Advanced Glycation End Products in Diabetes Mellitus

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Contributor: Jeongmin Lee, Jae-Seung Yun, Seung-Hyun Ko

Diabetes is well established as a chronic disease with a high health burden due to mortality or morbidity from the final outcomes of vascular complications. An increased duration of hyperglycemia is associated with abnormal metabolism. Advanced glycation end products (AGEs) are nonenzymatic glycated forms of free amino acids that lead to abnormal crosslinking of extra-cellular and intracellular proteins by disrupting the normal structure. Furthermore, the interaction of AGEs and their receptors induces several pathways by promoting oxidative stress and inflammation.

Keywords: diabetes mellitus ; hyperglycemia ; chronic complication ; oxidative stress ; glycation end products ; advanced

1. Introduction

Type 2 diabetes mellitus (DM) has become increasingly prevalent over the past several decades, with an estimated prevalence of over 366 million by 2030 and over 693 million by 2045 [1][2][3]. Moreover, DM is a multifactorial and chronic metabolic disease caused by impaired metabolism of carbohydrates, fats, and proteins and ranks as the 11th leading cause of death caused by chronic complications worldwide [4]. DM is associated with morbidity and mortality due to its vascular complications. Recent studies have reported that young-onset type 2 DM (diagnosis at <40 years) has been correlated with an increased risk and higher burden of emerging complications [5][6]. As a result, the identification of diabetic complications is of considerable importance. Over the decades, research has been conducted on several alternative methods for preventing diabetic complications. Acute complications, such as hypoglycemia and hyperglycemia with ketoacidosis or hyperosmolar hyperglycemic status combined into the most serious acute life-threatening condition, can have a sudden onset [7]. In contrast, chronic complications are associated with the duration of DM (long-term exposure to hyperglycemia) and the degree of glycemic control and are categorized as microvascular complications, due to damage to small blood vessels, and macro-vascular complications due to damage to the arteries. Microvascular complications include diabetic kidney disease, diabetic retinopathy, and neuropathy. Diabetic complications such as coronary artery disease (CAD), cerebrovascular disease, and peripheral vascular disease (PVD) are categorized as macrovascular complications.

A near-normal level of intensive glycemic control helps to prevent diabetic vascular complications. Classic, established, and large-scale randomized controlled studies, such as the Diabetes Control and Complications Trial (DCCT) [8], United Kingdom Prospective Diabetes Study (UKPDS) [9], Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) [10], and Action to Control Cardiovascular Risk in Diabetes (ACCORD) [11], have investigated whether intensive glycemic control resulted in risk reduction for chronic microvascular complications. Intensive glycemic control, defined as glycated A1c (HbA1c) below 6.5–7.0%, contributes to a reduction in long-term outcomes of microalbuminuria, macroalbuminuria, polyneuropathy, and photocoagulation for DM retinopathy [8][9][10][11]. Early-stage control of DM reduces the long-term effect of hyperglycemic metabolic memory [9]. Thus, intensive glycemic control in the early stage of DM is emphasized as an effective preventive strategy against DM microvascular complications [8][9][10][11]. However, the association between intensive glycemic control and cardiocerebrovascular diseases is still not clear. In the majority of patients enrolled in these studies, the progression of complications from cardiovascular disease (CVD) was not prevented [12].

In contrast to HbA1c, advanced glycation end products (AGEs) are products of glucose–protein or glucose–lipid interactions through glycation [13]. AGEs induce tissue damage. The mechanisms, pathogenesis, and consequences of AGEs on diabetic complications are diverse. The most crucial mechanisms involved in the progression of diabetic complications are induced by chronic hyperglycemia from decreased carbohydrate, protein, and lipid metabolism. Regarding hyperglycemia and its metabolism, chronic hyperglycemia induces an increase in oxidative stress, which is considered a factor of cellular, vascular, and tissue damage [14]. The concept of “metabolic memory” has been investigated from the perspective of nonenzymatic glycation of proteins, lipids, and nucleic acids [15].

2. Sources and Formation of AGEs

AGEs originate from either endogenous or exogenous sources [16]. Approximately 30% of AGEs are absorbed into the systemic circulation via gastrointestinal absorption and the influence of the systemic burden. A high burden of AGEs is related to oxidative stress, inflammation, impaired innate defense, and insulin resistance [17]. Heterogeneous AGEs rely on the specific structure of protein-bound AGEs and are divided into protein-bound, peptide-bound, or free forms of AGEs. Unabsorbed AGEs in the colon are crucial factors for compromised glycemic control [18].

In contrast, AGEs are generated predominantly through endogenous processes via the nonenzymatic reaction of glucose-derived carbonyls with amino groups of lysine and arginine protein residues by forming unstable Schiff bases and stable Amadori products or fructosyl lysine, such as glycated hemoglobin, which is used in the diagnosis of DM, or follow-up modalities, and fructosamine [19]. This process, involving the formation of Schiff bases and Amadori products, is known as the Maillard reaction [20]. Both of these compounds are reversible and react irreversibly with protein and peptide to form crosslinks.

AGEs have been categorized into two groups depending on their structure: the first group includes N-carboxymethyllysine (CML), pentosidine, crossline, pyrraline, and hydroimidazolone [21]; the second group includes AGE-1 (glucose-derived AGEs), AGE-2 (glyceraldehyde-derived AGEs), AGE-3 (glycolaldehyde-derived AGEs), AGE-4 (MGO/methylglyoxal-derived AGEs), AGE-5 (glyoxal-derived AGEs), AGE-6 (3-deoxyglucosone-derived AGEs), and acetaldehyde-derived AGEs (AA-AGEs) [22].

Thus, the formation and biochemistry of AGEs have been well-established elsewhere. AGEs formation extends the damage to macromolecules in tissue with structural and functional alterations [23]. Nevertheless, the mechanism of metabolic memory-related diabetic complications needs to be further investigated.

3. AGEs Interactions with Receptors

Exogenous AGEs and spontaneously produced endogenous AGEs interact through various signaling pathways and several AGEs receptors. AGEs bind into the extracellular transmembrane receptor and initiate signaling cascades. Among several receptors, the receptor for advanced glycation end products (RAGE) is a central transduction receptor of AGEs. RAGE, which is encoded on chromosome 6 near major histocompatibility complex III, is incorporated into a member of the immunoglobulin superfamily and recognized by its three-dimensional form rather than by specific amino acid sequences [24]. RAGE is expressed everywhere at a low level of RAGE ligand: endothelial cells, macrophages, monocytes, neurons, vascular smooth muscle cells, or chondrocytes [25][26]. However, RAGE is activated with an increase in the level of RAGE ligands in inflammation and its related responses. Thus, RAGE regulates inflammation via NF-κB, TNF-α, oxidative stress, and dysfunction of endothelial cells in type 2 DM [27]. In addition to the membrane-bound form of RAGE, there are two types of circulating soluble RAGEs (sRAGE) without transmembrane and cytoplasmic domains [28]. sRAGE is produced by cleavage of the cell surface receptor (cRAGE), which is generated by matrix metalloproteinases (MMPs) or by alternative splicing of endogenous secretory RAGE (esRAGE) [29]. Ligand binding enhances RAGE shedding, and serum sRAGE is considered representative of tissue RAGE expression [30]. Isoforms such as sRAGE and esRAGE bind RAGE ligands and block the interaction between membrane RAGE and cellular responses [31]. However, the exact function of sRAGE remains uncertain.

There is evidence of an increase in low-grade inflammation in type 2 DM. High levels of AGEs in type 2 DM patients are correlated with increased RAGE mRNA expression, protein carbonyl levels, and lipid peroxidation [32]. Moreover, the activation of signaling cascades, including NF-κB, and oxidative stress from AGE/RAGE interactions stimulate inflammation and tissue injury through the expression of vascular cell adhesion molecules, monocyte chemoattractant protein-1, endothelin-1, and plasminogen activator inhibitor-1 (PAI-1), and these factors are involved in vascular and tissue damage [33][34]. Therefore, AGEs with RAGE act as surrogate markers of inflammation, and their levels increase in chronic metabolic-inflammatory disorders [26].

In addition to RAGEs, the other classes of receptors are scavenger receptors, such as Stab1and Stab2, and AGE receptors (AGERs), such as AGE-R1~AGER [35][36]. These receptors can recognize and bind AGE ligands without the transduction of cellular signaling after engagement by AGEs. They have a role in the detoxification of AGEs and of AGE-specific ligand binding with degradation [37]. The expression of AGE-R1 was decreased, and AGE levels were elevated in DM patients [38][39]. AGE-R3 is hyperactive with hyperglycemia and high levels of AGEs [40].

4. Pathogenesis of Diabetic Vascular Complications and AGEs in Type 2 DM

Chronic complications of type 2 DM are caused by structural or functional modification of the vasculature. Structural modification results from extracellular or intracellular proteins or polypeptides that are vulnerable to modification by AGEs [41]. AGEs are found in the serum, the vasculature, the retina, and various renal compartments, such as the glomerulus and basement membrane [36]. Therefore, AGEs are involved in damage to multiple tissues or organs in type 2 DM after long-term exposure to hyperglycemia. Chronic hyperglycemia in uncontrolled type 2 DM accelerates the accumulation of AGE precursors, such as MGO, and activates the protein kinase C pathway, followed by increases in oxidative stress and inflammatory cytokine levels. Along with AGE accumulation, the AGE–RAGE axis is correlated with diabetic complications in patients with type 2 DM. Long-term DM complications are mainly categorized as microvascular complications, such as diabetic retinopathy (DR), nephropathy (DN), and peripheral neuropathy (DPN), and macrovascular complications, including cardiovascular disease, cerebrovascular disease, and PVD.

4.1. Microvascular Complications and AGEs

Microvascular complications are defined as the presence of retinopathy, nephropathy with albuminuria, and neuropathy [42][43]. Different organs are linked to these complications. DN is the leading cause of renal failure and is defined as estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2, and/or microalbuminuria > 3 mg/g, or an albumin-to-creatinine ratio (ACR) ≥ 3 mg/mmol in patients with DM [44][45]. The mechanism of DN is related to glomerular hypertrophy, renal oxidative stress, and fibrosis. Glomerular changes such as the thickening of tubular basement membranes, mesangial hypertrophy, and loss of podocytes are provoked by AGEs. RAGEs are also found in tubular epithelial cells and glomerular cells, including podocytes and mesangial cells. The activation of RAGE from AGEs enhances RAGE expression. Therefore, RAGE expression is prevalent where AGEs accumulate. Tubular cells are exposed to a large amount of AGEs and increase the activation of intracellular signaling pathways via their highly expressed RAGE [46]. This process is crucial for the development of interstitial fibrosis and glomerular dysfunction during the early phase in type 2 DM [46]. Therefore, recent studies have focused on the therapeutic effects of RAGE blockade in DN [47][48][49][50].

The AGE–RAGE pathway is activated via various signaling cascades, such as phosphoinositide 3-kinase (PI3K)/protein kinase B (PKB)/IκB kinase (IKK), and NF-κB activation [37]. NF-κB binds to the RAGE promoter and enhances RAGE expression. Increased levels of NF-κB in the kidney activate glomerular and tubular cell damage and induce renal injury. NF-κB also affects adhesion molecules and proinflammatory cytokines such as interleukin (IL)-6, tumor necrosis factor (TNF)-α, and monocyte chemoattractant protein (MCP)-1. These factors are involved in the development of DN. IL-6 is involved in pathologic changes in mesangial cells, and MCP-1 plays a role in mesangial cell proliferation. The AGE–RAGE interaction promotes reactive oxygen species (ROS), and ROS enhances the Janus kinase (JAK)-signal transducer and activator of the transcription (STAT) pathway [39][51][52]. JAK-STAT signaling has a crucial role in mesangial cells, podocytes, and epithelial cells and induces glomerular hypertrophy by inducing growth factors, including tumor growth factor (TGF)-β, platelet-derived growth factor (PDGF)-β, and IGF-binding protein-related protein-2 [53]. TGF-β regulates inflammation by upregulating MCP-1 and NF-κB [54].

AGEs themselves are involved in the progression of DN. AGEs form cross-links with matrix proteins such as collagen, leading to structural changes and inducing DM glomerulosclerosis with the accumulation of plasma proteins, lipid proteins, and immunoglobulin [55]. In addition to structural changes, the nonenzymatic glycation of type IV collagen provokes vascular permeability to albumin and the interaction with negatively charged proteoglycans [56]. In renal systems, the renin–angiotensin system (RAS), which comprises renin, angiotensinogen, angiotensin I, angiotensin-converting enzyme (ACE), angiotensin II, and their receptors, is a key factor in blood pressure and fluid balance. AGEs are involved in activated angiotensin II and trigger mesangial hypertrophy [56]. Angiotensin II also induces ROS production [57][58].

DR is characterized by abnormal vascular proliferation, which accompanies hemorrhage and ischemia in the retina. AGEs and CML are located in retinal vessels, and the levels are positively correlated with DR according to previous studies [40] [59]. The AGE–RAGE pathway induces the apoptosis of pericytes and increases oxidative stress via NF-κB production. Increased levels of NF-κB upregulate vascular endothelial growth factor (VEGF) and allow endothelial permeability [60]. ROS generation, as in DN, can aggravate angiogenesis and vascular permeability. These pathologic changes cause damage to the subretinal membrane and microvasculature [61].

The role of AGEs in DPN is well established. DPN is stratified into the endothelium of the vasa nervorum, the sensory neuron (dorsal root), and Schwann cells [62]. As with DR, vascular dysfunction via the accumulation of AGEs in the endothelium of the vasa nervorum causes damage to the vascular structure and ischemia or occlusion. AGEs reduce the conduction of sensory and motor nerves and nerve blood flow [63]. The glycation of collagen and laminin induces

alterations in the basement membrane and increases the permeability of vessels. Increased RAGE levels in dorsal root neurons activate the NF-kB cascade response [64]. The AGE–RAGE pathway promotes the intracellular activation of NADPH oxidase and the production of ROS. These pathological processes affect the majority of peripheral nerves [23].

4.2. Macrovascular Complications and AGEs

Atherosclerotic CVDs, including ischemic heart disease, cerebrovascular disease, and atherosclerosis, are leading causes of death worldwide, including in Korea [65][66]. Peripheral artery disease (PAD) with critical limb ischemia is also prevalent in type 2 DM. As previously mentioned, the etiology of DM complications is based on inflammation and changes in vasculature. Similar to the microvasculature, immune response and inflammation in vasculature are key factors in the pathogenesis of CVD. AGEs accumulation has been strongly related to cardiac pathophysiology. Recently, the role of AGEs in diabetic cardiomyopathy has been characterized by triggering the production of nitric oxide (NO) and inducing ventricular remodeling [67][68]. AGEs act in the progression of CVD through the modification of extracellular and intracellular proteins and signaling cascades via AGE–RAGE pathways.

References

1. Wild, S.; Roglic, G.; Green, A.; Sicree, R.; King, H. Global prevalence of diabetes: Estimates for the year 2000 and projections for 2030. Diabetes Care 2004, 27, 1047–1053.
2. Cho, N.H.; Shaw, J.E.; Karuranga, S.; Huang, Y.; da Rocha Fernandes, J.D.; Ohlrogge, A.W.; Malanda, B. IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. Diabetes Res. Clin. Pract. 2018, 138, 271–281.
3. Jung, C.H.; Son, J.W.; Kang, S.; Kim, W.J.; Kim, H.S.; Kim, H.S.; Seo, M.; Shin, H.J.; Lee, S.S.; Jeong, S.J.; et al. Diabetes Fact Sheets in Korea, 2020: An Appraisal of Current Status. Diabetes Metab. J. 2021, 45, 1–10.
4. Global, regional, and national disability-adjusted life-years (DALYs) for 315 diseases and injuries and healthy life expectancy (HALE), 1990–2015: A systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016, 388, 1603–1658.
5. Yang, Y.S.; Han, K.; Sohn, T.S.; Kim, N.H. Young-onset type 2 diabetes in South Korea: A review of the current status and unmet need. Korean J. Intern. Med. 2021, 36, 1049–1058.
6. Park, J.H.; Ha, K.H.; Kim, B.Y.; Lee, J.H.; Kim, D.J. Trends in Cardiovascular Complications and Mortality among Patients with Diabetes in South Korea. Diabetes Metab. J. 2021, 45, 120–124.
7. Brar, P.C.; Tell, S.; Mehta, S.; Franklin, B. Hyperosmolar diabetic ketoacidosis-- review of literature and the shifting paradigm in evaluation and management. Diabetes Metab. Syndr. 2021, 15, 102313.
8. Diabetes Control and Complications Trial (DCCT). Update. DCCT Research Group. Diabetes Care 1990, 13, 427–433.
9. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998, 352, 837–853.
10. Study rationale and design of ADVANCE: Action in diabetes and vascular disease--preterax and diamicron MR controlled evaluation. Diabetologia 2001, 44, 1118–1120.
11. Buse, J.B.; Bigger, J.T.; Byington, R.P.; Cooper, L.S.; Cushman, W.C.; Friedewald, W.T.; Genuth, S.; Gerstein, H.C.; Ginsberg, H.N.; Goff, D.C., Jr.; et al. Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial: Design and methods. Am. J. Cardiol. 2007, 99, 21i–33i.
12. Gaede, P.; Lund-Andersen, H.; Parving, H.H.; Pedersen, O. Effect of a multifactorial intervention on mortality in type 2 diabetes. N. Engl. J. Med. 2008, 358, 580–591.
13. Shamsi, A.; Shahwan, M.; Husain, F.M.; Khan, M.S. Characterization of methylglyoxal induced advanced glycation end products and aggregates of human transferrin: Biophysical and microscopic insight. Int. J. Biol. Macromol. 2019, 138, 718–724.
14. Koska, J.; Saremi, A.; Howell, S.; Bahn, G.; De Courten, B.; Ginsberg, H.; Beisswenger, P.J.; Reaven, P.D. Advanced Glycation End Products, Oxidation Products, and Incident Cardiovascular Events in Patients With Type 2 Diabetes. Diabetes Care 2018, 41, 570–576.
15. Testa, R.; Bonfigli, A.R.; Prattichizzo, F.; La Sala, L.; De Nigris, V.; Ceriello, A. The “Metabolic Memory” Theory and the Early Treatment of Hyperglycemia in Prevention of Diabetic Complications. Nutrients 2017, 9, 437.

16. Garay-Sevilla, M.E.; Rojas, A.; Portero-Otin, M.; Uribarri, J. Dietary AGEs as Exogenous Boosters of Inflammation. Nutrients 2021, 13, 2802.

17. Vlassara, H.; Cai, W.; Tripp, E.; Pyzik, R.; Yee, K.; Goldberg, L.; Tansman, L.; Chen, X.; Mani, V.; Fayad, Z.A.; et al. Oral AGE restriction ameliorates insulin resistance in obese individuals with the metabolic syndrome: A randomised controlled trial. Diabetologia 2016, 59, 2181–2192.

18. Sergi, D.; Boulestin, H.; Campbell, F.M.; Williams, L.M. The Role of Dietary Advanced Glycation End Products in Metabolic Dysfunction. Mol. Nutr. Food Res. 2021, 65, e1900934.

19. Henning, C.; Glomb, M.A. Pathways of the Maillard reaction under physiological conditions. Glycoconj. J. 2016, 33, 499–512.

20. Maillard, L.C. Action des acides amines sur les sucres; formation des melanoidines par voie methodique. Comptes R. Acad. Sci. 1912, 154, 66–68.

21. Miroliaei, M.; Aminjafari, A.; Ślusarczyk, S.; Nawrot-Hadzik, I.; Rahimmalek, M.; Matkowski, A. Inhibition of Glycation-induced Cytotoxicity, Protein Glycation, and Activity of Proteolytic Enzymes by Extract from Perovskia atriplicifolia Roots. Pharmacogn. Mag. 2017, 13, S676–S683.

22. Takeuchi, M.; Yamagishi, S. TAGE (toxic AGEs) hypothesis in various chronic diseases. Med. Hypotheses 2004, 63, 449–452.

23. Singh, V.P.; Bali, A.; Singh, N.; Jaggi, A.S. Advanced glycation end products and diabetic complications. Korean J. Physiol. Pharmacol. 2014, 18, 1–14.

24. Teissier, T.; Boulanger, É. The receptor for advanced glycation end-products (RAGE) is an important pattern recognition receptor (PRR) for inflammaging. Biogerontology 2019, 20, 279–301.

25. Prasad, K. Is there any evidence that AGE/sRAGE is a universal biomarker/risk marker for diseases? Mol. Cell. Biochem. 2019, 451, 139–144.

26. Dozio, E.; Massaccesi, L.; Corsi Romanelli, M.M. Glycation and Glycosylation in Cardiovascular Remodeling: Focus on Advanced Glycation End Products and O-Linked Glycosylations as Glucose-Related Pathogenetic Factors and Disease Markers. J. Clin. Med. 2021, 10, 4792.

27. Yu, W.; Tao, M.; Zhao, Y.; Hu, X.; Wang, M. 4’-Methoxyresveratrol Alleviated AGE-Induced Inflammation via RAGE-Mediated NF-κB and NLRP3 Inflammasome Pathway. Molecules 2018, 23, 1447.

28. Schmidt, A.M. Soluble RAGEs—Prospects for treating & tracking metabolic and inflammatory disease. Vasc. Pharmacol. 2015, 72, 1–8.

29. Lee, A.C.; Lam, J.K.; Shiu, S.W.; Wong, Y.; Betteridge, D.J.; Tan, K.C. Serum Level of Soluble Receptor for Advanced Glycation End Products Is Associated with A Disintegrin And Metalloproteinase 10 in Type 1 Diabetes. PLoS ONE 2015, 10, e0137330.

30. Colhoun, H.M.; Betteridge, D.J.; Durrington, P.; Hitman, G.; Neil, A.; Livingstone, S.; Charlton-Menys, V.; Bao, W.; Demicco, D.A.; Preston, G.M.; et al. Total soluble and endogenous secretory receptor for advanced glycation end products as predictive biomarkers of coronary heart disease risk in patients with type 2 diabetes: An analysis from the CARDS trial. Diabetes 2011, 60, 2379–2385.

31. Kalea, A.Z.; Schmidt, A.M.; Hudson, B.I. Alternative splicing of RAGE: Roles in biology and disease. Front. Biosci. (Landmark Ed.) 2011, 16, 2756–2770.

32. Chawla, D.; Bansal, S.; Banerjee, B.D.; Madhu, S.V.; Kalra, O.P.; Tripathi, A.K. Role of advanced glycation end product (AGE)-induced receptor (RAGE) expression in diabetic vascular complications. Microvasc. Res. 2014, 95, 1–6.

33. Matsui, T.; Oda, E.; Higashimoto, Y.; Yamagishi, S. Glyceraldehyde-derived pyridinium (GLAP) evokes oxidative stress and inflammatory and thrombogenic reactions in endothelial cells via the interaction with RAGE. Cardiovasc. Diabetol. 2015, 14, 1.

34. Kobori, T.; Ganesh, D.; Kumano-Kuramochi, M.; Torigoe, K.; Machida, S. Assay for advanced glycation end products generating intracellular oxidative stress through binding to its receptor. Anal. Biochem. 2020, 611, 114018.

35. Goldin, A.; Beckman, J.A.; Schmidt, A.M.; Creager, M.A. Advanced glycation end products: Sparking the development of diabetic vascular injury. Circulation 2006, 114, 597–605.

36. Kumar Pasupulati, A.; Chitra, P.S.; Reddy, G.B. Advanced glycation end products mediated cellular and molecular events in the pathology of diabetic nephropathy. Biomol. Concepts 2016, 7, 293–309.

37. Bucciarelli, L.G.; Wendt, T.; Rong, L.; Lalla, E.; Hofmann, M.A.; Goova, M.T.; Taguchi, A.; Yan, S.F.; Yan, S.D.; Stern, D.M.; et al. RAGE is a multiligand receptor of the immunoglobulin superfamily: Implications for homeostasis and chronic disease. Cell. Mol. Life Sci. CMLS 2002, 59, 1117–1128.

38. Lee, E.J.; Park, J.H. Receptor for Advanced Glycation Endproducts (RAGE), Its Ligands, and Soluble RAGE: Potential Biomarkers for Diagnosis and Therapeutic Targets for Human Renal Diseases. Genom. Inform. 2013, 11, 224–229.

39. Xie, J.; Méndez, J.D.; Méndez-Valenzuela, V.; Aguilar-Hernández, M.M. Cellular signalling of the receptor for advanced glycation end products (RAGE). Cell. Signal. 2013, 25, 2185–2197.

40. Goh, S.-Y.; Cooper, M.E. The Role of Advanced Glycation End Products in Progression and Complications of Diabetes. J. Clin. Endocrinol. Metab. 2008, 93, 1143–1152.

41. Li, Z.; Wang, G.; Zhu, Y.J.; Li, C.G.; Tang, Y.Z.; Jiang, Z.H.; Yang, M.; Ni, C.L.; Chen, L.M.; Niu, W.Y. The relationship between circulating irisin levels and tissues AGE accumulation in type 2 diabetes patients. Biosci. Rep. 2017, 37, BSR20170213.

42. Mishriky, B.M.; Cummings, D.M.; Powell, J.R. Diabetes-Related Microvascular Complications—A Practical Approach. Prim. Care 2022, 49, 239–254.

43. Buse, J.B.; Wexler, D.J.; Tsapas, A.; Rossing, P.; Mingrone, G.; Mathieu, C.; D'Alessio, D.A.; Davies, M.J. 2019 Update to: Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2020, 43, 487–493.

44. Arora, M.K.; Singh, U.K. Molecular mechanisms in the pathogenesis of diabetic nephropathy: An update. Vasc. Pharmacol. 2013, 58, 259–271.

45. Persson, F.; Rossing, P. Diagnosis of diabetic kidney disease: State of the art and future perspective. Kidney Int. Suppl. 2018, 8, 2–7.

46. Sun, H.; Yuan, Y.; Sun, Z. Update on Mechanisms of Renal Tubule Injury Caused by Advanced Glycation End Products. BioMed Res. Int. 2016, 2016, 5475120.

47. Matsui, T.; Yamagishi, S.; Takeuchi, M.; Ueda, S.; Fukami, K.; Okuda, S. Irbesartan inhibits advanced glycation end product (AGE)-induced proximal tubular cell injury in vitro by suppressing receptor for AGEs (RAGE) expression. Pharmacol. Res. 2010, 61, 34–39.

48. Fukami, K.; Yamagishi, S.; Coughlan, M.T.; Harcourt, B.E.; Kantharidis, P.; Thallas-Bonke, V.; Okuda, S.; Cooper, M.E.; Forbes, J.M. Ramipril inhibits AGE-RAGE-induced matrix metalloproteinase-2 activation in experimental diabetic nephropathy. Diabetol. Metab. Syndr. 2014, 6, 86.

49. Ojima, A.; Matsui, T.; Nishino, Y.; Nakamura, N.; Yamagishi, S. Empagliflozin, an Inhibitor of Sodium-Glucose Cotransporter 2 Exerts Anti-Inflammatory and Antifibrotic Effects on Experimental Diabetic Nephropathy Partly by Suppressing AGEs-Receptor Axis. Horm. Metab. Res.=Horm.-Und Stoffwechs.=Horm. Et Metab. 2015, 47, 686–692.

50. Sanajou, D.; Ghorbani Haghjo, A.; Argani, H.; Aslani, S. AGE-RAGE axis blockade in diabetic nephropathy: Current status and future directions. Eur. J. Pharmacol. 2018, 833, 158–164.

51. Matoba, K.; Kawanami, D.; Tsukamoto, M.; Kinoshita, J.; Ito, T.; Ishizawa, S.; Kanazawa, Y.; Yokota, T.; Murai, N.; Matsufuji, S.; et al. Rho-kinase regulation of TNF-α-induced nuclear translocation of NF-κB RelA/p65 and M-CSF expression via p38 MAPK in mesangial cells. Am. J. Physiol. Ren. Physiol. 2014, 307, F571–F580.

52. Matoba, K.; Takeda, Y.; Nagai, Y.; Kawanami, D.; Utsunomiya, K.; Nishimura, R. Unraveling the Role of Inflammation in the Pathogenesis of Diabetic Kidney Disease. Int. J. Mol. Sci. 2019, 20, 3393.

53. Tuttle, K.R.; Brosius, F.C., 3rd; Adler, S.G.; Kretzler, M.; Mehta, R.L.; Tumlin, J.A.; Tanaka, Y.; Haneda, M.; Liu, J.; Silk, M.E.; et al. JAK1/JAK2 inhibition by baricitinib in diabetic kidney disease: Results from a Phase 2 randomized controlled clinical trial. Nephrol. Dial. Transplant. 2018, 33, 1950–1959.

54. Zhang, M.H.; Feng, L.; Zhu, M.M.; Gu, J.F.; Jiang, J.; Cheng, X.D.; Ding, S.M.; Wu, C.; Jia, X.B. The anti-inflammation effect of Moutan Cortex on advanced glycation end products-induced rat mesangial cells dysfunction and High-glucose-fat diet and streptozotocin-induced diabetic nephropathy rats. J. Ethnopharmacol. 2014, 151, 591–600.

55. Anil Kumar, P.; Welsh, G.I.; Saleem, M.A.; Menon, R.K. Molecular and cellular events mediating glomerular podocyte dysfunction and depletion in diabetes mellitus. Front. Endocrinol. 2014, 5, 151.

56. Rabbani, N.; Thornalley, P.J. Advanced glycation end products in the pathogenesis of chronic kidney disease. Kidney Int. 2018, 93, 803–813.

57. Yadav, A.; Vallabu, S.; Arora, S.; Tandon, P.; Slahan, D.; Teichberg, S.; Singhal, P.C. ANG II promotes autophagy in podocytes. Am. J. Physiol. Cell Physiol. 2010, 299, C488–C496.

58. Seong, S.B.; Ha, D.S.; Min, S.Y.; Ha, T.S. Autophagy Precedes Apoptosis in Angiotensin II-Induced Podocyte Injury. Cell. Physiol. Biochem. 2019, 53, 747–759.

59. Stitt, A.W. Advanced glycation: An important pathological event in diabetic and age related ocular disease. Br. J. Ophthalmol. 2001, 85, 746–753.

60. Wu, M.Y.; Yiang, G.T.; Lai, T.T.; Li, C.J. The Oxidative Stress and Mitochondrial Dysfunction during the Pathogenesis of Diabetic Retinopathy. Oxidative Med. Cell Longev. 2018, 2018, 3420187.
61. Kang, Q.; Yang, C. Oxidative stress and diabetic retinopathy: Molecular mechanisms, pathogenetic role and therapeutic implications. Redox Biol. 2020, 37, 101799.
62. Münch, G.; Westcott, B.; Menini, T.; Gugliucci, A. Advanced glycation endproducts and their pathogenic roles in neurological disorders. Amino Acids 2012, 42, 1221–1236.
63. Jack, M.; Wright, D. Role of advanced glycation endproducts and glyoxalase I in diabetic peripheral sensory neuropathy. Transl. Res. 2012, 159, 355–365.
64. Saleh, A.; Smith, D.R.; Tessler, L.; Mateo, A.R.; Martens, C.; Schartner, E.; Van der Ploeg, R.; Toth, C.; Zochodne, D.W.; Fernyhough, P. Receptor for advanced glycation end-products (RAGE) activates divergent signaling pathways to augment neurite outgrowth of adult sensory neurons. Exp. Neurol. 2013, 249, 149–159.
65. Roth, G.A.; Mensah, G.A.; Johnson, C.O.; Addolorato, G.; Ammirati, E.; Baddour, L.M.; Barengo, N.C.; Beaton, A.Z.; Benjamin, E.J.; Benziger, C.P.; et al. Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019: Update From the GBD 2019 Study. J. Am. Coll. Cardiol. 2020, 76, 2982–3021.
66. Kim, H.C. Epidemiology of cardiovascular disease and its risk factors in Korea. Glob. Health Med. 2021, 3, 134–141.
67. Wang, M.; Li, Y.; Li, S.; Lv, J. Endothelial Dysfunction and Diabetic Cardiomyopathy. Front. Endocrinol. 2022, 13, 851941.
68. Avagimyan, A. The Pathophysiological Basis of Diabetic Cardiomyopathy Development. Curr. Probl. Cardiol. 2022, 19, 101156.