REVIEW ARTICLE

RECORDS OF PHARMACEUTICAL AND BIOMEDICAL SCIENCES

Role of AGE-RAGE Pathway in the Pathogenesis of Cardiovascular Disease as a Complication of Diabetes Mellitus

Sarah Ouda Bekheit [a, *], El-Sayed E. El-Awady [b], Eman Kolieb [c], Dina M. Khodeer [b]

[a] El-Sheikh Zuweid Health Administration, Health Affairs Directorate, North Sinai 45613, Egypt; [b] Department of Pharmacology and Toxicology, Faculty of Pharmacy, Suez Canal University, Ismailia 41522, Egypt; [c] Department of Medical Physiology, Faculty of Medicine, Suez Canal University, Ismailia 41522, Egypt.

Received: 22. 08. 2024

Revised: 24. 09. 2024

Accepted: 25. 09. 2024

*Corresponding Author:

Tel: + 201154611997

E-mail address:

saraouda97@gmail.com

Abstract

Diabetes mellitus (DM) is marked by hyperglycemia. An association has been discovered between extended durations of elevated blood glucose levels and a higher occurrence of both micro-and macrovascular diseases in individuals with diabetes. This correlation is present even after achieving glycemic control, indicating an inherent process known as "metabolic memory." Advanced glycation end products (AGEs) are proteins that have undergone glycation and are believed to have a role in metabolic memory. They are produced more in the presence of excessive blood glucose levels and have a sluggish turnover rate. Increased levels of AGEs may cause aberrant cross-linking of proteins in both the extracellular and intracellular spaces, resulting in disruptions in their typical arrangement and function. In addition, the activation of AGE receptor may initiate intricate signalling pathways that result in heightened oxidative stress, inflammation, elevated calcium deposition, and enhanced vascular smooth muscle cell death. All of these variables together lead to the advancement of atherosclerosis. AGEs are likely to substantially impact the increasing prevalence of cardiovascular disease (CVD). Furthermore, it is crucial to explore novel treatment strategies that specifically target AGEs and associated pathways in order to mitigate and treat CVD in individuals with diabetes metabolic disorders, with the goal of improving clinical results.

Keywords: Advanced glycation end products (AGEs); Cardiovascular disease (CVD); Diabetes Mellitus (DM).

1. Introduction

The incidence of type 2 diabetes mellitus (DM) has been consistently growing during the last few decades. It is anticipated that by 2030, there will be over 366 million cases, and by 2045, there will be over 693 million cases (**Wild et al., 2004; Jung et al., 2021)**. Furthermore, DM is a complex and long-lasting metabolic disorder resulting from dysfunctional glucose, lipid, and protein metabolism. It is also the 11th main prevalent reason of mortality due to long-term complications globally. DM is linked to illness and death as a result of its vascular consequences **(Yang et al., 2021)**. Diabetic metabolic disorders refer to a diverse set of ailments marked by long-term raised levels of blood glucose as a result of issues with insulin synthesis, function, or both. These disorders are linked to many consequences, such as abnormalities of the microvascular and macrovascular systems **(American Diabetes Association, 2013)**.

Cardiovascular disease (CVD) is a substantial trigger to illness and death in individuals with diabetes, responsible for almost 50% of all fatalities attributable to diabetes (Shah et al., 2015). Therefore, it is crucial to comprehend the pathophysiological processes that are responsible to an elevated risk of CVD in individuals with diabetes. This knowledge is essential for identifying new treatment targets and methods to enhance patient outcomes. The buildup of advanced glycation end products (AGEs), which are a diverse set of compounds generated by the non-enzymatic glycation of lipids, proteins, and nucleic acids, is a crucial contributor in the development of CVD linked with diabetes **(Singh et al., 2001)**. AGEs have been shown to have a role in the onset and advancement of vascular inflammation, endothelial dysfunction and atherosclerosis, along with other pathological mechanisms. This eventually results in an elevated risk of CVD in patients with diabetes **(Goh & Cooper, 2008)**. Although significant advancements have been made in comprehending the influence of AGEs on the progression of cardiovascular disorders in diabetic individuals, we still have an insufficient grasp of the exact molecular processes that connect AGEs to vascular damage.

Comprehending these pathways is essential for the advancement of specific therapeutic approaches designed to prevent or reduce vascular impairment in diabetes. This current review offers a comprehensive examination of the present understanding of the molecular pathways behind vascular damage caused by AGEs **(Figure 1)**. The emphasis is placed on the connection of these molecules and crucial cellular signalling pathways that are important for the progression of diabetic cardiovascular diseases **(Basta, 2008)**.

2. AGEs sources and formation

A wide variety of glycated proteins and lipoproteins, both naturally occurring and acquired by environmental or dietary means, are collectively known as advanced glycation end-products (AGEs). The manufacture of endogenous AGEs occurs via the complex Maillard reaction. In this process, reducing sugars are subjected to a sequence of non-enzymatic reactions, resulting in the production of reactive carbonyl molecules. Subsequently, these chemicals undergo metabolism with lipids, proteins, and nucleic acids, causing glycoxidation **(Chappey et al., 1997)**.

Glycolysis metabolism yields methylglyoxal, a carbonyl intermediate that plays a role in the synthesis of particular AGEs **(Singh et al., 2001)**. Under conditions of oxidative stress, lipids, amino acids and reducing sugars experience a process called autoxidation, resulting in the creation of reactive carbonyl radicals and a greater amount of AGEs. This process ultimately triggers the buildup of AGEs in tissues **(Ott et al., 2014)**. Moreover, the pace at which AGEs accumulate is governed by the equilibrium between their creation, breakdown, and removal. Diabetes may cause the accumulation of AGEs due to either impaired removal or increased production. The build-up of AGEs may then lead to the progression of diabetes problems **(Gugliucci & Menini, 2014)**.

3. Molecular pathways connecting AGEs to vascular damage

3.1. Inflammation along with oxidative stress

Advanced glycation end products (AGEs) are essential contributors to the progression of vascular damage in diabetes by triggering inflammation and oxidative stress. By binding of AGEs to their cell-surface receptors, specifically the receptor for advanced glycation end products (RAGE), AGEs are able to activate the nuclear factor kappa B (NF-κB) signalling pathway, therefore initiating the formation of reactive oxygen species (ROS) **(Yamagishi & Imaizumi, 2005)**. This activation results in an upregulation of adhesion molecules, chemokines, and pro-inflammatory cytokines which leads to the infiltration of inflammatory cells and the continuation of inflammation and damage in the wall of blood vessels **(Rohm et al., 2022)**.

3.2. Endothelial dysfunction

Experimental research has proven that advanced glycation end products (AGEs) impede the activity of endothelial cells, which is a critical first stage in the progression of diabetic vascular problems. AGEs have the capacity to directly hinder the generation of nitric oxide (NO) and enhance the permeability of the endothelium by causing the breakdown of endothelial glycocalyx and destroying the firm connections within endothelial cells **(Nieuwdorp et al., 2006)**. Furthermore, AGEs have the capacity to induce the proliferation of endothelial cells, encouraging the synthesis of chemicals that promote blood clotting and the

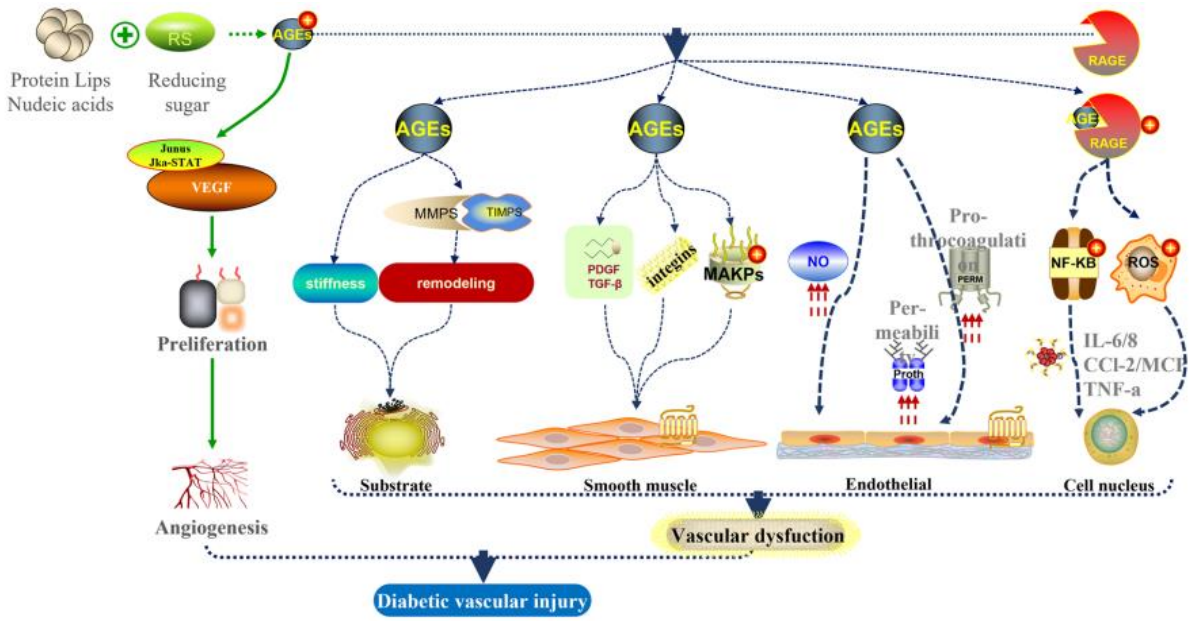

Figure 1. A review of the simplified methods by which AGEs generate vascular damage in diabetes patients, along with potential treatment options. Nuclear factor-kappa B (NF-κB), reactive oxygen species (ROS), interleukin-6/8 (IL-6/8), chemokine ligand-2 (CCL-2), tumour necrosis factor (TNFα), nitric oxide (NO), mitogen-activated protein kinases (MAPKs), platelet-derived growth factor (PDGF), and transforming growth factor-beta (TGF-β). TIMPs stand for tissue inhibitors of metalloproteinases, whereas MMPs stands for matrix metalloproteinases. Janus kinase-signal transducer and activator of transcription (JKA-STAT) and vascular endothelial growth factor (VEGF) **(Liu et al., 2023)**.

initiation of the coagulation process. This process leads to the development of blood clots and the advancement of vascular damage **(Shi & Vanhoutte, 2017)**.

3.3. Migration of smooth muscle cells and their simultaneous proliferation

AGEs may additionally stimulate the growth and movement of vascular smooth muscle cells (VSMCs), which leads to the development of neointima and changes in the structure of arteries in individuals with diabetes. AGEs stimulate the proliferation of mitogen-activated protein kinases (MAPKs) and the increase in the production of growth factors, which include transforming growth factor-beta (TGF-β) and platelet-derived growth factor (PDGF). Consequently, this results in a surge in the proliferation and migration of VSMCs **(Yuan et al., 2020)**. Furthermore, AGEs have the ability to increase the attachment of VSMCs to the extracellular matrix by boosting integrin and other adhesion-related molecule synthesis **(Monnier et al., 2014)**.

3.4. Extracellular matrix remodelling

AGEs that accumulate in the extracellular matrix (ECM) are responsible for causing decreased blood vessels performance and arterial stiffness in individuals with diabetes. AGEs have the ability to form chemical bonds with ECM proteins, including elastin and collagen. This process may lead to alterations in the structural characteristics of the vascular wall and a decrease in its flexibility, as seen by lower compliance **(Yamagishi & Matsui, 2018)**. Furthermore, AGEs are able to regulate the expression and function of tissue inhibitors of metalloproteinases (TIMPs) and matrix metalloproteinases (MMPs), which are crucial for the remodelling of the extracellular matrix (ECM) and maintaining a proper equilibrium between the production and breakdown of the ECM **(Forbes et al., 2003)**.

3.5. Impaired angiogenesis and neovascularization

It has been shown that AGEs are associated with poor neovascularization and angiogenesis, two processes that are common in diabetic vascular complications. AGEs can hinder the development, movement, and creation of tubes in endothelial progenitor cells. They also negatively affect the production of pro-angiogenic molecules, particularly vascular endothelial growth factor (VEGF) **(Barile et al., 2005)**. In addition, AGEs can stimulate the Janus kinase–signal transducer

and activator of transcription (JAK–STAT) signalling pathway. This pathway hinders the growth of endothelial cells and leads to defective formation of new blood vessels (angiogenesis) **(Huang et al., 2015)**.

4. Possible treatment approaches targeting AGEs in CVD

There is increasing data that shows the significance of AGEs in the progression of CVD in persons with diabetes. This suggests that treatment approaches that focus on AGEs may have potential advantages for this group of people.

4.1. Prevention of AGE generation and buildup

An effective strategy to minimize the impact of AGEs on vascular damage is suppressing their creation and buildup. Several substances, for instance, aminoguanidine and pyridoxamine, have shown the ability to hinder the production of AGEs by capturing reactive carbonyl species or impeding the Maillard process. This effectively restricts them from interacting with proteins **(Onorato et al., 2000)**. Trials assessing the effectiveness of these inhibitors in reducing problems related to diabetes have shown inconsistent results, necessitating more research **(Bucciarelli et al., 2002; Williams et al., 2007)**.

4.2. Blocking AGE–receptor interactions

As illustrated in **Figure 2**, another approach spots inhibiting the interaction of AGEs with their biological receptors, namely the receptor for advanced glycation end products (RAGE). One naturally occurring shorter variant of the receptor called soluble RAGE (sRAGE) has been shown to operate like a decoy for AGEs, blocking their binding with the RAGE receptors found on the surface of cells. Administration of sRAGE has shown beneficial benefits in animal models of CVD **(Bucciarelli et al., 2002)**. Furthermore, the use of small molecule antagonists that target the AGE-RAGE pathway has demonstrated potential in suppressing cellular signalling caused by AGE and avoiding diabetes consequences in experimental animals **(Yamagishi & Matsui, 2010)**.

4.3. Targeting downstream signaling pathways

Targeting the downstream pathways that are activated by AGE-receptor interactions might be a promising therapeutic strategy. Preclinical studies have shown that blocking important signalling components, like protein kinase C (PKC), mitogen-activated protein kinases (MAPKs), and nuclear factor-kappa B (NF-κB), might reduce the cellular reactions caused by AGEs and delay the onset of diabetes problems **(Heydari et al., 2022)**.

4.4. Therapeutics focusing on inflammatory response and oxidative stress

Due to the involvement of inflammation as well as oxidative stress in causing damage to blood vessels generated by AGE, researchers have investigated antioxidant and anti-inflammatory treatments as viable remedies. For example, N-acetylcysteine, a powerful antioxidant and a substance that helps produce the body's own ROS scavenger glutathione, has previously been proven to reduce the negative impacts of AGEs on the endothelial cells that line the blood vessels **(Cuzzocrea et al., 2000)**. Furthermore, it has been observed that anti-inflammatory substances, like angiotensin-converting enzyme inhibitors and statins, might improve vascular damage caused by AGEs by exerting their many impacts on oxidative stress and inflammation **(Rosenson, 2004)**.

Natural products are very useful reservoirs of inhibitors that effectively impede the development of AGEs. These antagonists provide the positive effects of being very safe and exhibiting little toxicity. Phenolic acids and flavonoids found in plants have been shown to be powerful inhibitors of glycation, according to current study **(Shen et al., 2017)**. Ferulic acid (FA) is considered to be one of the important natural compounds. According to a study by **Liu et al. (2018)**, FA may reduce the inflammatory reaction caused by AGEs by blocking the stimulation of NF-κB and p38 MAPK signalling cascades.

5. Conclusion

The pathophysiology of AGEs is intricately linked to the metabolism of glucose, lipids, and proteins. Chronic hyperglycemia leads to a complex relationship between their metabolism, oxidative stress, and inflammatory reactivation. AGEs have a key function in the advancement of diabetes complications, particularly CVD. For many years, clinical and experimental research has mostly focused on AGEs as potential indicators or targets for treatment in the pathologic consequences of DM. It is crucial to acknowledge the significance

of focusing on AGEs and their associated pathways in order to mitigate and treat cardiovascular disease in individuals with diabetes metabolic disorders. This approach has great prospects for therapy. Hence, it is essential to conduct extensive and longitudinally structured research investigations using validated detection methods for AGEs in order to advance the prevention of diabetes complications in real-life scenarios.

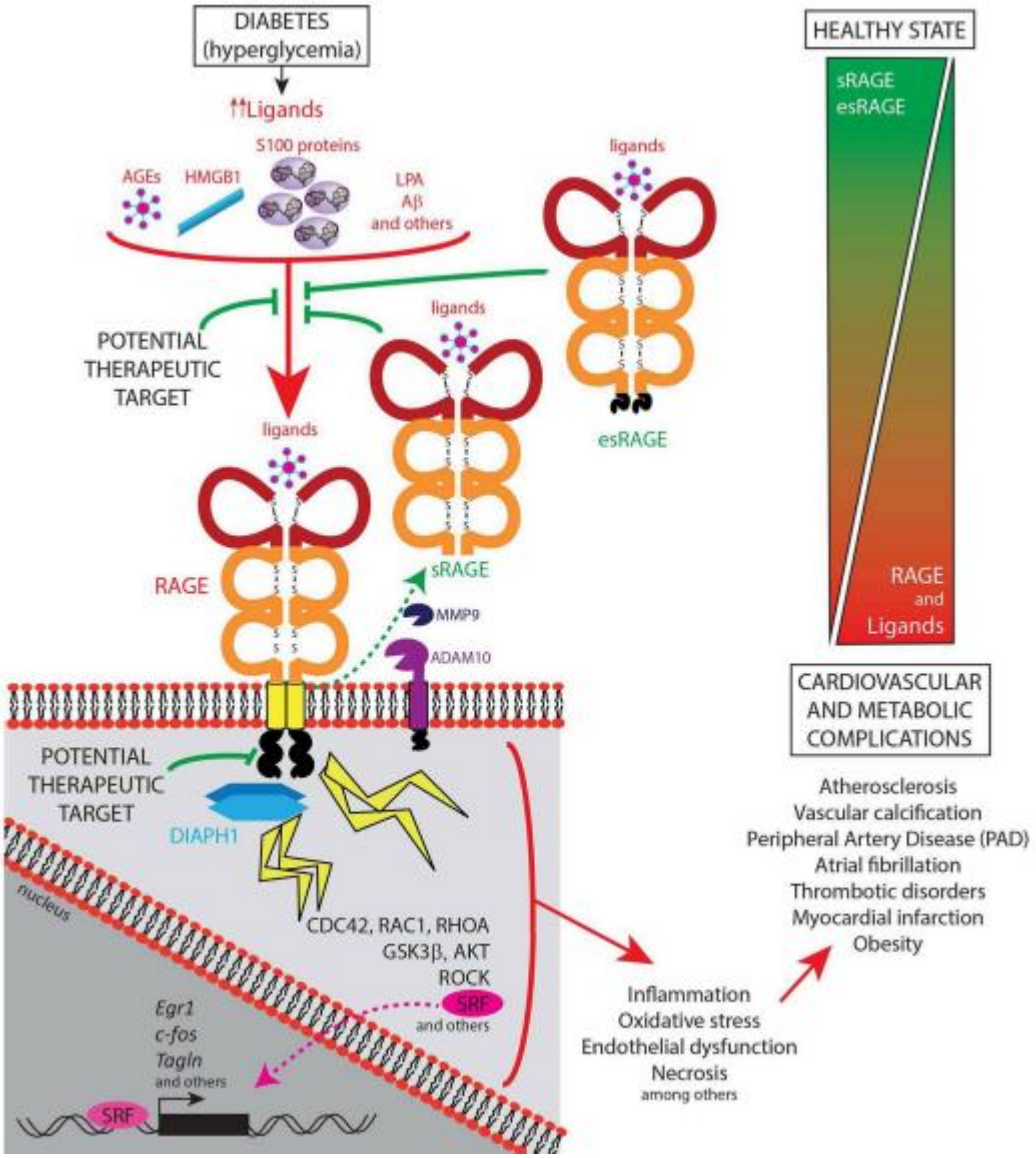

Figure 2. The diagram illustrates the function of the ligand-RAGE-DIAPH1 pathway in the progression of cardiometabolic complications in diabetes. The major way that the receptor for advanced glycation end products (RAGE), which is also called AGER, works is by attaching to the extracellular domains of RAGE its recognized ligands, which include AGEs, HMGB1, the S100 family of proteins, LPA, and Aβ. As can be shown in the figure, several downstream regulators and stress responses are initiated when the cytoplasmic portion of RAGE interacts with its cytoplasmic effector protein, Diaphanous1 (DIAPH1). Vascular calcification, peripheral artery disease, atherosclerosis, thrombotic disorders, myocardial infarction, obesity, and other metabolic and cardiovascular complications are thought to be caused by cellular stressors like endothelial dysfunction, oxidative stress, inflammation, and necrosis. Conversely, soluble RAGE variants like sRAGE and esRAGE are generated when the full-length receptor is cleaved by enzymes like A Disintegrin and Metalloproteinase Domain-Containing Protein-10 (ADAM10) and Matrix Metallopeptidase-9 (MMP9), or by a splice variant of AGER. In cases of cardiometabolic problems, these soluble forms have been shown to have a protective effect. They achieve this by inhibiting the interaction of RAGE ligands with the cell surface receptor, hence mitigating the stimulation of the RAGE-DIAPH1 signalling pathway. Therefore, blocking ligand-receptor interaction and breaking the link between RAGE and DIAPH1 are two of the current potential therapeutic targets **(Egaña-Gorroño et al., 2020)**.

References

American Diabetes Association. (2013). Diagnosis and classification of diabetes mellitus. Diabetes Care, 36 Suppl 1(Suppl 1), S67-74. https://doi.org/10.2337/dc13-S067

Barile, G. R., Pachydaki, S. I., Tari, S. R., Lee, S. E., Donmoyer, C. M., Ma, W., Rong, L. L., Buciarelli, L. G., Wendt, T., Hörig, H., Hudson, B. I., Qu, W., Weinberg, A. D., Yan, S. F., & Schmidt, A. M. (2005). The RAGE axis in early diabetic retinopathy. Investigative Ophthalmology & Visual Science, 46(8), 2916–2924. https://doi.org/10.1167/iovs.04-1409

Basta, G. (2008). Receptor for advanced glycation endproducts and atherosclerosis: From basic mechanisms to clinical implications. Atherosclerosis, 196(1), 9–21. https://doi.org/10.1016/j.atherosclerosis.2007.07.025

Bucciarelli, L. G., Wendt, T., Qu, W., Lu, Y., Lalla, E., Rong, L. L., Goova, M. T., Moser, B., Kislinger, T., Lee, D. C., Kashyap, Y., Stern, D. M., & Schmidt, A. M. (2002). RAGE blockade stabilizes established atherosclerosis in diabetic apolipoprotein E-null mice. Circulation, 106(22), 2827–2835. https://doi.org/10.1161/01.cir.0000039325.03698.36

Chappey, O., Dosquet, C., Wautier, M. P., & Wautier, J. L. (1997). Advanced glycation end products, oxidant stress and vascular lesions. European Journal of Clinical Investigation, 27(2), 97–108. https://doi.org/10.1046/j.1365-2362.1997.710624.x

Cuzzocrea, S., Mazzon, E., Costantino, G., Serraino, I., De Sarro, A., & Caputi, A. P. (2000). Effects of n-acetylcysteine in a rat model of ischemia and reperfusion injury. Cardiovascular Research, 47(3), 537–548. https://doi.org/10.1016/S0008-6363(00)00018-3

Egaña-Gorroño, L., López-Díez, R., Yepuri, G., Ramirez, L. S., Reverdatto, S., Gugger, P. F., Shekhtman, A., Ramasamy, R., & Schmidt, A. M. (2020). Receptor for Advanced Glycation End Products (RAGE) and Mechanisms and Therapeutic Opportunities in Diabetes and Cardiovascular Disease: Insights from Human Subjects and Animal Models. Frontiers in Cardiovascular Medicine, 7, 37. https://doi.org/10.3389/fcvm.2020.00037

Forbes, J. M., Cooper, M. E., Oldfield, M. D., & Thomas, M. C. (2003). Role of advanced glycation end products in diabetic nephropathy. Journal of the American Society of Nephrology: JASN, 14(8 Suppl 3), S254-258. https://doi.org/10.1097/01.asn.0000077413.41276.17

Goh, S.-Y., & Cooper, M. E. (2008). Clinical review: The role of advanced glycation end products in progression and complications of diabetes. The Journal of Clinical Endocrinology and Metabolism, 93(4), 1143–1152. https://doi.org/10.1210/jc.2007-1817

Gugliucci, A., & Menini, T. (2014). The axis AGE-RAGE-soluble RAGE and oxidative stress in chronic kidney disease. Advances in Experimental Medicine and Biology, 824, 191–208. https://doi.org/10.1007/978-3-319-07320-0_14

Heydari, A. H., Fathi, M., Heydari, S., & Heidari, M. E. (2022). Advanced Glycation End Product Blocker Drugs Have a Great Potential to Prevent Diabetic Cardiomyopathy in an Animal Model of Diabetes Mellitus Type-2. Cardiovascular Therapeutics, 2022, 7014680. https://doi.org/10.1155/2022/7014680

Huang, J.-S., Lee, Y.-H., Chuang, L.-Y., Guh, J.-Y., & Hwang, J.-Y. (2015). Cinnamaldehyde and nitric oxide attenuate advanced glycation end products-induced the Jak/STAT signaling in human renal tubular cells. Journal of Cellular Biochemistry, 116(6), 1028–1038. https://doi.org/10.1002/jcb.25058

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., Cho, Y., Han, S. J., Jang, H. M., Rho, M., Lee, S., Koo, M., Yoo, B., Moon, J.-W., Lee, H. Y., … Yoon, K. H. (2021). Diabetes Fact Sheets in Korea, 2020: An Appraisal of Current Status. Diabetes & Metabolism Journal, 45(1), 1–10. https://doi.org/10.4093/dmj.2020.0254

Liu, J., He, Y., Wang, S., He, Y., Wang, W., Li, Q., & Cao, X. (2018). Ferulic acid inhibits advanced glycation end products (AGEs) formation and mitigates the AGEs-induced inflammatory response in HUVEC cells. Journal of Functional Foods, 48, 19–26. https://doi.org/10.1016/j.jff.2018.06.024

Liu, J., Pan, S., Wang, X., Liu, Z., & Zhang, Y. (2023). Role of advanced glycation end products in diabetic vascular injury: Molecular mechanisms and therapeutic perspectives. European Journal of Medical Research, 28(1), 553. https://doi.org/10.1186/s40001-023-01431-w

Monnier, V. M., Sun, W., Sell, D. R., Fan, X., Nemet, I., & Genuth, S. (2014). Glucosepane: A poorly understood advanced glycation end product of growing importance for diabetes and its complications. Clinical Chemistry and Laboratory Medicine, 52(1), 21–32. https://doi.org/10.1515/cclm-2013-0174

Nieuwdorp, M., Mooij, H. L., Kroon, J., Atasever, B., Spaan, J. A. E., Ince, C., Holleman, F., Diamant, M., Heine, R. J., Hoekstra, J. B. L., Kastelein, J. J. P., Stroes, E. S. G., & Vink, H. (2006). Endothelial glycocalyx damage coincides with microalbuminuria in type 1 diabetes. Diabetes, 55(4), 1127–1132. https://doi.org/10.2337/diabetes.55.04.06.db05-1619

Onorato, J. M., Jenkins, A. J., Thorpe, S. R., & Baynes, J. W. (2000). Pyridoxamine, an inhibitor of advanced glycation reactions, also inhibits advanced lipoxidation reactions. Mechanism of action of pyridoxamine. The Journal of Biological Chemistry, 275(28), 21177–21184. https://doi.org/10.1074/jbc.M003263200

Ott, C., Jacobs, K., Haucke, E., Navarrete Santos, A., Grune, T., & Simm, A. (2014). Role of advanced glycation end products in cellular signaling. Redox Biology, 2, 411–429. https://doi.org/10.1016/j.redox.2013.12.016

Rohm, T. V., Meier, D. T., Olefsky, J. M., & Donath, M. Y. (2022). Inflammation in obesity, diabetes, and related disorders. Immunity, 55(1), 31–55. https://doi.org/10.1016/j.immuni.2021.12.013

Rosenson, R. S. (2004). Statins in atherosclerosis: Lipid-lowering agents with antioxidant capabilities. Atherosclerosis, 173(1), 1–12. https://doi.org/10.1016/S0021-9150(03)00239-9

Shah, A. D., Langenberg, C., Rapsomaniki, E., Denaxas, S., Pujades-Rodriguez, M., Gale, C. P., Deanfield, J., Smeeth, L., Timmis, A., & Hemingway, H. (2015). Type 2 diabetes and incidence of cardiovascular diseases: A cohort study in 1·9 million people. The Lancet. Diabetes & Endocrinology, 3(2), 105–113. https://doi.org/10.1016/S2213-8587(14)70219-0

Shen, Y., Xu, Z., & Sheng, Z. (2017). Ability of resveratrol to inhibit advanced glycation end product formation and carbohydrate-hydrolyzing enzyme activity, and to conjugate methylglyoxal. Food Chemistry, 216, 153–160. https://doi.org/10.1016/j.foodchem.2016.08.034

Shi, Y., & Vanhoutte, P. M. (2017). Macro- and microvascular endothelial dysfunction in diabetes. Journal of Diabetes, 9(5), 434–449. https://doi.org/10.1111/1753-0407.12521

Singh, R., Barden, A., Mori, T., & Beilin, L. (2001a). Advanced glycation end-products: A review. Diabetologia, 44(2), 129–146. https://doi.org/10.1007/s001250051591

Singh, R., Barden, A., Mori, T., & Beilin, L. (2001b). Advanced glycation end-products: A review. Diabetologia, 44(2), 129–146. https://doi.org/10.1007/s001250051591

Wild, S., Roglic, G., Green, A., Sicree, R., & King, H. (2004). Global Prevalence of Diabetes. Diabetes Care, 27(5), 1047–1053. https://doi.org/10.2337/diacare.27.5.1047

Williams, M. E., Bolton, W. K., Khalifah, R. G., Degenhardt, T. P., Schotzinger, R. J., & McGill, J. B. (2007). Effects of pyridoxamine in combined phase 2 studies of patients with type 1 and type 2 diabetes and overt nephropathy. American Journal of Nephrology, 27(6), 605–614. https://doi.org/10.1159/000108104

Yamagishi, S., & Imaizumi, T. (2005). Diabetic vascular complications: Pathophysiology, biochemical basis and potential therapeutic strategy. Current Pharmaceutical Design, 11(18), 2279–2299. https://doi.org/10.2174/1381612054367300

Yamagishi, S.-I., & Matsui, T. (2010). Advanced glycation end products, oxidative stress and diabetic nephropathy. Oxidative Medicine and Cellular Longevity, 3(2), 101–108. https://doi.org/10.4161/oxim.3.2.11148

Yamagishi, S.-I., & Matsui, T. (2018). Role of Ligands of Receptor for Advanced Glycation End Products (RAGE) in Peripheral Artery Disease. Rejuvenation Research, 21(5), 456–463. https://doi.org/10.1089/rej.2017.2025

Yang, Y. S., Han, K., Sohn, T. S., & Kim, N. H. (2021). Young-onset type 2 diabetes in South Korea: A review of the current status and unmet need. The Korean Journal of Internal Medicine, 36(5), 1049–1058. https://doi.org/10.3904/kjim.2021.379

Yuan, G., Si, G., Hou, Q., Li, Z., Xu, K., Wang, Y., Wang, W., Xu, X., Zhang, L., Sun, X., He, H., Zeng, H., & Liu, Y. (2020). Advanced Glycation End Products Induce Proliferation and Migration of Human Aortic Smooth Muscle Cells through PI3K/AKT Pathway. BioMed Research International, 2020, 8607418. https://doi.org/10.1155/2020/8607418