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# The Role of Metabolic and Environmental Factors in the Formation of Advanced Glycation and Products

## *İleri Glikasyon Son Ürünlerinin Oluşumunda Metabolik ve Çevresel Etkenlerin Rolü*

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***ABSTRACT***

*Advanced glycation end products (AGEs) are detrimental compounds formed through the non-enzymatic glycation and oxidation of proteins, lipids, and nucleic acids. Their accumulation, influenced by factors such as hyperglycemia, aging, obesity, chronic kidney disease, and inflammatory processes, poses significant health risks. Hyperglycemia, prevalent in diabetes, accelerates the formation of these compounds due to elevated levels of reactive dicarbonyls, including methylglyoxal. Aging contributes to the buildup of these products, potentially accelerating age-related physiological decline. Obesity exacerbates their accumulation through increased oxidative stress and insulin resistance. Environmental factors, such as dietary habits, cooking methods, and lifestyle choices, play crucial roles in the formation of these compounds. Protein- and fat-rich foods subjected to high temperatures tend to have higher concentrations of these harmful compounds. Foods rich in proteins and fats, particularly when subjected to high temperatures, exhibit higher concentrations of these harmful compounds. Lifestyle factors, including physical inactivity and smoking, further elevate their levels; conversely, regular physical activity is associated with lower concentrations. The aim of this review is to elucidate the factors influencing the formation of Advanced glycation end products and to identify strategies to reduce their adverse health effects.*

***Keywords:*** *Advanced glycation end products, Dietary, Lifestyle,*

***ÖZET***

*İleri glikasyon son ürünleri, proteinlerin, lipidlerin ve nükleik asitlerin enzimatik olmayan glikasyon ve oksidasyon yoluyla oluşan zararlı bileşiklerdir. Bu bileşenlerin birikimi, hiperglisemi, yaşlanma, obezite, kronik böbrek hastalığı ve inflamatuar süreçler gibi faktörlerden etkilenir ve önemli sağlık riskleri taşır Diyabette yaygın olan hiperglisemi, reaktif dikarbonillerin, özellikle metilgloksalin, yükselmiş seviyeleri nedeniyle bu bileşiklerin oluşumunu hızlandırır. Yaşlanma, bu ürünlerin birikimine katkıda bulunarak fizyolojik gerilemenin hızlanmasına yol açabilir. Obezite, artan oksidatif stres ve insülin direnci aracılığıyla birikimi artırır. Çevresel faktörler, beslenme alışkanlıkları, pişirme yöntemleri ve yaşam tarzı seçimleri, bu bileşenlerin oluşumunda kritik rol oynar. Yüksek sıcaklıkta pişirme yöntemleri, özellikle ızgara ve kızartma, yiyeceklerde bu bileşiklerin seviyelerini önemli ölçüde artırır; nemli pişirme yöntemleri ve daha düşük sıcaklıklar bu etkiyi azaltmaya yardımcı olur. Yüksek sıcaklıklara maruz kalan protein ve yağ açısından zengin besinler, bu zararlı bileşiklerin daha yüksek konsantrasyonlarına sahiptir. Fiziksel inaktivite ve sigara kullanma gibi yaşam tarzı faktörleri de seviyeleri yükseltirken, düzenli fiziksel aktivite daha düşük konsantrasyonlarla ilişkilidir. Bu çalışma, ileri glikasyon son ürünleri'nin oluşumunu etkileyen faktörleri açıklamayı ve olumsuz sağlık etkilerini azaltma stratejilerini tanımlamayı amaçlamaktadır.*

***Anahtar Kelimeler:*** *İleri glikasyon son ürünleri, Beslenme alışkanlıkları, Yaşam tarzı alışkanlıkları*

## INTRODUCTION

Advanced glycation end products (AGEs) represent a diverse array of irreversible compounds that arise from non-enzymatic glycation and oxidation processes affecting proteins, lipids, and nucleic acids. These substances accumulate in various tissues over time, with their formation being accelerated by factors such as aging, hyperglycemia, and chronic degenerative diseases. Modern cooking practices, such as high-temperature cooking, significantly increase AGEs levels in foods. Principal factors influencing AGE formation include food composition, cooking techniques, moisture content, and smoking, with smoking notably accelerating AGEs accumulation. Conversely, regular physical activity is correlated in particular reduced AGE levels (Byun et al., 2017; Jud & Sourij, 2019; van Dongen et al., 2022).

AGEs influence the body through two primary mechanisms: receptor-mediated and receptor-independent pathways. AGEs can form direct cross-links with cellular proteins, potentially altering their structural integrity and functionality, or induce inflammatory responses through interaction with specific AGE receptors. Significant AGE derivatives, including Pentosidine and N-carboxymethyl-lysine (CML), are commonly utilized as biomarkers for the quantification of AGE accumulation (Mouanness & Merhi, 2022; van Dongen et al., 2022).

Approximately 10% to 30% of dietary AGEs are absorbed by the gastrointestinal system and subsequently transported to the liver and other tissues, with about one-third of these compounds being excreted in the urine. The remaining AGEs accumulate in the body. Excessive accumulation of AGEs is associated with oxidative stress and inflammation, playing a significant role in the pathogenesis of various chronic diseases, including cardiovascular diseases, Type 2 Diabetes Mellitus, neurodegenerative disorders, and chronic kidney disease (Twarda-clapa et al., 2022, Sergi et al., 2021;). The aim of this review is to elucidate the factors influencing the formation of AGEs and to identify strategies to reduce their adverse health effects.

### Formation Mechanisms of AGEs

AGEs primarily arise from the Maillard reaction, a non-enzymatic process first characterized by Louis Camille Maillard in 1912 (Maillard, 1912). This reaction involves the interaction between the carbonyl groups of carbohydrates and the amino groups of proteins, leading to the formation of various AGE compounds. While the Maillard reaction contributes to the flavor, aroma, and color of foods, it also decreases protein digestibility and generates potentially harmful substances such as acrylamide and heterocyclic aromatic amines (Mouanness & Merhi, 2022).

AGEs formation progresses through several pathways. Initially, glucose forms reversible Schiff bases with amino acids, lipids, or deoxyribonucleic acid (DNA). In hyperglycemic conditions, these Schiff bases are converted into Amadori products, such as HbA1c. Over time, Amadori products undergo dehydration, oxidation, or polymerization, resulting in irreversible AGEs. This transformation can span from weeks to years (O'Brien & Morrissey, 1989). Additionally, the polyol pathway generates reactive carbonyls, such as methylglyoxal (MGO), through the reduction of glucose to sorbitol and its subsequent conversion to fructose (Perrone et al., 2020). Other pathways, including the auto-oxidation of Amadori products and various oxidative reactions, also contribute to AGE formation (Shen et al., 2020).

### Association of AGEs with Diseases

AGEs play a role in the pathogenesis of various diseases through mechanisms that are both receptor-independent and receptor-mediated. In receptor-independent pathways, AGEs disrupt the structural and functional characteristics of proteins by creating cross-links with macromolecules both inside and outside the cells. Such alterations can result in detrimental tissue changes. For example, the cross-linking of collagen and elastin by AGEs can lead to increased arterial stiffness, which may contribute to vascular damage and related conditions. Additionally, AGEs can impact cellular lipids, signaling molecules, and DNA, thereby compromising cellular function and structural integrity. In receptor-mediated mechanisms, AGEs interact with the Receptor for AGE (RAGE), initiating a cascade of cellular responses that include oxidative stress, inflammation, and the production of pro-inflammatory cytokines. These interactions can exacerbate disease progression. Understanding AGEs-related pathways in these diseases provides valuable insights into potential therapeutic targets and strategies designed to reduce AGE-related damage and enhance patient outcomes (Hegab,

2012; Prasad & Mishra, 2018; Rhee & Kim, 2018; Zeng et al., 2019; Lee et al., 2021; Twarda-Clapa et al., 2022; van Dongen et al., 2022).

Understanding AGEs-related pathways in various diseases provides valuable insights into potential therapeutic targets and strategies designed to reduce AGE-related damage and enhance patient outcomes.

**Factors Influencing AGEs Formation**

Various endogenous and environmental factors can significantly enhance the rate at which AGEs are formed in the body. Endogenous factors include metabolic disturbances and physiological conditions that promote AGE formation, while environmental factors encompass lifestyle choices and external exposures that contribute to this process (Jud & Sourij, 2019). A comprehensive examination of these influencing factors, including their mechanisms and effects, is provided in the following sections.

**Endogenous Factors**

***Hyperglycemia***

In healthy individuals, the formation of endogenous AGEs occurs at a relatively slow rate. Hyperglycemia significantly accelerates this process. A key outcome of chronic hyperglycemia is the increased production of AGEs, which subsequently leads to elevated oxidative stress. Hyperglycemic conditions lead to a significant rise in the levels of intracellular sugars, including fructose and fructose-3-phosphate, which exhibit higher reactivity compared to glucose (Baynes, 2002; Szwergold et al., 1990). In individuals with diabetes, there is a pronounced accumulation of intracellular dicarbonyl compounds, particularly MGO, which exhibits significant cross-linking potential and is instrumental in the pathogenesis of diabetic complications. MGO is produced through pathways such as anaerobic glycolysis and also results from the oxidation of polyunsaturated fatty acids and fructose through the polyol pathway. This accumulation of MGO contributes to the heightened formation of AGEs and the associated pathological effects observed in diabetic conditions (Ahmed, 2005).

***Aging***

The connection between AGEs and the aging process remains a topic of considerable discussion. Certain researchers suggest that the aging process may accelerate the accumulation of AGEs. They propose that with advancing age, there is a heightened propensity for the formation and accumulation of AGEs in tissues, which may be associated with a progressive deterioration in physiological functions and a higher susceptibility to age-associated diseases (Semba et al., 2010; Kim et al., 2017; Moldogazieva et al., 2019). Conversely, other researchers propose that the accumulation of AGEs could play a crucial role in the natural advancement of the aging process. According to this perspective, AGEs are not merely a byproduct of aging but are actively involved in the biological mechanisms that underpin aging. This view posits that AGEs contribute to cellular damage, inflammation, and other pathophysiological changes that are characteristic of aging (Aragno & Mastrocola, 2017; Perkins et al., 2019).

The conflicting viewpoints highlight the complexity of the relationship between AGEs and aging, suggesting that both the accumulation of AGEs and their involvement in the aging process may be interrelated factors influencing age-associated physiological changes.

***Obesity***

Obesity is associated with a heightened risk of developing conditions such as insulin resistance, type 2 diabetes mellitus, non-alcoholic fatty liver disease, hypertension, and cardiovascular disorders. The interplay of factors including increased caloric intake, diminished energy expenditure, persistent hyperglycemia, elevated lipid levels, and heightened oxidative stress in obesity fosters the enhanced production of reactive intermediates and specific AGEs, including CML. AGEs promote inflammation in adipose tissue by activating adipocytes and macrophages, leading to the production of inflammatory mediators. Levels of AGEs in both tissue and plasma are higher in obese individuals compared to those who are non-obese. Furthermore, morbidly obese individuals have lower levels of soluble receptor for AGEs (sRAGE), a decoy receptor that helps to neutralize circulating AGEs and mitigate their harmful effects. Weight loss is linked to elevated levels of sRAGE and a concomitant reduction in AGE levels. In addition to the increased AGE formation seen in obesity, disturbances in the glyoxalase system further contribute to AGE accumulation. Studies have demonstrated that Glyoxalase I (GLO1), the primary cellular defense system against AGEs, is reduced in most tissues in obesity (Skapare et al., 2012; Gaens et al., 2013;

Deo et al., 2017; Sánchez et al., 2017).

***Chronic Kidney Disease***

Plasma levels of AGEs are markedly increased in individuals with renal impairment, independent of their diabetic condition. AGEs undergo filtration through the renal glomeruli, followed by reabsorption in the proximal renal tubules where they are subjected to catabolic processes or biochemical modification. Subsequently, these compounds are excreted in the urine. Cells in the renal proximal tubules are essential for the clearance of plasma AGEs. In individuals with chronic kidney disease, elevated levels of AGEs are strongly associated with the development of cardiovascular diseases, type 2 diabetes, neurodegenerative disorders, and atherosclerosis, independent of diabetes status (Oleniuc et al., 2011).

***Glyoxalase I Deficiency***

Deficiency of GLO-I impairs the detoxification processes of AGEs. The production of GLO-I in endothelial cells is essential for preventing the accumulation of intracellular AGEs and counteracting the increased uptake of macromolecules into the bloodstream due to elevated blood glucose levels. Additionally, GLO-I diminishes AGE accumulation and oxidative stress associated with hyperglycemia in mesangial cells. Additionally, GLO-I has been shown to mitigate cellular damage by reducing the toxic levels of AGEs, thus protecting cells from glycation stress (Shen et al., 2020; Trellu etal., 2019, Hollenbach, 2017).

***Autoimmune and Inflammatory Responses***

Elevated plasma concentrations of AGEs are observed across various conditions, including autoimmune disorders, rheumatic inflammatory diseases, neuroinflammatory and neurodegenerative conditions, neuropsychiatric disorders, and certain cancers. Inflammatory responses activate innate immune cells such as macrophages, dendritic cells, microglia, and astrocytes, leading to a metabolic shift toward glycolysis in these cells. This metabolic pathway results in the production of MGO from glyceraldehyde-3-phosphate and dihydroxyacetone phosphate, while glyoxal (GO) is directly derived from glucose. MGO reacts with lysine residues to form CML, and GO interacts with lysine to produce carboxyethyl lysine (CEL). To counteract the detrimental effects of elevated MGO and GO, the body activates the methylglyoxal and glyoxalase systems, which involve GLO-I and GLO-II, to metabolize these AGEs precursors (Delrue et al., 2023; Maessen et al., 2015).

***Environmental Factors***

Lifestyle choices considerably influence the overall body burden of AGEs, the expression of RAGE and its isoforms, and the associated metabolic consequences. Dietary sources of AGEs play a crucial role in increasing the body's AGEs pool and contributing to cardiometabolic disorders. Various modifiable factors, such as the content of foods, cooking temperatures, and personal lifestyle habits, influence AGEs formation. It is also well established that smoking has a substantial effect on AGEs production and tissue accumulation (Ottum & Mistry, 2015).

***Nutrition***

The rate and diversity of AGEs formation in foods are affected by various factors, including food composition, the presence of precursors, transition metals, and antioxidants. It is well established that cooking time and temperature, as well as concentrations of reactants, moisture, and pH, critically impact the Maillard reaction rate, which is central to AGEs formation. Specifically, the Maillard reaction proceeds more slowly at acidic pH levels, with an increase in pH accelerating both the reaction rate and AGEs formation. Higher moisture content can dilute reactants, reducing the reaction rate, while dry heat cooking methods significantly enhance AGEs accumulation (Gill et al.,2019). Conversely, employing moist cooking methods, reducing cooking durations, using lower temperatures, and incorporating acidic ingredients have been found to reduce AGEs formation (Erim et al., 2022).

Foods high in proteins and fats typically contain higher AGEs levels compared to carbohydrate-rich foods. Among various food groups, meats have the highest AGEs contents, with beef and cheese having the highest levels. Other sources of high AGEs content include poultry, pork, fish, and eggs. Lamb generally has a lower AGEs content than many other types of meat. Fatty and aged cheeses, such as Parmesan, have higher AGEs levels compared to low-fat cheeses like mozzarella, cheddar, and cottage cheese. The high AGEs content in uncooked animal-derived foods like cheese is likely due to pasteurization and/or extended periods at ambient temperatures during processes like hardening or aging, which continue

to promote glycation-oxidation reactions over time (Uribarri et al., 2005, Uribarri et al. 2010).

High-fat spreadable products, including butter, cream cheese, margarine, and mayonnaise, as well as cooking oils and nuts, are among those with the highest levels of AGEs. These products often acquire high AGEs levels due to the heat involved in their extraction and purification processes. The choice of cooking oil can also affect AGEs production (Goldberg et al., 2004).

In contrast, carbohydrate-rich foods generally have lower AGEs concentrations due to their higher water content, antioxidants, fiber, and vitamins, which may help mitigate AGEs formation. However, carbohydrate foods subjected to dry heat processing, such as crackers, chips, and cookies, tend to have elevated AGEs levels due to the incorporation of added fats and oils. Grains, legumes, vegetables, fruits, and milk—when not prepared with additional fats—are among the lowest in AGEs content. Skim milk and high-water-content dairy products, such as yogurt, pudding, and ice cream, contain fewer AGEs compared to whole milk (del Castillo et al., 2020; Zawada et al., 2022).

Ingredients such as flour, baking powder, salt, sugar, and vegetable oils significantly influence AGEs concentrations. The degree of saturation in vegetable oils also affects AGEs content, with olive oil, rice bran oil, canola oil, and grape seed oil showing varying AGEs levels. Spices and other ingredients used in cooking can further alter AGEs concentrations, with many seasonings containing AGEs (Uribarri et al., 2010; del Castillo et al., 2020).

Fructose, commonly used as a sweetener, is one of the most potent glycation agents when compared to other sugars. High-fructose diets are associated with increased AGEs accumulation in plasma, liver, muscle, and hippocampus. Consumption of foods and beverages containing high-fructose corn syrup is associated with increased levels of AGEs in serum and urine, and a high fructose-to-glucose ratio in foods may facilitate AGEs formation in the digestive tract (Guilbaud et al., 2016; DeChristopher, 2017).

Plant-based compounds, particularly polyphenols like phenolic acids, flavonoids, stilbenes, and lignans, demonstrate notable anti-AGEs activity. These compounds can inhibit AGEs biosynthesis through antioxidant properties, metal chelation, and RAGE receptor blockade. Green tea, rich in catechins such as epicatechin and epigallocatechin-3-gallate, has been shown to significantly reduce AGEs formation. Epigallocatechin-3-gallate, in particular, prevents intracellular AGEs formation by capturing reactive dicarbonyl species, thereby reducing pro-inflammatory cytokine production and LDL oxidation. Green tea is considered a healthy choice due to its low AGEs content and its ability to lower endogenous AGEs pools (McKay & Blumberg, 2002; Wu et al., 2010; Chen et al., 2016).

Heat treatment enhances flavor, digestibility, and shelf life of foods but significantly accelerates Maillard reactions, leading to numerous AGEs products. The Maillard reaction rate doubles with every 10°C increase in temperature, and water activity also influences the reaction rate. Dry heat methods, such as grilling, frying, and roasting, increase AGEs levels, with levels potentially rising up to 100 times higher than in uncooked foodsIn contrast, aqueous cooking methods, such as boiling and steaming, combined with reduced cooking times and lower temperatures, result in lower levels of AGEs formation (del Castillo et al., 2020).

The starting pH of the reactants and the system's buffering capacity are critical determinants of AGEs formation. The Maillard reaction exhibits a low rate under acidic conditions and reaches its optimum at a pH of 10. Therefore, the use of acidic substances, such as lemon juice or vinegar, can effectively reduce the formation of AGEs (Sharma et al., 2015).

AGEs formation continues during food storage, with higher temperatures and longer storage times leading to increased AGEs concentrations. Monitoring storage conditions is essential to control AGEs levels in foods (Uribarri et al., 2010).

**Physical Activity Level**

Increased physical activity has been proposed as a potential strategy for lowering serum AGEs. Conversely, reduced physical activity is significantly correlated with elevated levels of AGEs in the serum. Studies have shown that individuals who engage in regular exercise tend to have lower average AGEs levels compared to those who are physically inactive (Drenth et al., 2018; Hooshiar et al., 2022)The majority of AGEs accumulate in adipose tissue. Regular exercise contributes to a reduction in fat mass, which in

turn is associated with lower AGEs levels (Gaens et al., 2013).

Improvement in glycemic control may provide another explanation for the impact of exercise on AGEs. Generally, lower serum glucose levels correlate with reduced AGEs formation in body tissues. This effect may be attributed to a noticeable reduction in peripheral insulin resistance, which can decrease AGEs accumulation (Macías-Cervantes et al., 2015). Exercise reduces oxidative stress, inflammatory markers, and the concentration of highly reactive intermediate products involved in AGEs production (Hooshiar et al., 2022).

**Smoking**

AGEs precursors present in tobacco products and cigarette smoke can rapidly engage with biological macromolecules, resulting in the generation of AGEs metabolites. Research indicates that smokers exhibit significantly higher tissue levels of AGEs compared to non-smokers. Furthermore, it has been shown that AGEs originating from tobacco accumulate in vascular tissues and the ocular structures (Cerami et al., 1997).

Plasma levels of AGE-apolipoprotein B and AGE-albumin are significantly higher in smokers than in non-smokers. One of the tobacco components, nornicotine—a metabolite of nicotine—catalyzes aldol reactions in aqueous environments, leading to abnormal protein glycation. Smoking enhances AGEs formation and decreases sRAGE levels, which consequently increases the risk of cardiovascular diseases (K. Prasad et al., 2014, Yue et al., 2011, Koetsier et al., 2010).

**Body's Defense Mechanisms Against AGEs**

The body possesses a range of both endogenous and exogenous defensive mechanisms designed to mitigate the harmful effects of AGEs. The most effective means of preventing AGEs formation and accumulation include lifestyle modifications and improved glycemic control (Nenna et al., 2015; C. Prasad et al., 2014). Studies shows that limiting the intake of AGE-rich foods and ceasing smoking can lead to significant reductions in both skin and serum AGEs levels (Macías-Cervantes et al., 2015; K. Prasad et al., 2014). Additionally, regular physical activity has been demonstrated to enhance glycemic control, lower the levels of reactive precursors involved in glycation, and consequently reduce the buildup of AGEs (Kim et al., 2017).

Comprehensive research has shown that pharmacological agents targeting various stages of the glycation process yield promising results (Borg & Forbes, 2016). These medications generally function through multiple mechanisms: they obstruct the intake of external AGEs, inhibit their production within the body, promote the breakdown of existing AGEs, and interfere with their binding to cellular receptors. These therapeutic strategies may help mitigate in alleviating the negative impacts of AGEs and enhancing overall health outcomes (Fujimoto et al., 2013; Garg et al., 2013; Mirmiranpour et al., 2013; Oudegeest-Sander et al., 2013; Derosa et al., 2014; Yubero-Serrano et al., 2015).

**Endogenous Protective Mechanisms**

Endogenous protective mechanisms against AGEs involve several key processes. These include enzymatic systems that facilitate the breakdown of AGEs, such as those involving GLO-I and GLO-II, which help to neutralize these harmful compounds. Additionally, receptor-mediated mechanisms are essential for the degradation of AGEs, with particular receptors on the cell membrane facilitating the binding and subsequent removal of these compounds. An important element of this protective mechanism is sRAGE, which functions as a decoy receptor by binding AGEs and thereby inhibiting their interaction with cellular receptors that could otherwise induce harmful effects. Together, these mechanisms function to alleviate the adverse effects of AGEs on cellular function and overall health (K. Prasad & Mishra, 2018, Kuhla et al., 2006).

**Enzymatic Pathways for the Breakdown of AGEs**

The enzymatic breakdown of AGEs involves key components such as GLO1 and GLO2, which act on reactive dicarbonyls before AGEs formation can occur. During hyperglycemic conditions, elevated levels of GLO1 in endothelial cells contribute to the reduction of dicarbonyl compounds, which is linked to the restoration of angiogenic processes and vascular relaxation. Similarly, in lens and retinal capillary pericytes, increased GLO1 production offers protective effects against protein modifications and cell apoptosis induced by hyperglycemia. As a crucial enzyme in the glyoxalase pathway, GLO1 is instrumental in the antiglycation defense system by reducing the buildup of reactive dicarbonyls (Mannervik, 2008; Kuhla et al., 2006, Shinohara et al., 1998).

**Receptor-Mediated Degradation of AGEs**

AGEs can bind to various cell surface receptors beyond RAGE, including AGER1, AGER2, and AGER3. AGER1, the first cell receptor identified to mediate the endocytosis of AGEs, displays a notable specificity for binding AGEs, which is reflected in its designation (Yang et al., 1991). This receptor is extensively distributed among different cell types and tissues, such as macrophages, mesangial cells, and mononuclear cells, and is essential for the renal uptake and metabolism of AGEs. AGER1 effectively inhibits the generation of reactive oxygen species and pro-inflammatory cytokines by disrupting the interaction between AGEs and RAGE. Additionally, AGER1 alleviates AGE-induced oxidative stress by inhibiting RAGE signaling pathways. However, diets high in AGEs and conditions such as diabetes can impair AGER1 function. Given that AGER1 and RAGE compete for AGE binding, a reduction in AGER1 levels leads to increased AGE-RAGE interactions, thereby exacerbating oxidative stress and inflammatory responses (Lu et al., 2004; Coughlan et al., 2007; Cai et al., 2006; He et al., 2001).

Although AGER2 does not directly bind AGEs, it is phosphorylated in response to AGE exposure and plays a role in the initial stages of AGEs signaling pathways. Conversely, AGER3 exhibits a strong affinity for AGE binding; however, its precise functional role remains to be fully elucidated. It is hypothesized that AGER3 may play a regulatory role in the AGEs cycle and contribute to the maintenance of tissue integrity. Soluble receptors function to impede the interaction between AGEs and RAGE and can also act as scavenger receptors for circulating AGEs. sRAGE serves as a decoy receptor by competing with RAGE for AGE binding, thereby mitigating the adverse effects associated with AGE-RAGE interactions. AGEs preferentially bind to sRAGE prior to interacting with RAGE. Reduced serum levels of sRAGE facilitate increased AGE-RAGE interactions, which can result in deleterious cellular effects (K. Prasad & Mishra, 2018, Vlassara et al., 1995; Yang et al., 1991).

**Exogenous Protective Mechanisms**

Exogenous strategies are essential for reducing the formation and accumulation of AGEs. Key approaches include dietary changes, such as choosing foods lower in AGEs and using cooking methods that minimize AGEs formation, like steaming or boiling. Additionally, adopting preventative measures during food preparation, such as marinating meats or using spices that inhibit AGEs, can be beneficial. Smoking cessation is also essential because tobacco smoke represents a major external source of AGEs. Together, these strategies effectively lower AGEs levels in the body and contribute to better health outcomes (Erim et al.,2022; Uribarri et al., 2015; Cerami et al., 1997).

**Reduction of Dietary AGE Intake**

Research suggests that enhancing the intake of vegetables, fruits, legumes, low-fat dairy products, fish, and whole grains, while reducing the consumption of solid fats, fatty meats, full-fat dairy products, and heavily processed foods, can substantially lower both dietary intake of AGEs and the body's overall AGEs levels (Uribarri et al., 2015). These dietary adjustments are consistent with the recommendations provided by major health authorities worldwide, which advocate for a diet rich in fresh, whole foods and low in processed and high-fat items to promote overall health and prevent chronic diseases. By adhering to such dietary guidelines, individuals can substantially lower their exposure to AGEs and mitigate their associated health risks (American Diabetes Association, 2010).

**Prevention of AGE Formation During Food Preparation**

The method employed in food preparation significantly impacts the formation of AGEs. Employing moist heat cooking techniques, such as boiling, steaming, or braising, as opposed to dry heat methods like frying, grilling, or roasting, can markedly decrease the formation of AGEs in foods. Furthermore, substituting high-sugar, fat-based sauces with acidic alternatives such as lemon juice, vinegar, or tomato juice can effectively lower AGEs content in meals. Phytochemicals derived from fruits such as pomegranates, grapes, and red and purple berries have demonstrated the ability to inhibit AGEs formation. Additionally, certain vitamins and compounds, including Benfotiamine (a derivative of vitamin $B_1$), pyridoxamine (a natural form of vitamin $B_6$), as well as vitamins C, D, and E, have been found to possess anti-glycation properties, thus contributing to a reduction in AGEs levels. Implementing these cooking and dietary strategies can help minimize the formation of AGEs and improve overall health outcomes (K. Prasad & Mishra, 2018; Erim & Ersoy, 2024).

### Smoking Cessation

Tobacco products are recognized sources of compounds that can significantly elevate AGEs levels. Research has shown that glycotoxins from cigarette smoke are inhaled into the alveoli of the lungs, subsequently entering the bloodstream and interacting with other glycated molecules throughout the body. The resultant increase in serum AGEs levels is a well-documented consequence of smoking. Therefore, smoking cessation is strongly recommended as a means to reduce serum AGEs levels and mitigate associated health risks. Quitting smoking not only reduces AGEs concentrations but also enhances overall health and diminishes the likelihood of developing diseases associated with AGEs (Darabseh et al., 2021; Cerami et al., 1997).

## CONCLUSION

The formation and accumulation of AGEs are influenced by several factors, including high blood sugar levels, aging, obesity, and chronic kidney disease, all of which increase health risks. Additionally, lifestyle factors such as diet, exercise, and smoking play a significant role in regulating AGE levels.

Effective management of AGE-related health risks involves a combination of dietary modifications, improved cooking techniques, and lifestyle changes. Reducing intake of AGE-rich foods, employing moist heat cooking methods, and ceasing smoking can significantly lower AGEs levels and mitigate associated health impacts. Additionally, enhancing the body's endogenous defense mechanisms through proper glycemic control and maintaining enzymatic and receptor-mediated clearance of AGEs is crucial.

Overall, a comprehensive approach combining lifestyle adjustments, dietary strategies, and potential pharmacological interventions is essential for addressing AGE-related health challenges and improving overall well-being.

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Idea/Concept: B.E.; Design: B.E.; Supervision/Consulting: B.E.; Analysis and/or Interpretation: B.E.; Literature Search: B.E.; Writing the Article: B.E.; Critical Review: B.E.

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**Conflict of Interest**

The authors have no conflict of interest to declare.

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