of hyperglycemia [8]. Also, the formation of AGEs occurs in all tissues and body fluids under physiological conditions through glycation reactions [9]. It occurs in a spontaneous way with a small proportion of absorbed, simple sugars [10]. Moreover, AGEs can be formed from a variety of precursors for the Maillard reaction. The formation of AGE is usually endogenous but can be derived from exogenous sources such as tobacco smoke or food [11].

Exogenously, AGEs are a complex group of compounds that are formed through the Maillard reaction [12]. This reaction involves of some stages the first stage, glycation is started by the covalent attachment of reducing sugars to amino groups of proteins, lipids, or nucleic acids to produce reversible and an unstable Schiff base. Then, the Schiff base may undergo Amadori reorganization and alteration to a more stable Amadori product [9]. Consequently, Amadori products undergo more structural alterations through oxidation, dehydration, and degradation of lastly yield extremely stable AGEs compounds [9, 12]. Furthermore, a diversity of other pathways such as autoxidation of glucose, ascorbate or lipid peroxidation, can also lead to AGE creation. The producers of this pathway usually are dicarbonyl intermediates such as methylglyoxal (MGO), glyoxal (GO), 3-deoxyglucosone (3-DG), glycolaldehyde, 1-deoxyglucosone [13] and free radicals [14].

In biological systems, the process of AGEs formation begins under certain conditions, such as. Hyperglycemia, and/or an increase oxidative stress condition [15], also affecting short-lived substrates like hormones, enzymes, amino acids or lipids, and thus inducing functional and/or structural changes [16]. AGEs are formed continuously in the body, as a part of normal metabolism, but if the amount of AGEs is excessively high in circulation and tissue, they have possibilities to become pathogenic, which may cause the advancement and generation of chronic diseases [12]. The toxic effects of AGEs are specially related to their ability to promote inflammation and oxidative stress by binding to cell surface receptors or cross-linking with body proteins, altering their structure and function [17].

Mechanism of Action

The biological significances of AGEs can be exerting their impacts within the body by two different mechanisms. First one is structural distortion or stimulates crosslinking of body proteins, and the other one is interacting with AGE receptors. AGEs encourage protein cross linking and promote protein aggregation or tissue stiffness that contribute to losing their original function and stimulated endogenous generation of AGEs in diabetes complication [18].

AGEs cross-linking with proteins depends on both the concentration of blood glucose and the rate turnover level of body proteins. Long-lived proteins are therefore more often changed by AGEs [19]. The proteins collagen and low-density lipoprotein (LDL) are also responsive to AGE cross-linking, subsequently stimulated arterial thickness and reduced uptake by LDL receptors [20]. Usually, AGEs accumulate in different organs appears to be correlated to diabetic micro -vascular complications and atherosclerotic [21]. Moreover, AGE deposition of collagen leads to changes in the biochemical and structural property of the basement membrane affecting for instance, its elasticity, ionic charge, and stiffness [22]. Consequently, it has been demonstrated that accretion of AGE–cross-linking formed with vessel-wall collagen and basement membrane proteins, can lead to vascular dysfunction [23].

AGEs Receptors

One of the main mechanisms of action of AGEs may be via AGE sensitive receptors. These include AGEs

receptor (RAGE), oligosaccharyltransferase complex protein 48 (OST-48 or AGER1), 80 K-H proteins (AGER2), galectin-3 (AGER3), and some scavenger receptors [24]. These receptors are present on vascular, renal, hemopoietic, and neuronal/ glial cells, and they serve in the regulation of AGEs uptake and removal. The AGEs receptors also modify cell stimulation, growth-related mediators, and cell proliferation, hence influencing organ structure and function. Furthermore, these receptors have been shown to play distinct functional roles in AGEs toxicity or detoxification [25]. Among the AGE -binding proteins, RAGE and AGER1 seem to be the most important, and in particular, RAGE has been thoroughly investigated [26].

RAGE Passive Enable of Inflammation

RAGE is a single trans-membrane multi-ligand receptor which belongs to the immunoglobulin superfamily, whose members involve AGE-R, SR-A (macrophage scavenger receptor types I and II), and SR- B (SR-B type and CD36) [27]. RAGE receptors are physiologically mostly expressed in a varied range of tissues, including the vascular, endothelial, smooth muscle cells, neural tissue, and mononuclear cells [28].

The interaction between AGEs and RAGE prompted the stimulating of the mitogen-activated protein kinases (MAPKs), the phosphatidylinositol-3 kinase (PI3-K), and the nicotinamide adenine dinucleotide phosphate-oxidase (NADPH) [29]. The stimulation of these pathways could lead to the stimulation of the transcription factor NF-kB (nuclear factor kappa B) which activates the transcription of genes for proinflammatory cytokines, growth factors and adhesive molecules, such as tumor necrosis factor a (TNF-a), interleukin 6 (IL-6) and vascular cell adhesion molecule 1 (VCAM-1) [30]. Induction of these pro-inflammatory molecules might contribute to cellular dysfunction and damage target to organs, and in the end lead to complications as atherosclerosis, cardiovascular disease, and nephropathy [31]. Also, dietary AGEs have been shown to act as RAGE ligands and activate major signal transduction pathways in vitro [32].

Factors that Influence the Formation of AGEs During Food Heat Treatment

Factors that influence the rate of AGEs generation depend on nutrient components, thermal processing, and water content during cooking, pH condition, the presence of precursors, availability of some metal ions, and pro-antioxidants [33]. Also, low moisture, prolonged cooking time [34]. At higher moisture levels, a decrease in reaction rate is observed due to dilution of the reactants in the aqueous phase. Water is a product of the reaction and it is probable that the law of mass action also leads to a decreased rate of reaction at high moisture levels [35]. Thus, foods with higher protein or lipid content are more susceptible to accelerate of AGEs formation during dry-heat processing [36]. The methods of heat treatment of foods seem to be more important to AGE generation than period of cooking time. An increase in temperature increases the rate of Maillard browns. More dAGE values are produced in foods exposed to dry heat cooking (grilling, frying, roasting, baking, and barbecuing) than foods cooked at lower temperatures for longer time periods in the presence of higher water content (boiling, steaming, poaching, stewing, or slow cooking) [37]. Excessive browning by high-heat cooking causes unpleasant changes in the food products and may produce potential mutagenic agents, such as Acryl amide, heterocyclic amines, and poly cyclic aromatic hydrocarbons [38].

There are many plans to decrease the dAGE intake by adding some herbs and spices; it has been described to have essential anti-glycation activity [39]. For example, Pre-marinating in acidic solution has been confirmed to impede the new AGE generation in cooked meat established that Phenolic compounds such as; rosemary, sage and marjoram are good strong inhibitors of CML production [8].

Spice extracts, such as cloves and cinnamon, were also found to inhibit CML generation in foods than herb extracts[58]. Since foods, mainly composed of carbohydrate group generally contain lower amounts of AGEs due to the higher content of water and non-reducing sugars compared with meat and fats [8, 40].

Dietary AGEs: Intestinal Absorption and Bioavailability

Lack understanding about the activity and metabolic effect of dietary AGEs. In recent years, it has become clear that knowledge about the creation of AGEs and their precursors within the food. In food, glycated amino acids are bound in protein and cannot be absorbed intestinally until the proteins are digested by gastric and intestinal peptidases into peptides and free amino acids. AGE-modified peptides are able to penetrate the gastrointestinal mucin layer, where they undergo further proteolytic cleavage into di- and tri-peptides at the intestinal brush-border in order to facilitate their absorption [41].

Low-molecular-weight AGEs (AGEs on free amino acids and those bound to di- and tri-peptides) are likely to be well absorbed by either simple diffusion or by peptide transporter proteins such as peptide transporter-1 [42]. However, cross linking low molecular- weight AGEs are less available for absorption because of their resistance to digestive enzymes. Moreover, most higher-molecular-weight AGEs also escape digestion in the upper gastrointestinal tract, primarily as an absolute result of cross linking and protein aggregation, and pass through to the large intestine, eventually being excreted in the feces and/or acting as a fermentation substrate for colonic microorganisms. Following bacterial fermentation, amino acids may become available as substrates for the formation of further toxic metabolites [43].

Kinetic studies have assessed that 10% to 30% of the diet obtained AGEs consumed are entering the intestinal metabolism and circulation system [44]. This suggests that the digestive barrier limits the bioavailability of food-derived AGEs, but the small amount absorbed could participate in the carbonyl stress, mainly in the case of associated diseases, such as diabetes or nephropathy [45]. The fate of the remaining 70%–90% of dietary AGEs that escape digestion and absorption in the human small intestine warrants further investigation. Since amino acids molecularly modified by heat are more probable to escape digestion in the upper gut [2] a significant proportion of dietary Maillard reaction products (MRPs) reach the colon, where they may modulate gut microbial growth [46].

Recent studies indicate that consumption of a high-AGE diet for 2 weeks is sufficient to alter the colonic bacteria profile in humans [47]. Some studies have confirmed that a high-AGE diet results in significantly higher plasma AGEs levels (increased by 64.5%, $p = 0.02$), and increased mediators (tumor necrosis factor α, IL-1β, IL-6, and vascular adhesion molecule) of vascular dysfunction [27]

Dietary AGEs and Health Implications

Nutrient composition, temperature processing used in food processing and type of food preparation, cooking can influence the creation of AGEs in foods. Methods, Preparation by dry or high heat processed foods that containing sugars and/or lipids and proteins increase AGEs generation than carbohydrates boiled for the long time. Non-enzymatic browning reactions and generate AGEs [48].

Food-derived AGEs induce protein cross-linking and intracellular oxidant stress similar to their endogenous equivalents when tested in vitro using human-derived endothelial cells [49]. These pro oxidant and pro-inflammatory properties are as well found in the circulating AGE portions obtained from these exogenous AGEs. In a group of diabetic patients, dietary AGE restriction was associated with significant reduction of two biomarkers of inflammation, plasma

CRP and peripheral mononuclear cell TNF-α, in addition to of VCAM-1, an indicator of endothelial dysfunction [26]. These consequences were later extended to chronic renal failure patients on maintenance peritoneal dialysis, in whom dietary AGE restriction was linked with a parallel decrease of serum AGEs and CRP [50]. The parallel changes of serum AGEs and CRP succeeds dietary AGE alterations are highly indicative of a role for dietary AGEs in promoting inflammation processes. Continuous exposure to raised levels of endogenous and exogenous AGEs or advanced lip oxidation end products are thought to stimulate the pathogenesis and development of a variety of chronic conditions connected with immune cell activation and low-grade inflammation [51].

Diabetic Complications Pathogenesis are Correlated with AGES

AGEs contribute to aging and disease by diverse mechanisms. The formation of AGEs and accumulation in the body is natural processes during ageing, also increase rates of AGE accretion can accelerate the aging process [52]. The aggregate of AGEs depends on the degree of formation, determined by ROS and decreasing sugars, and the rate of removal, determined by the activity of the glyoxalase system, where glyoxalase I (Glo I) is able to detoxify reactive carbonyl compounds [53]. Aging can affect an imbalance in this system, since ROS is present in a larger extent while Glo I activity is decreased. Glycation produces AGEs compounds with toxic properties linked with inflammation and oxidative stress [3]. In addition, AGE accumulation is aggravated in some chronic diseases. AGEs can impair cells and tissues through several mechanisms and thereby contribute to aging or disease [54].

In diabetes or renal disease, AGEs generate more rapidly due to glycative and oxidative stress or weakened renal clearance [55]. Then that lead to stimulate the progression and development of diabetes problems, including micro vascular complication. AGEs employ their negative effects on cell functions by several mechanisms such as the creation of free radicals, altering enzyme activity, adapting immunogenicity, oxidation of nucleic acids or lipids or interact with AGEs receptors on the cell surface [56].

AGEs and Cardiovascular Diseases

AGEs could contribute to the development of heart failure by different mechanisms; AGEs can affect the physiological properties of proteins in the ECM by inducing the formation of cross-links. Also, AGEs can cause intracellular changes in vascular and myocardial tissue via interaction with AGE receptor [57]. The collagen-AGEs cross linking will produce stiffness of blood vessels [58]. Vascular stiffening alters the elasticity of large arteries and induces increased systolic pressures, with deleterious consequences on the heart, including cardiac hypertrophy and increased ventricular oxygen consumption [59]. Additionally, AGEs may exert the cardiovascular system impairment by reduction of LDL uptake by cell receptor [60]. AGE also induces the release of pro-fibrotic proteins, Transforming Growth Factor (TGF) and pro-inflammatory cytokines, such as IL-6 and TNF-α [61]. AGE concentration correlates with free fatty acids levels, which are increased in patients with visceral fat, who are at high risk for cardiovascular diseases[62]. Consequently, AGEs accumulation could describe some of the cardiovascular alterations related to the cardiac diseases seen in diabetes, such as vascular stiffening, endothelial dysfunction and diastolic dysfunction [4].

AGEs and Diabetes Micro-Vascular Complications

AGEs in Diabetic Retinopathy

Retinopathy is a severe vascular complication of diabetes, which may progressively lead to blindness. In diabetic retinopathy, the accumulation of AGEs leads to disorders like thickening of the capillary basement membrane, enhancing

of permeability of capillaries and vascular leakage, apoptosis of pericytes [63]. Apoptosis of pericytes is a key factor in retinopathy by triggering endothelial activation and dysfunction, leading tone angiogenesis and thrombogenesis [64]. Hyperglycemia stimulates an excessive expression of RAGE on pericytes and endothelial cells, leading to a deterioration of pericytes and loss of pericytes ,which result in vascular damage and clinical expression of retinopathy [65]. In addition, subjects with retinopathy were found to have increased levels of AGEs and IL-6 in the eye vitreous. IL-6 could also promote angiogenesis by increasing expression of the vascular endothelial growth factor [9]. which leads to blindness or poorness of vision [66].

AGEs in Diabetic Nephropathy

A progressive loss of kidney function has been clearly demonstrated in diabetic patients, correlating with increasing circulating AGE levels [67]. Patients with diabetic nephropathy have a dual form of damage; an increased formation of serum AGEs and reducing in their clearance [68]. Diabetic nephropathy is characterized by a thickening of the basement membrane, expansion of the mesangium, decreased filtration, albuminuria, and renal failure. The number of AGEs that have been detected in renal tissues were correlated with the severity of diabetic nephropathy [69].

AGEs play a key role in glomerular nephropathy as they accumulate in glomerular basement membrane and interact with mesangial cells, endothelial cells, and podocytes, to trigger oxidative stress, inflammatory signaling, and apoptosis [70]. Hyperglycemia and serum elevation of AGEs enhance the level of transforming growth factor-b (TGF-b), which stimulates the formation of the collagen matrix and basal membrane thickening [71]. Furthermore, accretion of growth factors that promote vascular permeability and reduces barrier activities, which may result in a kidney malfunction. Oxidative stress and the secretion of growth factors and cytokines are involved in AGEs-induced nephropathy and are entangled with the activation of the reninangiotensin system, which also generates ROS and growth factors [72].

AGEs in Diabetic Neuropathy

Diabetic neuropathy is characterized by segmental demyelination and axonal degeneration of peripheral neurons, with functional abnormalities such as reduced nerve conduction and blood flow. Peripheral neuropathy is a common diabetes complication associating nerve dysfunction and loss of pain perception, associated with an increased risk for developing ulcerations and necrosis, particularly diabetic foot, and impaired wound healing (potentially leading to lower-limb amputation) [73]. High levels of AGEs have also been found in the peripheral nerves of diabetic patients [24]. In vitro studies have shown an increased glycation of myelin in diabetes. Nerve demyelination seen in diabetic neuropathy could be explained by phagocytosis of the glycated myelin by macrophages [74]. The AGE-RAGE interactions determine the upregulation of nuclear factor kappa B (NF-kB), protein kinase Cβ2 and various NFkB facilitated pro-inflammatory genes, an augmented neurological dysfunction, including altered pain sensation and stimulation of the creation of new glycoxidation products such as N-epsilon-(carboxymethyl)-lysine and pentosidine [75]. In animal studies, when AGEs are injected into peripheral nerves there is a reduction of sensory-motor conduction velocities, nerve action potentials, and blood flow [9]. However, the mechanism by which AGEs could be involved in diabetic neuropathy is not clear.

CONCLUSIONS

The process of advanced glycation seems to be improved in the diabetes mellitus as a result of hyperglycemia and other stimuli such as oxidative stress and generation of pro-inflammatory pathways, which further leads to the progression and development of diabetic complications. Endogenous AGEs and dietary AGE intake contribute significantly to the body

AGE pool. Dietary AGEs are now considered as pathogenic disease precursor that employ multiple molecular mechanisms to affect cell and tissue physiology via activating pro-oxidant and pro-inflammatory signaling pathways. Finally, large clinical trials are demanded to study the effects of dietary AGEs in as an important approach to reduce diabetic complications and the optimal strategies must be prepared to minimize AGE -related pathology.

REFERENCES

1. *Gkogkolou P, Böhm M. Advanced glycation end products: key players in skin aging?. Dermato-endocrinology 2012;4(3):259-70.*
2. *Ahmed N, LüTHEN R, Häussinger D, ŠebekovÁ K, Schinzel R, Voelker W, Heidland A, Thornalley PJ. Increased protein glycation in cirrhosis and therapeutic strategies to prevent it. Annals of the New York Academy of Sciences 2005;1043(1):718-24.*
3. *Ramasamy R, Yan SF, Schmidt AM. Advanced glycation endproducts: from precursors to RAGE: round and round we go. Amino Acids. 2012;42(4):1151-61.*
4. *Fukami KE, Ueda S, Yamagishi SI, Kato S, Inagaki Y, Takeuchi M, Motomiya Y, Bucala R, Iida S, Tamaki K, Imaizumi T. AGEs activate mesangial TGF-β–Smad signaling via an angiotensin II type I receptor interaction. Kidney International 2004;66(6):2137-47.*
5. *Zieman SJ, Kass DA. Advanced glycation endproduct crosslinking in the cardiovascular system. Drugs 2004;64(5):459-70.*
6. *Chilelli NC, Burlina S, Lapolla A. AGEs, rather than hyperglycemia, are responsible for microvascular complications in diabetes: a "glycoxidation-centric" point of view. Nutrition, Metabolism and Cardiovascular Diseases 2013;23(10):913-9.*
7. *Luévano-Contreras C, Garay-Sevilla ME, Wrobel K, Malacara JM, Wrobel K. Dietary advanced glycation end products restriction diminishes inflammation markers and oxidative stress in patients with type 2 diabetes mellitus. Journal of clinical Biochemistry and Nutrition 2013;52(1):22-6.*
8. *Ghanem AA, Elewa A, Arata LF. Pentosidine and N-carboxymethyl-lysine: biomarkers for type 2 diabetic retinopathy. European Journal of Ophthalmology 2011;21(1):48.*
9. *Ahmed N. Advanced glycation endproducts—role in pathology of diabetic complications. Diabetes Research and Clinical Practice 2005;67(1):3-21.*
10. *Omsland TK, Bangstad HJ, Berg TJ, Kolset SO. Advanced glycation end products and hyperglycaemia. Tidsskriftfor den Norske Laegeforening: Tidsskrift for PraktiskMedicin, nyRaekke 2006;126(2):155-8.*
11. *Nicholl ID, Stitt AW, Moore JE, Ritchie AJ, Archer DB, Bucala R. Increased levels of advanced glycation endproducts in the lenses and blood vessels of cigarette smokers. Molecular Medicine 1998;4(9):594.*
12. *Vlassara H. Recent progress in advanced glycation end products and diabetic complications. Diabetes 1997;46:S19.*
13. *Méndez JD, Xie J, Aguilar-Hernández M, Méndez-Valenzuela V. Trends in advanced glycation end products research in diabetes mellitus and its complications. Molecular and Cellular Biochemistry 2010;341(1-2):33-41.*

14. *Zhang Q, Ames JM, Smith RD, Baynes JW, Metz TO. A perspective on the Maillard reaction and the analysis of protein glycation by mass spectrometry: probing the pathogenesis of chronic disease. Journal of Proteome Research 2008;8(2):754-69.*

15. *Elosta A, Ghous T, Ahmed N. Natural products as anti-glycation agents: possible therapeutic potential for diabetic complications. Current Diabetes Reviews 2012;8(2):92-108.*

16. *Schiekofer S, Andrassy M, Chen J, Rudofsky G, Schneider J, Wendt T, Stefan N, Humpert P, Fritsche A, Stumvoll M, Schleicher E. Acute hyperglycemia causes intracellular formation of CML and activation of ras, p42/44 MAPK, and nuclear factor κB in PBMCs. Diabetes 2003;52(3):621-33.*

17. *Hunter SJ, Boyd AC, O'Harte FP, McKillop AM, Wiggam MI, Mooney MH, McCluskey JT, Lindsay JR, Ennis CN, Gamble R, Sheridan B. Demonstration of glycated insulin in human diabetic plasma and decreased biological activity assessed by euglycemic-hyperinsulinemic clamp technique in humans. Diabetes 2003;52(2):492-8.*

18. *Nin JW, Jorsal A, Ferreira I, Schalkwijk CG, Prins MH, Parving HH, Tarnow L, Rossing P, Stehouwer CD. Higher plasma levels of advanced glycation end products are associated with incident cardiovascular disease and all-cause mortality in type 1 diabetes: a 12-year follow-up study. Diabetes Care 2011;34(2):442-7.*

19. *Uribarri J, del Castillo MD, de la Maza MP, Filip R, Gugliucci A, Luevano-Contreras C, Macías-Cervantes MH, MarkowiczBastos DH, Medrano A, Menini T, Portero-Otin M. Dietary advanced glycation end products and their role in health and disease. Advances in nutrition. 2015 Jul 7;6(4):461-73.*

20. *Thorpe SR, Baynes JW. Maillard reaction products in tissue proteins: new products and new perspectives. Amino Acids 2003;25(3-4):275-81.*

21. *Brownlee M. The pathological implications of protein glycation. Clinical and investigative medicine. MedecineClinique et Experimentale1995;18(4):275-81.*

22. *Zieman SJ, Kass DA. Advanced Glycation End Product Cross□Linking: Pathophysiologic Role and Therapeutic Target in Cardiovascular Disease. Congestive Heart Failure 2004;10(3):144-51.*

23. *Goh SY, Cooper ME. The role of advanced glycation end products in progression and complications of diabetes. The Journal of Clinical Endocrinology & Metabolism 2008;93(4):1143-52.*

24. *Reddy MA, Natarajan R. Role of epigenetic mechanisms in the vascular complications of diabetes. InEpigenetics: Development and Disease 2013 (pp. 435-454), Springer Netherlands.*

25. *Šebeková K, Somoza V. Dietary advanced glycation end products (AGEs) and their health effects–PRO. Molecular Nutrition & Food Research 2007;51(9):1079-84.*

26. *Uribarri J, Woodruff S, Goodman S, Cai W, Chen X, Pyzik R, Yong A, Striker GE, Vlassara H. Advanced glycation end products in foods and a practical guide to their reduction in the diet. Journal of the American Dietetic Association 2010; 110(6):911-6.*

27. *Thornalley PJ. Cell activation by glycated proteins. AGE receptors, receptor recognition factors and functional classification of AGEs. Cellular and Molecular Biology (Noisy-le-Grand, France) 1998;44(7):1013-23.*

28. *Vlassara H, Cai W, Crandall J, Goldberg T, Oberstein R, Dardaine V, Peppa M, Rayfield EJ. Inflammatory mediators are induced by dietary glycotoxins, a major risk factor for diabetic angiopathy. Proceedings of the National Academy of Sciences 2002;99(24):15596-601.*

29. *Han C, Lu Y, Wei Y, Liu Y, He R. D-ribose induces cellular protein glycation and impairs mouse spatial cognition. PLoS One 2011;6(9):e24623.*

30. *Nedić O, Rattan SI, Grune T, Trougakos IP. Molecular effects of advanced glycation end products on cell signalling pathways, ageing and pathophysiology. Free Radical Research 2013;47(sup1):28-38.*

31. *Boyer F, Vidot JB, Dubourg AG, Rondeau P, Essop MF, Bourdon E. Oxidative stress and adipocyte biology: focus on the role of AGEs. Oxidative Medicine and Cellular Longevity 2015;2015.*

32. *Brett J, Schmidt AM, Du Yan S, Zou YS, Weidman E, Pinsky D, Nowygrod R, Neeper M, Przysiecki C, Shaw A, Migheli A. Survey of the distribution of a newly characterized receptor for advanced glycation end products in tissues. The American Journal of Pathology 1993;143(6):1699.*

33. *Bierhaus A, Humpert PM, Morcos M, Wendt T, Chavakis T, Arnold B, Stern DM, Nawroth PP. Understanding RAGE, the receptor for advanced glycation end products. Journal of Molecular Medicine 2005;83(11):876-86.*

34. *Fleming TH, Humpert PM, Nawroth PP, Bierhaus A. Reactive metabolites and AGE/RAGE-mediated cellular dysfunction affect the aging process–a mini-review. Gerontology 2011;57(5):435-43.*

35. *Penfold SA, Coughlan MT, Patel SK, Srivastava PM, Sourris KC, Steer D, Webster DE, Thomas MC, MacIsaac RJ, Jerums G, Burrell LM. Circulating high-molecular-weight RAGE ligands activate pathways implicated in the development of diabetic nephropathy. Kidney International 2010;78(3):287-95.*

36. *Somoza V, Wenzel E, Lindenmeier M, Grothe D, Erbersdobler HF, Hofmann T. Influence of feeding malt, bread crust, and a pronylated protein on the activity of chemopreventive enzymes and antioxidative defense parameters in vivo. Journal of Agricultural and Food Chemistry 2005;53(21):8176-82.*

37. *Vlassara H, Uribarri J. Glycoxidation and diabetic complications: modern lessons and a warning?. Reviews in Endocrine and Metabolic Disorders 2004;5(3):181-8.*

38. *Lee TC, Kimiagar M, Pintauro SJ, Chichester CO. Physiological and safety aspects of Maillard browning of foods. Progress in food & nutrition science 1981;5(1-6):243.*

39. *Mark AB, Poulsen MW, Andersen S, Andersen JM, Bak MJ, Ritz C, Holst JJ, Nielsen J, de Courten B, Dragsted LO, Bügel SG. Consumption of a diet low in advanced glycation end products for 4 weeks improves insulin sensitivity in overweight women. Diabetes Care 2014; 37(1):88-95.*

40. *Goldberg T, Cai W, Peppa M, Dardaine V, Baliga BS, Uribarri J, Vlassara H. Advanced glycoxidation end products in commonly consumed foods. Journal of the American Dietetic Association 2004; 104(8):1287-91.*

41. *Jaegerstad M, Skog K. Genotoxicity of heat-processed foods. Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis 2005 ;574(1):156-72.*

42. *Corzo-Martínez M, Sánchez CC, Moreno FJ, Patino JM, Villamiel M. Interfacial and foaming properties of bovine β-lactoglobulin: Galactose Maillard conjugates. Food Hydrocolloids 2012;27(2):438-47.*

43. *Dearlove RP, Greenspan P, Hartle DK, Swanson RB, Hargrove JL. Inhibition of protein glycation by extracts of culinary herbs and spices. Journal of Medicinal Food 2008;11(2):275-81.*

44. *Hellwig M, Bunzel D, Huch M, Franz CM, Kulling SE, Henle T. Stability of individual Maillard reaction products in the presence of the human colonic microbiota. Journal of Agricultural and Food Chemistry 2015;63(30):6723-30.*

45. *Hellwig M, Geissler S, Matthes R, Peto A, Silow C, Brandsch M, Henle T. Transport of Free and Peptide□Bound Glycated Amino Acids: Synthesis, Transepithelial Flux at Caco□2 Cell Monolayers, and Interaction with Apical Membrane Transport Proteins. Chem Bio Chem 2011;12(8):1270-9.*

46. *Tuohy KM, Hinton DJ, Davies SJ, Crabbe MJ, Gibson GR, Ames JM. Metabolism of Maillard reaction products by the human gut microbiota–implications for health. Molecular Nutrition & Food Research 2006;50(9):847-57.*

47. *Faist V, Erbersdobler HF. Metabolic transit and in vivo effects of melanoidins and precursor compounds deriving from the Maillard reaction. Annals of Nutrition and Metabolism 2001;45(1):1-2.*

48. *Koschinsky T, He CJ, Mitsuhashi T, Bucala R, Liu C, Buenting C, Heitmann K, Vlassara H. Orally absorbed reactive glycation products (glycotoxins): an environmental risk factor in diabetic nephropathy. Proceedings of the National Academy of Sciences 1997;94(12):6474-9.*

49. *Rai V, Touré F, Chitayat S, Pei R, Song F, Li Q, Zhang J, Rosario R, Ramasamy R, Chazin WJ, Schmidt AM. Lysophosphatidic acid targets vascular and oncogenic pathways via RAGE signaling. Journal of Experimental Medicine 2012;209(13):2339-50.*

50. *Seiquer I, Rubio LA, Peinado MJ, Delgado□Andrade C, Navarro MP. Maillard reaction products modulate gut microbiota composition in adolescents. Molecular Nutrition & Food Research 2014;58(7):1552-60.*

51. *Poulsen MW, Hedegaard RV, Andersen JM, de Courten B, Bügel S, Nielsen J, Skibsted LH, Dragsted LO. Advanced glycation endproducts in food and their effects on health. Food and Chemical Toxicology 2013;60:10-37.*

52. *Cai J, Boulton M. The pathogenesis of diabetic retinopathy: old concepts and new questions. Eye 2002;16(3):242.*

53. *Uribarri J, Peppa M, Cai W, Goldberg T, Lu M, He C, Vlassara H. Restriction of dietary glycotoxins reduces excessive advanced glycation end products in renal failure patients. Journal of the American Society of Nephrology 2003;14(3):728-31.*

54. *Šebeková K, Boor P, Valachovičová M, Blažíček P, Parrák V, Babinská K, Heidland A, Krajčovičová□Kudláčková M. Association of metabolic syndrome risk factors with selected markers of oxidative status and microinflammation in healthy omnivores and vegetarians. Molecular Nutrition & Food Research 2006;50(9):858-68.*

55. *Jin K. Modern biological theories of aging. Aging and Disease 2010;1(2):72.*

56. *Xue M, Rabbani N, Thornalley PJ. Glyoxalase in ageing. InSeminars in cell & developmental biology 2011 May 1 (Vol. 22, No. 3, pp. 293-301). Academic Press.*

57. *Lander HM, Tauras JM, Ogiste JS, Hori O, Moss RA, Schmidt AM. Activation of the receptor for advanced*

glycation end products triggers a p21 ras-dependent mitogen-activated protein kinase pathway regulated by oxidant stress. Journal of Biological Chemistry 1997;272(28):17810-4.

58. *Basta G, Lazzerini G, Massaro M, Simoncini T, Tanganelli P, Fu C, Kislinger T, Stern DM, Schmidt AM, De Caterina R. Advanced glycation end products activate endothelium through signal-transduction receptor RAGE: a mechanism for amplification of inflammatory responses. Circulation 2002;105(7):816-22.*
59. *Magalhães PM, Appell HJ, Duarte JA. Involvement of advanced glycation end products in the pathogenesis of diabetic complications: the protective role of regular physical activity. European Review of Aging and Physical Activity 2008;5(1):17.*
60. *Bodiga VL, Eda SR, Bodiga S. Advanced glycation end products: role in pathology of diabetic cardiomyopathy. Heart Failure Reviews 2014;19(1):49-63.*
61. *Norton GR, Candy G, Woodiwiss AJ. Aminoguanidine prevents the decreased myocardial compliance produced by streptozotocin-induced diabetes mellitus in rats. Circulation 1996 ;93(10):1905-12.*
62. *Smit AJ, Lutgers HL. The clinical relevance of advanced glycation endproducts (AGE) and recent developments in pharmaceutics to reduce AGE accumulation. Current Medicinal Chemistry 2004;11(20):2767-84.*
63. *Posch K, Simecek S, Wascher TC, Jürgens G, Baumgartner-Parzer S, Kostner GM, Graier WF. Glycated low-density lipoprotein attenuates shear stress-induced nitric oxide synthesis by inhibition of shear stress-activated L-arginine uptake in endothelial cells. Diabetes 1999;48(6):1331-7.*
64. *Lichiardopol R, Florentiu A, Radoi V. Body composition and the metabolic impact of weight excess in patients with type 1 and type 2 diabetes mellitus. ActaEndocrinologica 2010 ;6(4): (1841-0987)*
65. *Kavitha M, Aruna S & Valli G, Effectiveness of Cognitive Behavioural Nursing Intervention on Self Efficacy among Patinets with Type-II Diabetes Mellitus, International Journal of Humanities and Social Sciences (IJHSS), Volume 7, Issue 3, April-May 2018, pp. 19-26*
66. *Milne R, Brownstein S. Advanced glycation end products and diabetic retinopathy. Amino Acids 2013;44(6):1397-407.*
67. *Wautier JL, Schmidt AM. Protein glycation: a firm link to endothelial cell dysfunction. Circulation Research 2004;95(3):233-8.*
68. *Yamagishi SI, Nakamura K, Matsui T. Advanced glycation end products (AGEs) and their receptor (RAGE) system in diabetic retinopathy. Current Drug Discovery Technologies 2006;3(1):83-8.*
69. *Yamagishi SI. Role of advanced glycation end products (AGEs) and receptor for AGEs (RAGE) in vascular damage in diabetes. Experimental Gerontology 2011 ;46(4):217-24.*
70. *Genuth S, Sun W, Cleary P, Sell DR, Dahms W, Malone J, Sivitz W, Monnier VM. Glycation and carboxymethyllysine levels in skin collagen predict the risk of future 10-year progression of diabetic retinopathy and nephropathy in the diabetes control and complications trial and epidemiology of diabetes interventions and complications participants with type 1 diabetes. Diabetes. 2005 Nov 1;54(11):3103.*
71. *Yamagishi SI, Matsui T. Advanced glycation end products, oxidative stress and diabetic nephropathy. Oxidative*

Medicine and Cellular Longevity 2010;3(2):101-8.

72. *Sugiyama S, Miyata T, Horie K, Iida Y, Tsuyuki M, Tanaka H, Maeda K. Advanced glycation end-products in diabetic nephropathy. Nephrology Dialysis Transplantation 1996;11(supp5):91-4.*
73. *Fukami K, Yamagishi SI, Ueda S, Okuda S. Role of AGEs in diabetic nephropathy. Current Pharmaceutical Design 2008;14(10):946-52.*
74. *Tan KC, Shiu SW, Chow WS, Leng L, Bucala R, Betteridge DJ. Association between serum levels of soluble receptor for advanced glycation end products and circulating advanced glycation end products in type 2 diabetes. Diabetologia 2006;49(11):2756-62.*
75. *Huijberts MS, Schaper NC, Schalkwijk CG. Advanced glycation end products and diabetic foot disease. Diabetes/metabolism Research and Reviews 2008 1;24(S1).*
76. *Sugimoto K, Yasujima M, Yagihashi S. Role of advanced glycation end products in diabetic neuropathy. Current Pharmaceutical Design 2008;14(10):953-61.*