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## Advanced glycation end products signaling, and metabolic complications: Dietary approach

Khan MI *et al.* AGEs signaling and metabolic complications

### INTRODUCTION

Advanced-glycation end products (AGEs) are heterogeneous compounds formed when glucose or other saccharides post-translationally alter macromolecules such as proteins, lipids, and nucleic acids without the use of enzymes (fructose and pentose). Age-related illnesses and physiological aging are associated with higher plasma amounts of AGEs, which are toxic chemicals<sup>[1,2]</sup>, causing diabetes mellitus (DM)<sup>[3]</sup>, and autoimmune/inflammatory rheumatic diseases, including systemic lupus erythematosus<sup>[4]</sup>, rheumatoid arthritis<sup>[5]</sup>, systemic sclerosis<sup>[6]</sup>, and psoriasis<sup>[7]</sup>. More than 20 different AGEs have been discovered in dietary items, human blood, and tissues. These AGEs can be arbitrarily classified as fluorescent or non-fluorescent<sup>[8]</sup>. The three non-fluorescent substances that are most significant are pyrraline, carboxymethyl-lysine (CML), and carboxyethyl-lysine (CEL)<sup>[9]</sup>. The two fluorescent AGEs of most significance are pentosidine and methylglyoxal-lysine dimer (MOLD)<sup>[10]</sup>. The presence of lysine residue in the molecules serves as these AGEs' primary distinguishing property. The AGEs are discharged from the kidneys after being catabolized in renal proximal tubular cells on a metabolic level<sup>[11]</sup>. AGE formation after binding with AGE receptor (RAGE) can result in metabolic burdens such as hyperglycemia, hyperlipidemia, oxidative stress, inflammatory responses, and endothelial dysfunction<sup>[12]</sup>. AGE formation may be accelerated by a number of environmental factors, such as sedentary lifestyles, high-carbohydrate and high-calorie diets, food cooked at high temperatures, and cigarette smoke<sup>[13]</sup>. Dietary AGE concentrations in a variety of commercial cow-based, goat-based, and soy-based infant formulas were measured using UPLC-MS/MS, the degree of protein glycation in infant formulas is determined by the protein source, protein

composition, and the number and type of carbohydrates. The soy-based formula studied contained significantly more arginine and arginine-derived dietary AGEs (dAGEs) than the cow- and goat-based formulas. The concentrations of dAGEs in infant formula with hydrolyzed proteins were higher than those in infant formula containing intact proteins, and lactose-containing formula was more susceptible to glycation than sucrose- and maltodextrin-containing formula<sup>[14]</sup>. Bakery products, with respect to their formation during baking, generate AGE content and have health effects. Phenolic components added to the formulation in bakery products greatly decrease the formation of AGEs; among these, ferulic acid showed the most significant lowering effect on AGEs. Dihydromyricetin outperformed the flavanones evaluated in the model cookie system in terms of AGE reduction. Furthermore, the addition of components that reduce water activity, such as dietary fiber, and the high temperature used in baking both enhance the formation of AGEs and the addition of fat, sugar, and protein-rich ingredients to bakery product formulations usually increases the AGE content. As a result, the food industry should concentrate on optimizing food production to reduce AGE formation while maintaining bakery product safety and organoleptic properties<sup>[15]</sup>. In light of this, AGEs may establish a clear connection between modern nutrition and health<sup>[16]</sup>.

Among the various AGEs receptors presently identified, RAGE is a critical receptor for AGEs to exert the main mechanism of cells and new pattern recognition receptor. RAGE is a one of the members of the immunoglobulin superfamily. Numerous cells, including macrophages, mesangial cells, and endothelial cells, have RAGE receptors expressed on their surfaces<sup>[17]</sup>. Which can join forces with AGEs to create the AGE-RAGE axis, which activates intracellular signaling pathways and starts a chain of intracellular events.

AGE RAGE interaction has been demonstrated in experimental investigations to alter cell signaling, stimulate gene expression, generate oxidative stress, and cause the release of proinflammatory chemicals<sup>[18]</sup>. RAGE expression levels are extremely low in healthy individuals, but when the body's cells are stimulated or under stress, RAGE

expression levels in damaged cells are markedly elevated. In light of this, RAGE is crucial to understanding how numerous diseases, including diabetes, Alzheimer's disease, vascular damage, and tumors, progress. RAGE can also identify a variety of ligands, including some endogenous ligands like S100/calgranulins and high mobility group box-1<sup>[19]</sup>, which interact with RAGE after being released by injured cells, activating some signaling pathways to enhance tissue damage and inflammation<sup>[20]</sup>. Nuclear factor-light-chain enhancer of activated B cells, also known as NF-κB, is translocated into the nucleus as a result of RAGE activation, which upregulates RAGE expression in a hyperglycemic environment<sup>[21]</sup>.

## **MAILLARD REACTION AND AGES FORMATION**

To create AGEs, the Maillard reaction (MR) proceeds through a series of processes. The primary regulators of AGEs formation including glycation of cellular and tissue proteins, are the rate of protein turnover, degree of hyperglycemia, and degree of oxidative stress<sup>[22]</sup>. The next sections explain the three stages of AGEs development *in vivo* (Figure 1).

### ***Initial phase***

The carbonyl group of reducing sugars, such as glucose, fructose, or ribose, reacts with amino groups of proteins, primarily lysine and arginine residues, to create schiff base, which can also be formed *via* the polyol route. This unstable Schiff base is further modified to produce more stable ketoamines known as amadori products (AP), which can create free radicals and irreversible crosslinks with proteins and peptides. However, APs are still reversible, dependent on the minimal substrate concentration and time<sup>[23]</sup>.

### ***Proliferation phase***

Glyoxal (GO), methylglyoxal (MG), and 3-deoxyglucosone (3-DG) are examples of AP that undergo additional chemical rearrangements in the presence of transitional metal ions to form active carbonyl intermediate groups known as dicarbonyls, which are

precursors for the production of AGEs at an advanced stage. The previous phase's glucose, fructose, and Schiff base can also be transformed and stored into dicarbonyls, which are known as "carbonyl stress", and which have a propensity to react with amino and sulfhydryl groups of proteins to cause browning and cross-linking<sup>[24,25]</sup>.

#### <sup>4</sup> ***Advanced phase***

Dicarbonyls are eventually directly rearranged with AP and proteins as a result of multiple chemical modifications such as oxidation, non-oxidation, hydration, dehydration, glycation, glycosylation, fructosylation, and acid hydrolysis to create stable, irreversible AGEs such as DOLD, GOLD, MG-derived imidazolium crosslinking, and 3-deoxygluco, Table 1 depicts the key characteristics, sources, modes of production, and pathophysiology of the various forms of AGEs.

## **LITERATURE REVIEW**

### ***Strategy of article selection***

The present narrative review of the literature was performed based on the data search from PubMed, Google Scholar, Scopus, The National Library of Medicine database, and Web of Science, at beginning of 2023 focusing on keywords focusing on AGEs, AGEs generation, pathways, foods containing AGEs, and food sources for AGEs. The entire articles were screened for duplicate information and removed sequentially.

### ***Search terms, keywords and data extraction***

Research retrieves information from various reputed biomedical reports/articles published till 2023. The information from prestigious journals using the keywords such as AGEs, AGEs production through sequential pathways, food items containing AGEs, and country data on AGEs was systematically compiled in tables and presented as narrative review. Based on the scientific search engine, the articles were screened for relevant information available in AGEs research and review articles, which were compiled in table, figures and presented in the current review article.

## **DIETARY AGES IN DAILY FOOD PRODUCTS**

People are modifying restaurant meals rather than traditional/conventionally cooked due to industrialization and marketing methods (Table 1). Non-vegetarian food contains more dietary AGEs than vegetarian food. Age level is directly influenced by cooking temperature and time<sup>[26]</sup>. The foods with the highest AGEs are those that are fried, barbecued, baked, or boiled<sup>[27]</sup>. Dry-heat processed foods like crackers, chips, and cookies had the highest AGEs level per gram of food in this group. This is most likely owing to the addition of components like as butter, oil, cheese, eggs, and nuts, which significantly enhance dAGE formation during dry-heat processing<sup>[28]</sup> (Table 1)<sup>[29-58]</sup>.

### ***Acrylamide***

In the world, potatoes are a sustainable dietary alternative and a source of energy from carbohydrates for all age groups. This root food is readily available all year, and boiling potatoes makes MR products more likely to occur<sup>[59]</sup>. Non-enzymatically, the reducing sugars glucose and fructose react with asparagine to make N-glucoside, which then produces melanoidin and the end product of the Schiff base reaction, which is decarboxylated to form acrylamide (ACR)<sup>[60]</sup>. Bread, coffee, fried potatoes, baked goods, and bread are the main sources of ACR<sup>[61]</sup>, and browning increases its concentration<sup>[62]</sup>. The highest ACR production in diverse foods occurs at 120 °C<sup>[63]</sup>. Products made from cereal, coffee, and cocoa beans include 3-aminopropionamide<sup>[64]</sup> subsequently transformed into ACR in an aqueous mallard reaction<sup>[65]</sup>. Due to the fact that the MR occurs at the bread's surface, the ACR concentration is higher in the crust and lower in the crumb. Similar to this, fried chips with a double layer of chips create a large amount of ACR<sup>[66]</sup>. Fried potatoes can expose you to an estimated 272-570 g/kg of ACR, as can bread goods (75-1044 g/kg) and breakfast cereals (149 g/kg)<sup>[67]</sup>.

### ***Furan***

Furan has a planar enol-carbonyl structure, a cyclic dicarbonyl structure, and a caramel-like scent due to the MR<sup>[68]</sup>. It is created through a number of processes, including as thermal deterioration, oxidation of polyunsaturated fatty acids, and the MR, which is the thermal rearrangement of carbohydrates in the presence of amino acids<sup>[69]</sup>. Acetaldehyde and glycolaldehyde are produced through the breakdown of serine and cysteine amino acids, and the addition of an aldol group allows for the production of furans<sup>[70]</sup>. Numerous chemical processes, such as the Strecker reaction and the oxidation of polyunsaturated fatty acids, take place during the heat processing of food<sup>[71]</sup>. High concentrations of furan are directly correlated with higher cooking temperatures (150-200 °C), yet some furan is vaporized when cooking in an open pan<sup>[72]</sup>. Reports from the Fromberg *et al*<sup>[73]</sup> study in open vessel cooking, furan is reduced by 50%, and chocolate has a low concentration. Furans provide meals with a variety of flavors and aromas, including sweet, fruity, nutty, meaty, and burnt. In the course of manufacturing infant foods, cereal, coffee, preserved foods, meat, and fish, furan and its derivatives are created<sup>[74]</sup>. Studies have shown that coffee is one of the most widely consumed non-alcoholic beverages, with little negative effect<sup>[75]</sup>. The processing of coffee and its products is thought to contribute the largest furan concentration, followed by baked cookies, bread, and chips. Furan levels are also high in packaged and bottled meals<sup>[76]</sup>. Due to variations in macronutrient ratios and processing methods, furan concentration in foods for infants varies. Infant meals with a meat foundation as opposed to ones with mixed fruits were shown to contain higher levels of furan<sup>[74]</sup>.

### ***Hydroxymethylfurfural***

Hydroxymethylfurfural (HMF) is produced by the 1,2-enolation reaction in a mild alkaline medium, and HMF (6-carbon hetrocyclic aldehyde) is the main intermediate product of the Amadori rearrangement<sup>[77]</sup>. HMF is created *via* a variety of processes, including the thermal breakdown of sugars and interactions with other intermediates<sup>[78]</sup>. Under acidic conditions, disaccharide (sucrose) mostly degrades to glucose and fructose, which are then enolized and dried out to produce fructofuranosyl.

Further, at high temperatures, this cation changes to HMF<sup>[79]</sup>. Alternatively, the carbonyl group of reducing sugars like maltose or glucose can join with lysine or another amino acid as a precursor. As a result, under controlled heat conditions, a sugar pyrolysis reaction occurs, forming browning and HMF<sup>[80]</sup>. Within a pH-controlled environment, the polymerization of HMF with a food product containing nitrogen results in melanoidins, which give the surface a brown color<sup>[81]</sup>. The presence of HMF in honey is utilized as a quality and freshness index indication. In honey and fruit juices, the level of thermal breakdown of sugar that results in the production of hazardous metabolites may also be clearly seen. Samples of honey from 29 different nations were shown to be directly correlated with storage temperature, time, and HMF content levels. According to country-specific honey samples, Malaysian honey had a value of 1132 mg/kg after more than two years of storage at 30 °C, Turkey's honey had a value of 0.0-11.5 mg/kg, and India's honey had a value of 0.15-1.70 mg/kg<sup>[82]</sup>. Other parameters that affect HMF levels, such as pH, water activity, kind of sugar, mineral content, and its origin, were explored by Kamboj *et al*<sup>[83]</sup>. Fructose-rich high fructose corn syrup (HFCS), which is used in a variety of beverages and drinks. According to a study, fresh HFCS syrup has modest levels of HMF, which rise with temperature and storage time<sup>[84]</sup>. Similar findings revealed that HMF level increases eight times in highly acidic media heated to 110 °C for 40 min<sup>[85]</sup> HMF levels in apple juice range from 0.06 mg/L to 18.12 mg/L as a result of heat exposure<sup>[86]</sup>. Date Syrup: Fresh 1000-2675 mg/kg and Industrial 12-456 mg/kg<sup>[87]</sup>, Malaysian tropical fruit juices range 0.08-91.50 mg/L<sup>[88]</sup>. Towards the end of the baking process, volatile chemicals are formed. Longer periods of higher temperatures can lead to increased HMF production<sup>[89]</sup> and in biscuits and cookies, many aromas, such as "bready", "almond", "pungent", and "sweet", form<sup>[90]</sup>. A recent study found that breakfast cereal had an HMF content of 13.3 mg/kg, but ultra-processed cereal had a content of 32.1 mg/kg. The HMF level of all cereals ranged from 0.3 mg/kg to 159.6 mg/kg. Due to the addition of sugar, refined wheat flakes have an elevated level of 159.6 mg/kg<sup>[91]</sup>.

### *GO and methyl-GO formation in food products*

While ketose (fructose) creates an equivalent Heyns compound, simple sugars like glucose form an amadori intermediate (1-amino-1-deoxy-2-ketose) by losing a water molecule. Amadori or Heyns compound breakdown then produces dicarbonyl intermediates<sup>[92]</sup>. Reactive dicarbonyl structures are created as intermediates during MR as a result of a series of chemical events, including isomerization, dehydration, fragmentation, and redox reactions. These compounds have an affinity to react with the side chains of the amino groups' lysine and arginine, producing stable protein adducts. Recent molecular structure investigations have shown that the amino acids arginine and lysine react with the molecules GO, methyl-GO (MGO), and 3-DG to form a number of cross linkages<sup>[93]</sup>. Dehydration of hexose sugar produces 3-DG, and fragmentation of intermediate MR products produces 2,3-Butanedione, GO, and MGO. On the other hand, these chemicals also developed as a byproduct of the breakdown of lipids<sup>[94]</sup>. Carbonyl synthesis by lipid oxidation is supported by the advanced lipoxidation end products (ALE) process<sup>[95]</sup>. Group I of chemicals as a result of lipid peroxidation includes the following Acrolein, 4-hydroxy-2-nonenal, 4-hydroxy-hexenal, and 4-hydroxy-nonenal are examples of, -unsaturated aldehydes. Group (1): Di-aldehydes include malondialdehyde and GO compounds. Group (3): Cheto-aldehydes include MGO, 4-oxo-nonenal, and levuglandins<sup>[92]</sup>. By using a lipidomic technique, 35 aldehydes and ketones have so far been isolated from various fatty acid-rich sources. The researcher also highlighted how the oxidation of oleic acid and eicosapentaenoic acid helps to produce GO<sup>[96]</sup>. Depending on the manner of cooking and the type of processing used, these MR products alter the texture and flavor of food<sup>[97]</sup>. The production of MR intermediates is affected by caramelization and heat processing. Dicarbonyl concentration rises during baking in foods high in sugar and low in moisture. Cookies have been shown to have varying concentrations of 3-DG, GO, and MGO<sup>[98]</sup>. Early on, coffee roasting rises<sup>[99]</sup>. Due to non-enzymatic browning and fermentation, GO is primarily found in soybean paste, soy sauce, alcoholic beverages,

and fermented coffee<sup>[100]</sup>. However, in both vegetarian and non-vegetarian food preparation, MGO production occurs during glycolysis<sup>[101]</sup>.

### *Furosine*

Early-stage MR products such as furosine bind to proteins that contain N-substituted 1-amino-1-deoxy-2-ketose, including fructose-lysine, lactulose-lysine, and maltose-lysine<sup>[102]</sup>. The N-substituted 1-amino-1-deoxy-2-ketose found in proteins such as fructose-lysine, lactulose-lysine, and maltose-lysine is bound by the early-stage MR product furosine. Degradation of the Amodori product results in the formation of the dicarbonyl molecule, which either interacts with free amino acids to produce Strecker aldehydes or with amino groups of amino acids, peptides, and proteins to rearrange and produce AGEs. An amine group on a protein or peptide combines with a reducing sugar to produce various aromatic compounds and melanoidins, which are cross-linked proteins. This process is known as the dehydroalanine route<sup>[103]</sup>. Lactulosyl-lysine, a protein-bound AP, is the first stable chemical created during milk's MR process, and furosine is created following acid digestion. The primary causes of lysine blockage are temperature, time, and length of storage. Ten percent in ultra high temperature (UHT) milk, 15% in sterilized container milk, and 25%-30% in newborn formula make up the percentage of lysine that is unavailable<sup>[104]</sup>. Dairy products' nutritional value is evaluated by their low furosine content. In their analysis of the furosine content of several heat-treated milk samples, Shi *et al*<sup>[51]</sup> found that charcoal-flavored fermented milk had the highest concentration, followed by flavored fermented milk, and low temperature (LT) pasteurized fresh milk had the lowest concentration of furosine. In hydrolyzed dairy samples, Montilla *et al*<sup>[105]</sup> estimated that furosine level ranged from 235-820 mg/100 g protein and rose by up to 90% after 4 mo of storage at 20 °C. Boitz and Mayer<sup>[106]</sup> calculated the amount of furosine in whipping cream for retailed pasteurised, extended shelf life, and UHT cream samples were 47.8 mg ± 14.0 mg, 72.2 mg ± 36.6 mg, and 172.5 mg ± 17.7 mg in 100g<sup>-1</sup> protein. The amounts of furosine in soy and whey hydrolyzed protein-based infant formula were 379 mg/100 g and 1459

mg/100 g, respectively. Similar to the subsequent formula and other partially hydrolyzed milk formulas, casein makes up 945 mg/100 g of the protein in the latter<sup>[107]</sup>. Due to its higher lactose content than other dairy foods, infant food is more likely to include furosine. According to Lund *et al*<sup>[107]</sup>, whey protein concentrate (WPC) underwent a number of alterations to the protein as a result of thermal treatment. The time of storage also enhances the quantity of furosine in both types of (DI-IF and IN-IF) processing, and recently, the role of WPC has created more furosine than other whey protein ingredients<sup>[107]</sup>. Other authors have noted that various newborn formulas contain furosine concentrations ranging from 471.9 mg/100 g to 639.5 mg/100 g<sup>[108]</sup>. Another investigation examined the impact of drying heat on various pasta samples. Artisanal pasta had the lowest furosine level, ranging from 107 to 186 mg/100 g protein, as a result of the LT drying method<sup>[109]</sup>. Due to the usage of durum wheat flour and other chemical components, whole grain pasta has a furosine concentration ranging from 229 to 836 mg/100 g protein<sup>[110]</sup>. Gluten-free spaghetti contains lower furosine 19-134 mg/100 g protein in another study by Gasparre *et al*<sup>[111]</sup> than durum wheat pasta.

### **CML and CEL**

Animal proteins and processed plant foods contain furosine, ACR, heterocyclic amines (HCA), and HMF<sup>[112]</sup>. Specifically cooked beef products and other processed foods include the amino acid furosine (2-furoil methyl lysine)<sup>[113]</sup>. High concentrations of CML, CEL, and MG-O are found in heat-treated non-vegetarian foods, peanut butter, and cereal items<sup>[114]</sup>. Infant milk formula contains CML as well because of the milk proteins in it. Lysines and other amino acids are released more freely after hydrolysis<sup>[115]</sup>. According to the AGE database, processed canned meats and nuts have the highest AGE levels, whereas fruits, vegetables, and butter have the lowest levels<sup>[116]</sup> (Figure 2).

### **FACTORS INVOLVED IN AGE<sub>s</sub> FORMATION**

Several endogenous factors may hasten the generation of AGE in the body.

### ***Hyperglycemia***

AGEs production and the stimulation of oxidative damage are two of hyperglycemia's main side effects (OX)<sup>[117]</sup>. Obese but healthy individuals could avoid the formation of AGEs and OX during metabolic stress by increasing the fractional excretion of AGEs via renal clearance. In particular, hyperglycemia induces excessive ROS production and OS, which in turn promotes the formation of AGEs, events eventually result in the development of insulin resistance, impaired insulin secretion, and endothelial dysfunction<sup>[118]</sup>.

### ***Aging, oxidative stress, and aging-related inflammatory disease***

It is still unclear whether AGEs cause the aging process or aging process speeds up the buildup of AGEs<sup>[119]</sup>. In the natural progression of the aging process, some writers hypothesized that AGE production played a critical role<sup>[117]</sup>. AGEs generate oxidative stress and, as a result, inflammatory and thrombogenic reactions via contact with RAGE, as well as metabolic changes<sup>[119]</sup>. Son *et al*<sup>[120]</sup> conclude that circulating glycotoxins are undoubtedly linked to oxidative stress and an inflammatory response that cause cell malfunction. They concluded that visceral fat was involved in the pathogenesis of inflammatory problems in the elderly. Biological aging, neuron related inflammatory illnesses, DM and its complications, bone-degenerative diseases, and renal disorders are all examples of AGE-related diseases<sup>[121]</sup>. The authors came to the conclusion that the common contributing factors to the inflammatory state in these noncommunicable chronic inflammatory disorders were AGE-RAGE signaling abnormalities.

### ***Obesity***

Obesity is typically linked to an higher risk of metabolic syndrome, which includes insulin-resistant type 2 DM, hypertension, fatty liver, and vascular problems due to the unnecessary production of adipokines by fat cells. Gaens *et al*<sup>[122]</sup> reported that obesity

was associated with higher plasma and tissue levels of MGO, AGEs, and ALE surrogated by CML. Brix *et al*<sup>[123]</sup> showed that in patients with MO, soluble-form RAGE (sRAGE) levels were significantly lower than in the non-obese group. But following bariatric surgery to lose weight, which stopped the AGE-mediated inflammatory process, sRAGE levels rose. Similarly, Sanchez *et al*<sup>[124]</sup> with an AGE reader, and skin autofluorescence (SAF) in the forearm to measure AGE buildup. It was found that SAF levels were higher in metabolic syndrome-affected MO patients than in non-obese people. SAF remained high following bariatric surgery until glycemic memory failed. Deo *et al*<sup>[125]</sup> examined how weight loss in overweight participants without diabetes affected their CML levels. After losing weight, CML readings dropped by 17%, but this was less beneficial in people with diabetes or prediabetes who weren't overweight. These findings might imply that AGE formation and tissue accumulation in the body are influenced by both obesity and hyperglycemia.

### *Chronic renal insufficiency*

Patients with uremia, whether they had diabetes or not, had significantly higher amounts of AGEs in their plasma<sup>[126]</sup>. Miyata *et al*<sup>[127]</sup> investigated the destiny of AGEs by administering pentosidine, a synthetic AGE, intravenously to rats. Pentosidine was found to be eliminated in urine after being filtered by the renal glomeruli, reabsorbed in the proximal renal tubules, and subjected to catabolic or metabolic changes. Later, Asano *et al*<sup>[128]</sup> studied the metabolism of protein-linked pentosidine using three cell lines: Proximal tubular, distal tubular, and nonrenal, in contrast to the distal tubular and nonrenal cell lines, they showed that pentosidine was quickly found in the cytoplasm of the proximal renal tubular cell line. They came to the conclusion that renal proximal tubular cells were crucial for the elimination of plasma pentosidine. Adriamycin-induced chronic nephropathy in non-diabetic rats was directly associated with renal pentosidine buildup<sup>[129]</sup>. Chronic heart failure, cardiovascular illnesses, diabetes, neurological diseases, osteoarthritis, and non-diabetic atherosclerosis all developed together with AGE accumulation in chronic kidney disease<sup>[130]</sup>. A high-AGE

diet may also increase the chance of developing chronic illnesses, including chronic kidney disease<sup>[131]</sup>. According to Inagi, this alleged “glycation stress” was discovered to be directly related to kidney aging<sup>[132]</sup>.

### *Glyoxalase I deficiency*

Reactive carbonyl compounds, which are pentosidine’s precursors, are detoxicated by glyoxalase in a hemodialysis patient with uremia. By chance, the authors discovered that this patient’s renal blood vessels (RBVs) had far higher plasma levels of pentosidine and CML than those of hemodialysis patients. Further analysis revealed that this patient’s RBVs had very low glyoxalase activity. They came to the conclusion that high AGE levels in uremia patients were largely caused by glyoxalase I deficiency (GLO-I), which was unable to detoxify AGEs<sup>[133]</sup>. In addition, Shinohara *et al*<sup>[134]</sup> reported that the bovine endothelial cells that overexpress GLO-I reduce intracellular AGE production and stop hyperglycemia from causing an increase in macromolecular endocytosis in the circulation. Similarly, Brouwers *et al*<sup>[135]</sup> revealed that in mesangial cells taken from diabetic rats and mice, overexpression of GLO-I decreased hyperglycemia-induced AGE formation and oxidative stress. Furthermore, Kurz *et al*<sup>[136]</sup> demonstrated that glycation stress may be prevented from causing cell damage by reducing the hazardous levels of MGO, GO, and other AGEs. Xue *et al*<sup>[137]</sup> explored the molecular underpinnings of erythroid 2-related factor 2’s transcriptional regulation of GLO-I. The team identified a defense mechanism against stress caused by decarbonyl glycation (MGO) in high glucose concentration, inflammation, cell aging, and senescence as a result. Recently, Garrido *et al*<sup>[138]</sup> reported that MGO-derived AGE buildup might be prevented by fatty acid production working with GLO-I to protect against glycation damage.

### **AGES AND METABOLIC DISORDERS**

The fast rise in the consumption of foods and beverages with added sugar during the past three decades, in both industrialized and developing nations, has been linked to an

increase in metabolic illnesses. The function of Advanced Glycation Endproducts in the pathophysiology of metabolic illnesses associated with modern nutrition is a new area of research (AGEs) (Figure 3)<sup>[139]</sup>.

### ***Diabetes and related complications***

*In vivo* AGE formation is dependent on particular intracellular and extracellular circumstances. The rate at which proteins are turned over, oxidative stress in the intra- or extracellular environment, and the degree of hyperglycemia are some of the elements that have been explored as contributing to the creation of AGEs<sup>[140]</sup>. After 1 wk of hyperglycemia, endothelial cells have been shown to produce considerably more intracellular AGEs. Additionally, the type of reducing sugar has an impact on how quickly AGEs form when combined with intracellular proteins, with glucose having the slowest reaction when compared to fructose, glyceraldehyde-3-phosphate, and glucose-6-phosphate<sup>[140]</sup>. Healthy aging individuals have been shown to accumulate AGEs in their blood and tissues, and this buildup is greater when their blood glucose levels are high. In addition, in situations of metabolic and vascular illnesses such as DM, atherosclerosis, and renal disease, AGEs have been observed to be raised in human tissues, plasma, and urine<sup>[141]</sup>. Semba *et al*<sup>[142]</sup> showed that higher circulating AGEs were a reliable indicator of renal function in an older group. Study found that after three and six years of follow-up, the estimated glomerular filtration rate (a measure of kidney function) at baseline and chronic kidney disease were independently related with a higher plasma content of CML<sup>[143]</sup> and results indicate that the overall population of older community-dwelling persons may be affected by the potential negative effects of AGEs on the kidney<sup>[143]</sup>. In a different investigation, 51.6% of the 548 women from the Women's Health and Aging Study I in Baltimore had worse glomerular filtration rates, which were linked to higher serum levels of CML and sRAGE (the soluble form of RAGE)<sup>[143]</sup>. Normal renal function involves the kidneys clearing circulating AGEs, although elevated AGE levels have been seen in individuals with uremia and diabetic nephropathy, likely due to insufficient renal clearance<sup>[144]</sup>.

Additionally, individuals with DM have peripheral nerves with high amounts of AGEs<sup>[145]</sup>. Ahmed conducted a recent study and discovered that diabetes has been linked to increased myelin glycation in *in vitro* investigations. By phagocytosing the glycated myelin, macrophages could explain the nerve demyelination found in diabetic neuropathy. When AGEs are injected into peripheral nerves in animal tests, blood flow, nerve action potentials, and sensory motor conduction velocities all decrease<sup>[146]</sup>.

In terms of developmental diseases, AGE accumulation and obesity interact with health risk factors, as a result, the development of glucose levels is influenced and said that AGEs, HbA1c, and obesity are all linked to glucose levels, and obesity may be one of the health risk factors pathophysiological mechanisms leading to increased glucose level due to AGE accumulation; thus, obesity could be health risk factors leading to increased glucose level in AGE accumulation<sup>[147]</sup>. Local inflammatory response is linked to elevated systemic inflammatory cytokines, which are responsible for impaired glucose regulation<sup>[148]</sup>. It is now well established that external AGEs considerably contribute to the body's AGE pool<sup>[149]</sup>. The increased inflammation further triggers the activation of additional mediators which increases inflammation, as well as induces insulin resistance in muscles<sup>[150]</sup>. Under identical settings of hyperglycemia and AGE accumulation, the interaction of RAGE-induced cellular dysfunction, protein kinases, and inflammation leads to a reduction in insulin sensitivity in target cells<sup>[151]</sup>. Hofmann et colleagues demonstrated in a RAGE knock-out mouse model that both AGEs and RAGE are implicated in aortic leaflet calcification and consequent aortic stenosis<sup>[152]</sup>. Reduced sRAGE and endogenous secretory receptor for RAGE (esRAGE), both of which are assumed to be protective against AGEs, have been identified as an early indicator of first target organ damage in moderate hypertensives<sup>[153]</sup> or diabetics have negative coronary artery remodeling<sup>[154]</sup>. In DM patients, AGEs and RAGE build within stenotic aortic valves, and the extent of this accumulation is related to the severity of the aortic stenosis and plasma AGE and sRAGE levels were linked to aortic valve area, they may be regarded novel biomarkers of the aortic stenosis course in patients with type 2 diabetes<sup>[155]</sup>, dual character of RAGE, combined with increased AGE consumption by

sRAGE in people with poor glucose metabolism, may disrupt direct correlations between RAGE and markers reflecting the degree of aortic stenosis<sup>[156]</sup>.

### *Cardiovascular complications*

Insulin resistance and hyperglycemia can impact numerous human tissues and organs, leading to long-term difficulties in a number of systems and organs, including the cardiovascular system<sup>[157,158]</sup>. Left ventricular concentric hypertrophy, perivascular fibrosis, and interstitial fibrosis are signs of pathological remodeling of the heart, which results in diastolic dysfunctions<sup>[159]</sup>. Cardiovascular illness affects the former more severely and extensively than the latter, has a worse prognosis, and manifests earlier in the former. Heart failure is 2-4 times more likely to occur in people with type 2 diabetes than in people without the disease<sup>[160]</sup>. About 70%-80% of diabetics pass away from cardiovascular issues at the end<sup>[161]</sup>. Additionally, almost 3/4 of people with type 2 diabetes also have a number of cardiovascular risk factors, including obesity, dyslipidemia, and hypertension. The accumulation of these risk factors may directly encourage the development of diabetic cardiovascular problems<sup>[162]</sup>. The primary fundamental mechanism thought to be responsible for diabetic cardiovascular disorders is increased oxidative stress<sup>[163]</sup>. In diabetic cardiovascular problems, hyperglycemia causes NADPH oxidase to become active<sup>[164]</sup>, oxidative stress causes myocardial fibrosis, endothelial dysfunction, hypertrophy and apoptosis of cardiomyocytes, inflammation, endothelial dysfunction, decreased left ventricular compliance, diastolic dysfunction, and ultimately heart failure, arrhythmia, and/or sudden cardiac death<sup>[165]</sup>. Nin *et al*<sup>[166]</sup> confirmed that plasma AGE levels in fatal or nonfatal coronary artery disease are related to all-cause mortality. Steine *et al*<sup>[167]</sup> found that Plasma AGE levels are related to left ventricular dysfunction in people with type 1 diabetes. Jia *et al*<sup>[159]</sup> also found that the plasma AGE levels are related to left ventricular dysfunction in people with type 1 diabetes. Type IV collagen and laminin, two extracellular matrix proteins of endothelial cells, can be directly modified by AGEs<sup>[168]</sup>. This mechanism accelerates cardiac fibrosis and damages the natural structure and function of blood vessels<sup>[169]</sup>. In

addition to harming endothelium cells, AGEs also cause endothelial progenitor cells to die and become dysfunctional<sup>[170]</sup>. Atherosclerosis can be accelerated by circulating AGEs, which can increase lipid oxidation and deposition in atherosclerotic plaques and encourage macrophage infiltration, T cell migration, and proliferation<sup>[171]</sup>. Additionally, recent research has demonstrated that AGEs' binding to the platelet membrane receptor CD36 results in the production of thrombi, which may be a key mechanism by which AGEs encourage myocardial ischemia episodes in diabetes patients<sup>[172]</sup>. As a result of the AGE-RAGE interaction, numerous signal transduction cascades and downstream pathways are activated, including MAPK, ERK1/2, p38, and NF- $\kappa$ B. This causes oxidative stress to increase, ROS to be produced, and the development of cardiovascular problems in diabetes<sup>[173]</sup>. Additionally, it was discovered that AGEs increased endothelial cells' NADPH oxidase production and activity, which is a significant source of oxidative stress in diabetic cardiovascular problems<sup>[174,175]</sup>. Currently, it is accepted that diabetic patients who take metformin regularly can lower their chance of developing cardiovascular disease<sup>[176]</sup>. Its antioxidant qualities that lower XO activity and lipid peroxidation in type 2 diabetic patients are responsible for its cardiovascular protective benefit<sup>[177]</sup>. Metformin treatment reduced AGE plasma levels in diabetic rats, decreasing AGE-induced heart remodeling and oxidative stress<sup>[178]</sup>.

Interestingly, sustained high dietary AGEs have been shown to cause increased arterial stiffness, which leads to an increase in systolic blood pressure and inflammatory activation, leading to vascular issues in type 2 diabetes<sup>[179]</sup>. Regardless of aortic diameter, elevated circulating sRAGE levels have been connected to the presence of bicuspid aortic valves and linked aortopathies<sup>[180]</sup>. The AGEs/sRAGE ratio has been recommended as a more effective biomarker of organ damage than either AGEs or sRAGE variants alone<sup>[181]</sup>. Furthermore, differing prediction abilities of sRAGE and cRAGE as cardiovascular risk factor markers have recently been demonstrated<sup>[182]</sup>. AGEs can also glycate and crosslink basement membrane protein, changing cell-matrix interactions and reducing endothelial cell adhesion leading microvascular and

macrovascular problems<sup>[183]</sup>. AGEs cause oxidative stress, as well as inflammatory and fibrotic reactions, all of which contribute to the development and progression of life-threatening cardiovascular illnesses<sup>[184]</sup>. AGEs mainly induce arterial damage and exacerbate the development of atherosclerotic plaques by triggering cell receptor-dependent signal resulting in arterial wall injury and plaque formation<sup>[185]</sup>.

## CONCLUSION

The worldwide increase in consumption of highly processed, calorie-dense food is fueling an obesity, diabetic, kidney, and cardiometabolic disease crisis. Focusing on the effects of dietary AGEs has been shown to increase circulating AGEs, accumulate in tissues, to affect endothelial function, increase pro-inflammatory cytokines and oxidation markers, and to act as a ligand for the advanced glycation end products receptor (RAGE). AGEs intake was higher in participants with obesity, diabetes, cardiovascular disease complications when compared with those without complications. AGEs have been found in dietary items, human blood, and tissues such as pyrraline, CML, CEL, pentosidine and MOLD. In both industrialized and developing countries over the past three decades, consumption of AGE-containing foods and beverages has been associated with an increase in metabolic diseases. Cardiovascular disorders are made worse by diabetes, and patients with diabetic cardiovascular problems have worse clinical outcomes. Since AGEs not only influence oxidative stress but also are impacted by it, it is well known that AGEs and oxidative stress play a central role in the cardiovascular problems associated with diabetes. However, many of these mechanisms are still unclear and require more explanation. Beyond blood glucose control in this population, it has been discovered that glucose-lowering medications have a protective effect on the cardiovascular system.

## **Figure Legends**

**Figure 1 Factors involved in accelerating advanced glycation end product formation and accumulation in the body.** CML: Carboxymethyl-lysine; CEL: N'-(1-carboxyethyl)lysine; MOLD: Methylglyoxal-lysine dimer. CEA: N7-(1-

carboxyethyl)arginine; CEC: Carboxyethyl cysteine; MODIC: 2-ammonio-6-({2-[4-ammonio-5-oxido-5-oxopentyl]amino}4-methyl-4,5-dihydro-1H-imidazol-5-ylidene)amino)hexanoate; DOLD: 1,3-, di(N'-lysino)-4-(2,3,4-trihydroxybutyl)-imidazolium; DODIC: N6-{2-[[{(4S)-4-ammonio-5-oxido-5-oxopentyl]amino}-5-[(2S,3R)-2,3,4-trihydroxybutyl]-3,5-dihydro-4H-imidazol-4-ylidene]-L-lysinate.

**Figure 2 Sources of dietary advanced glycation end products.** CML: Carboxymethyl-lysine; CEL: Carboxyethyl-lysine; GO: Glyoxal; MGO: Methylglyoxal; HMF: Hydroxymethylfurfural.

**Figure 3 Advanced glycation end products, advanced glycation end products receptor mediated pathways, production of cytokines, oxidative stress and organ involvement.** AGEs: Advanced glycation end products; RAGE: Advanced glycation end products receptor; JAK: Janus kinase; PI3K: Phosphoinositide 3-kinase; mTOR: Mammalian target of rapamycin; ROS: Reactive oxygen species; ERK: Extracellular signal regulated kinase; ISRE: Interferon sensitive response element.

**Table 1 Advanced glycation end products content in carbohydrates rich food ready to eat food products and country origin**

Type of AGEs	Country	Food products	AGEs level	Ref.
Acrylamide	Poland	French fries	63-2175 µg/kg	[29]
		Potato chips	113-3647	
		Crispbread	65-1271 µg/kg	
		Crackers	566-2017 µg/kg	
		Daily Bread	35-110 µg/kg	
	United States	Biscuits	5-1796 µg/kg	[30]
	India	Potato chips	1456.5 µg/kg	[31]
		Biscuits bakery	126-665 µg/kg	[32]
		French fries	825.96-1143.15	
	Saudi Arabia	Biscuits	90-182 µg/kg	[33]
Furan	Arabia	Chocolate pies	439 µg/kg	
	Brazil	Biscuits	38.1-105.3 µg/kg	[34]
	Belgium	Jarred baby food	61.7 µg/kg	[35]
	Spain	Vegetable-based baby food	10.9 to 143.0 µg/kg	[36]
		Fruit-based baby food	7.7 to 32.1	
	Germany	Ready to drink coffee	2-108 µg/kg	[37]
	Denmark	Instant coffee	39-1330 µg/kg	[38]

		powder		
		Dried fruits	387 µg/kg	
HMF	Malaysia	Stored honey	118.47-1139.95 mg/kg	[39]
	Bangladesh	Stored honey	3-703 mg/kg	[40]
	Turkey	Traditionally coffee	213-239 mg/kg	[41]
	Brazil	Corn syrup	406-2121 mg/kg	[42]
		Cane syrup	109-893 mg/kg	
	Polish Market	Roasted coffee	348 mg/kg	[43]
		Instant coffee	3351 mg/kg	
		Fruit juices	1-110 mg/L	
		Cola-carbonated drinks	2-40 mg/L	
	Syria	Instant coffee	526-1800 mg/kg	[44]
GO	Italy	Sugar cookies	362 mg/kg	[45]
	Spain	Commercial cookies	4.8-26.0 mg/kg	[46]
	Netherlands	Apple molasses	0.01-37.00 mg/kg	[47]
MGO	Italy	Sugar cookies	293.0 mg/kg	[45]
	Turkey	Dried apricots	20-41 mg/kg	[48]
	Netherlands	Dutch spiced cake, rusk, apple molasses	0.04-736.00 mg/kg	[47]
	Spain	Commercial cookies	3.7-81.4 mg/kg	[46]
Furosine	Denmark	Standard infant	1700-2800 mg/kg	[49]

		formula	P	
	Netherland	Standard infant	4719-6394 mg/kg	[50]
		formula	P	
	China	Charcoal-flavored milk	593.2 mg/100 g	[51]
		Branded	25.40-1661.05	[52]
		fermented milk	mg/100 g P	
		Posturized	12.58-61.80	[53]
		milk	mg/100 g P	
		Raw milk	8.85 mg/100 g P	
CML	United States	Fried beef	20.03 mg/100 g P	[54]
		Baked beef	14.31 mg/100 g P	
		Fried chicken breast	17.17 mg/100 g P	
		Baked chicken breast	13.58 mg/100 g P	
	China	Ground beef	3.00-19.96 mg/100 g P	[55]
		Fish	0.66-2.00 mg/100 g P	[56]
		Sea food (dry)	44.8-439.0 mg/100 g P	[57]
		Canned saury fishes	250-1608 mg/100 g P	[58]
CEL	China	Fish	3.08 mg/100 g P	[56]
		Canned saury fishes	721-3653 mg/100 g P	[58]

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AGEs: Advanced glycation end products; HMF: 5-Hydroxymethylfurfural; GO: Glyoxal; MGO: Methyl glyoxal; CML: Carboxymethyl-lysine; CEL: N'-(1-carboxyethyl)lysine; MOLD: Methylglyoxal-lysine dimer.

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