Role of gut microbiota in the modulation of the health effects of advanced glycation end-products (Review)

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Received December 7, 2022; Accepted March 21, 2023

DOI: 10.3892/ijmm.2023.5247

Abstract. The aim of the present review was to summarize the potential interactive effects between the gut microbiota and advanced glycation end-product (AGE) accumulation and toxicity in the host, and to reveal potential the mediatory effects of the gut microbiota on AGE-related health effects. The existing data demonstrate that dietary AGEs can have a significant impact on the richness and diversity of the gut microbiota, although the particular effect is dependent on the type of species, as well as the exposure dose. In addition, the gut microbiota may metabolize dietary AGEs. It has been also demonstrated that the characteristics of the gut microbiota, including its richness and relative abundance of certain taxa, is tightly associated with AGE accumulation in the host organism. In turn, a bilateral interplay between AGE toxicity and the modulation of the gut microbiota may contribute to pathogenesis of ageing and diabetes-associated diseases. Bacterial endotoxin lipopolysaccharide appears as the molecule that mediates the interactions between the gut microbiota and AGE toxicity, specifically via the modulation of the receptor for AGE signaling. Therefore, it is proposed that the modulation of the gut microbiota using probiotics or other dietary interventions may have a significant impact on AGE-induced glycative stress and systemic inflammation.

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Key words: gut microbiota, microflora, glycative stress, protein glycation, lipopolysaccharide, inflammation, diabetes

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1. Introduction

Advanced glycation end-products (AGEs) are highly heterogeneous group of chemical species formed through non-enzymatic reactions of glucose or other carbohydrates with proteins and other biomolecules (1). AGEs are formed due to condensation between the carbonyl group of a reducing sugar and free amine group of proteins, lipids or nucleic acids with the irreversible formation of end-products (2). Depending on the molecules involved in glycation, AGEs have been classified into three groups as follows: i) Glycated proteins [e.g., glycated hemoglobin (HbA1c), ApoB100, crystallin, etc.]; ii) low molecular weight AGEs [pyrraline, carboxyethyl lysine (CEL), carboxymethyl lysine (CML), pentosidine, imidazole]; iii) AGEs formed by modification with a particular glycating

agent [glucose (AGE-1), glyceraldehyde (AGE-2), glycolaldehyde (AGE-3), methylglyoxal (AGE-4), glyoxal (AGE-5), 3-deoxyglucosone (AGE-6) and acetaldehyde (AA-AGE)] (3). AGEs have also been classified as fluorescent (pentosidine, methylglyoxal-lysine dimer) and non-fluorescent (CML, CEL and pyrraline) (1).

AGEs are formed both endogenously and exogenously through a number of mechanisms (Fig. 1). One of the mechanisms of AGE formation termed the Maillard reaction involves a series of non-enzymatic reactions with the formation of a Schiff base and its subsequent rearrangement into a more stable Amadori product. AGEs are also formed through the interaction of reactive carbonyl species, including glyoxal or methylglyoxal with protein amino acid residues (4). At the same time, multiple other mechanisms may also contribute to the formation of AGEs (5,6).

Endogenously formed AGEs are generated at high amounts in diabetes mellitus due to insulin resistance and persistent hyperglycemia (7). AGEs impart toxic effects to cells through the induction of oxidative stress, endoplasmic reticulum stress, mitochondrial dysfunction, apoptosis and inflammation dysregulation (8,9). Excessive AGE formation along with its toxicity in diabetes mellitus is considered a potential mechanism linking diabetes with other metabolic disorders (10). In addition to diabetes and metabolic syndrome (11), AGEs have been shown to be involved in the pathogenesis of a variety of other diseases, including neurodegeneration (12), cancer (13), osteoporosis (14), infertility (15), chronic kidney disease (16) and aging (17,18). Correspondingly, the results of a recent meta-analysis demonstrated a significant association between circulating AGEs and their soluble receptor levels and both all-cause and cardiovascular mortality (19).

Dietary AGE intake also significantly contributes to AGE accumulation and toxicity (20). Western diets which are based on highly processed and heat-treated foods are known to contain high levels of AGEs (21). Given these associations, AGEs are considered a potential link between the modern diet and adverse health outcomes (22).

It has been proposed that the modulation of the gut microbiota significantly contributes to the effect of AGEs on human health (23), and mediates the differences observed between the effects of low and high molecular mass glycation products in the organism (24). However, the existing data are inconsistent and the potential contribution of the gut microbiota in the modulation of AGE-induced toxicity and glycation stress, as well as the health effects of AGE accumulation are unclear. Therefore, the aim of the present review was to summarize and discuss the potential interactive effects between the gut microbiota and AGE accumulation and toxicity in the host, as well as to reveal the potential mediatory effects of the gut microbiota on AGE-related health effects.

2. Bacterial AGE metabolism

The existing data demonstrate that the gut microbiota may be considered as a source of AGEs. Specifically, it has been demonstrated that *Escherichia coli* (*E. coli*) cultures release AGEs during growth (25). Such an effect may be mediated by the bacterial secretion of methylglyoxal (MGO), which is considered as a reactive carbonyl species and an AGE precursor (4). High MGO-producing activity has been demonstrated for *Proteus* spp. (26), *E. coli* (27), *Pediococcus acidilactici* and other bacteria (28).

MGO is formed in bacterial cells as a product of multiple metabolic processes (29), although its overaccumulation with a subsequent increase in AGE formation has been shown to exert toxic effects (30) and limit bacterial growth (31).

The main source of MGO is glucose catabolism, including both enzymatic and non-enzymatic reactions. The key mechanism of MGO synthesis is the transformation of dihydroxyacetone phosphate catalyzed by methylglyoxal synthase (MgsA). In turn, non-enzymatic MGO formation may result from the fragmentation of triosephosphates via phosphoenediolate intermediate (29).

The toxicity of MGO for bacterial cells is associated with its high reactivity and modification of nucleic acids and proteins, resulting in AGE formation (30). Specifically, it has been demonstrated that MGO exposure is toxic to both Gram-positive (*Bacillus subtilis* and *Staphylococcus aureus*) and Gram-negative (*Pseudomonas aeruginosa* and *E. coli*) bacteria, inhibiting their growth and inducing structural alterations in bacterial fimbriae and flagella (31).

To overcome the toxic effects of increasing MGO concentrations and subsequent cell death (32), MGO decomposition is strictly regulated by a number of mechanisms involving glyoxalases and NAD-dependent enzymes (Fig. 2). Glyoxalases I and II catalyze the glutathione (GSH)-dependent conversion of MGO to D-lactate through the formation of S-D-lactoylglutathione, whereas glyoxalase III catalyzes this conversion without consuming GSH. The NAD-dependent enzymes, glycerol dehydrogenase (GldA) and aldehyde dehydrogenase (AldA), catalyze the transformation of MGO to D-lactate through D-lactaldehyde (30). The resulting D-lactate may be subsequently transformed to pyruvate or excreted (33).

In addition to MGO, which is considered a precursor of AGEs, existing data demonstrate that gut bacteria can metabolize other AGEs. Specifically, it has been demonstrated that the human gut microbiota is able to degrade Maillard reaction products with a substantial reduction at 24 h observed for fructosyllysine (100%) > carboxymethyllysine (41%) > pyrraline (20%), but not maltosine (34). A recent study by Bui *et al* (35) demonstrated that the gut microbiota is capable of anaerobic carboxymethyllysine degradation to carboxymethylated biogenic amines and 11 carboxylic acids with *Oscillibacter* and *Cloacibacillus evryensis* being the potential responsible taxa. It has been demonstrated that adult fecal microbiota and particularly *Intestinimonas* spp. can convert Nε-fructosyllysine to butyrate, whereas such a property in bacteria isolated from 3-4-month-old infants was dependent on the type of feeding. Specifically, the microbiota of breast-fed infants was unable to degrade Nε-fructosyllysine, whereas that of formula-fed infants possessed a Nε-fructosyllysine-converting ability due to the presence of this AGE in infant formulas following thermal exposure, thus being indicative of the adaptation of microbiota metabolism to dietary compounds (36). In addition, *E. coli* has been shown to metabolize CML with the formation of three metabolites, N-carboxymethylcadaverine, N-carboxymethylaminopentanoic acid and the N-carboxymethyl-Δ1-piperideinium ion, although the particular end-product may be strain-specific (37).

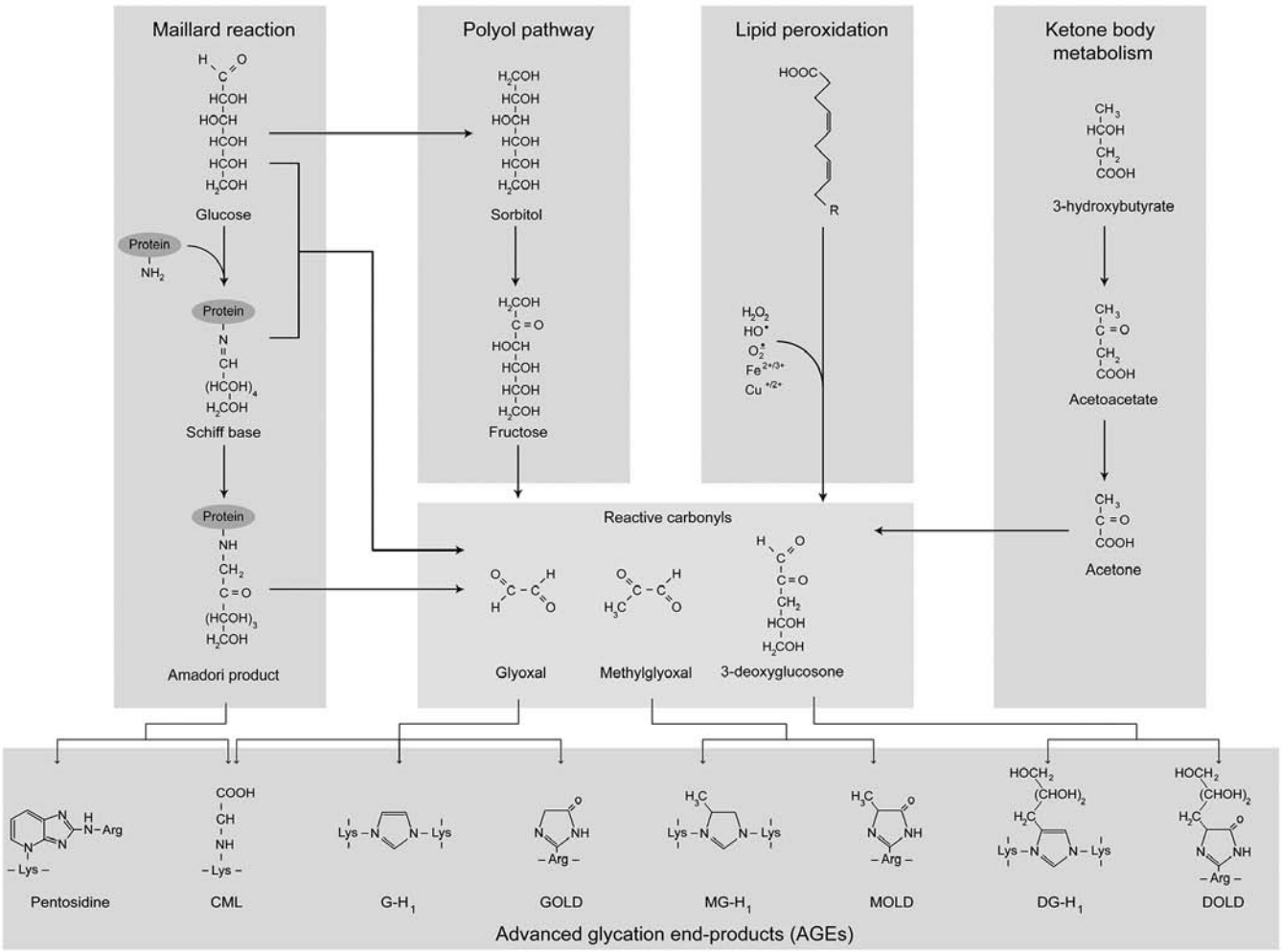

Figure 1. Common pathways of AGE formation *in vivo*. The first step of the Maillard reaction includes a reaction between the carbonyl group of a reducing sugar with a free protein amino group with the formation of a Schiff base that is transformed to a more stable Amadori product through a series of rearrangements. Following a series of rearrangements, oxidation and dehydration reactions, Amadori products are transformed into AGEs, such as CML and pentosidine. Another mechanism of AGE formation involves the generation of reactive carbonyls, glyoxal, methylglyoxal and 3-deoxyglucosone that are considered AGE precursors. Specifically, the interaction of glyoxal, methylglyoxal and 3-deoxyglucosone with protein molecules yields CML, GOLD and G-H1, MOLD and MG-H1, as well as DOLD and 3DG-H1, respectively. In addition, other sources of reactive carbonyls may include polyol pathway, lipid peroxidation and ketone body metabolism. AGE, advanced glycation end-product; CML, carboxymethyllysine; GOLD, glyoxal-lysine dimer; G-H1, glyoxal-derived hydroimidazolone; MOLD, methylglyoxal-derived di-lysine imidazolium crosslink; MG-H1, methylglyoxal-derived hydroimidazolone; DOLD, desoxyglucosone lysine dimer; 3DG-H1, 3-deoxyglucosone-derived hydroimidazolone 1.

It has also been demonstrated that bacterial metabolites can modulate AGE toxicity. The existing data demonstrate that gut microbiota-derived metabolite trimethylamine N-oxide (TMAO) can increase the production of AGEs in the aorta, thus promoting arterial stiffening (38), and underlying the role of TMAO and AGEs in the progression of cardiovascular and chronic kidney diseases (39).

3. The impact of dietary AGE exposure on gut microbiota characteristics and host metabolism

Diet has a significant impact on the biodiversity and metabolism of the gut microbiota (40). Correspondingly, the results of a recent systematic review demonstrated that the characteristics of dietary protein, including protein glycation can modulate gut biodiversity, although significant inconsistencies still exist (41).

Adverse effects of dietary AGEs on the gut microbiota. Consistent with the overall understanding of AGEs as perilous molecules, several studies have demonstrated that the dietary intake of AGEs induces the dysfunction of the gut microbiota along with unfavorable effects in the host organism. Specifically, in a human study, it was demonstrated that the increased exposure to glycated BSA significantly affected the colonic microbiota sampled from the feces of both healthy subjects and patients with ulcerative colitis, with a profound decrease in beneficial bacteria (eubacteria and bifidobacteria) and an increased abundance of more hazardous phyla (clostridia, bacteroides, sulfate-reducing bacteria) (42). The detailed study by Seiquer *et al* (43) revealed the significant association between AGEs intake and gut microbiota composition both in humans and rats. Specifically, the relative abundance of lactobacteria was inversely associated with dietary hydroxymethylfurfural and carboxymethyl-lysine, whereas the relative numbers of bifidobacterial were inversely associated with the intake of Amadori compounds in adolescents. Similarly, in rats, the dietary intake of the Amadori compounds, hydroxymethylfurfural and carboxymethyl-lysine, was negatively associated with both total bacteria and lactobacteria (43).

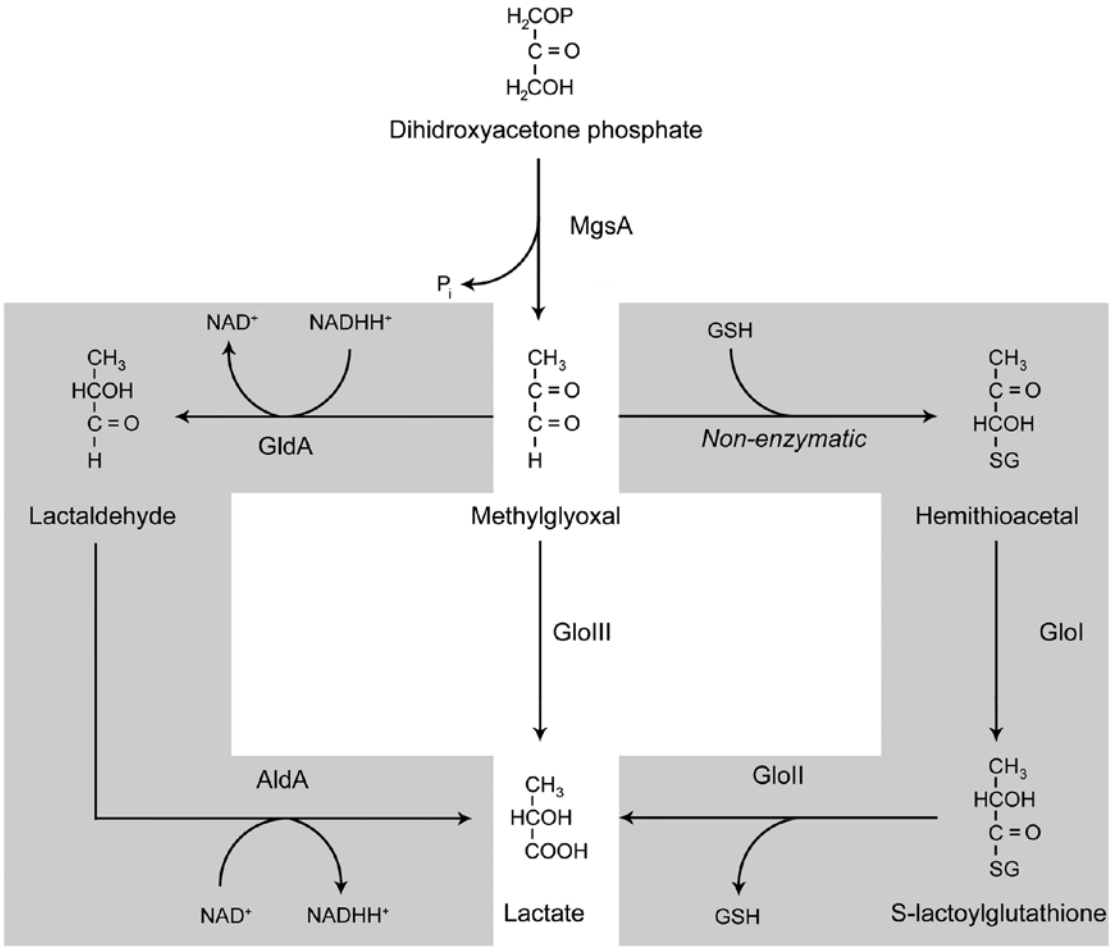

Figure 2. Mechanism of MGO detoxication in bacteria. The bacterial MGO decomposition is generally catalyzed by two enzymatic systems: GSH-dependent and GSH-independent glyoxalases and NAD-dependent dehydrogenases. Glyoxalases I and II catalyze the GSH-dependent conversion of MGO-derived hemithioacetal to D-lactate through the formation of S-D-lactoylglutathione. In turn, glyoxalase III catalyzes D-lactate from MGO without using GSH as a cofactor. NAD-dependent GldA mediates the transformation of MGO to D-lactaldehyde that is subsequently transformed to D-lactate using AldA. MGO, methylglyoxal; GSH, glutathione; GldA, glycerol dehydrogenase; AldA, aldehyde dehydrogenase.

In a laboratory study, it was demonstrated that AGE-rich food significantly aggravated alterations in gut microbiota biodiversity in a time-dependent manner, being more profound at 18 weeks of exposure, as compared to 6 and 12 weeks. Furthermore, it was shown that the high-AGE group ws characterized by a significant decrease in the abundance of Ruminococcaceae, Lachnospiraceae, *Alloprevotella*, Mollicutes, Christensenellaceae, *Treponema*, *Prevotellaceae*, *Sphaerochaeta*, *Elusimicrobium*, *Butyrivibrio* and *Anaeroplasma*, whereas that of *Oscillibacter*, *Allobaculum*, *Anaerotruncus*, *Barnesiella*, *Fusicatenibacter* and Veillonellaceae was elevated (44). Feeding rats with a heat-treated diet rich in AGEs resulted in a significant increase in the relative abundance of *Parabacteroides, Alloprevotella, Helicobacter,* Ruminococcaceae_UCG-014, and unclassified Rhodospirillaceae, whereas populations of *Desulfovibrio, Rikenellaceae,* Lachnospiraceae and *Alistipes*, were significantly reduced, being associated with perturbations of microbial metabolites and certain metabolic pathways, including impaired carbohydrate and amino acid metabolism (45). Correspondingly, in another study, the administration of an AGE-rich diet, obtained by heating the standard chow, to C57BL/6 mice resulted in a significant increase in circulating and tissue AGEs levels, systemic inflammation, and the alteration of the gut microbiota mainly characterized by the increased abundance of *Clostridium*_sensu_stricto_1, *Turicibacter* and *Parasutterella*, and in particular, *Dubosiella* at the genera level, as well as the increased abundance of Clostridiaceae_1, Erysipelotrichaceae and Burkholderiaceae families (46).

Dietary AGE-induced effects on gut microbiota have also been linked to several diseases. Specifically, a previous study demonstrated that feeding C57BL/6 mice with an AGE-rich diet significantly increased systemic AGE (CML) levels, protein glycosylation, receptor for AGEs (RAGE) expression in the ileum and submandibular glands, as well as complex alterations in gut microbiota composition. AGE intake significantly increased *Lawsonia, Parabacteroides* and *Ruminococcus* abundance, whereas the relative numbers of *Lactobacillus, Prevotella, Anaerostipes* and *Candidatus* Arthromitus were significantly reduced, altogether being associated with impaired insulin signal transduction (47). It has been also demonstrated that feeding rats with casein glycated with methylglyoxal 5-hydro-5-methylimidazolone significantly affects the intestinal microbiota, which may at least in part be responsible for a reduction in systemic gastric inhibitory polypeptide

and glucagon-like peptide-1 levels, consistent with an altered incretin-insulin axis, as well as with the overproduction of the pro-inflammatory cytokines, interleukin (IL)-1β and IL-17 and plasminogen activator inhibitor-1 (48).

Potentially beneficial effects of dietary AGEs on the gut microbiota. In contrast to the aforementioned findings, a number of studies have demonstrated that administration of dietary AGEs can afford beneficial effects, both to the gut microbiota and host metabolism. It is notable that the majority of results demonstrating the positive influence of AGEs on gut microbiota were attributable to administration of glycated fish proteins. Specifically, the glycation of dietary grass carp myofibrillar proteins resulting in increased furosine levels in glycoconjugates significantly increased gut microbiota biodiversity and butyrate production that was positively associated with the relative abundance of *Mitsuokella*, Lachnospiraceae_UCG-004, *Sutterella*, *Salinimicrobium*, *Fodinibius* and *Nitriliruptor*, being inversely associated with that of *Enterococcus*, *Dorea*, *Escherichia-Shigella* and *Phascolarctobacterium*, thus being indicative of the potential beneficial effects of protein glycation on gut health (49). Correspondingly, another study demonstrated that the administration of glycated fish protein to rats significantly increased the relative abundance of *Allobaculum*, *Akkermansia*, *Turicibacter* and *Lactobacillus animalis*, and reduced that of *Escherichia-Shigella*, *Fusobacterium* and *Erysipelatoclostridium* in the caecum, altogether being associated with the increased production of butyrate from fructoselysine (50). Similar findings were obtained in another study, where the administration of fish peptide glycated with galactooligosaccharide resulted in increased abundance of the Veillonellaceae, Prevotellaceae and Coriobacteriaceae families, and increased the abundance of the genera, *Anaerovibrio*, *Collinsella*, *Prevotella*_9, as well as reduced *Alloprevotella*, *Holdemanella*, *Escherichia-Schigella* and *Streptococcus* when compared to the control rats (51). Increasing fish protein glycation through heating for 24 or 48 h with its subsequent *in vitro* fermentation in a model of human distal colon significantly increased the relative abundance of *Lactococcus* in parallel with a decrease in *Bacteroides*. Moreover, the exposure of gut bacteria to glycated fish protein heated for 48 h resulted in a greater abundance of *Holdemania*, *Streptococcus*, *Enterococcus* and *Lactobacillus*, as well as a reduction of *Parabacteroides* when compared to a less glycated protein (24 h of heating). These changes, and particularly a decrease in *Bacteroides*, *Dialister* and *Parabacteroides*, were associated with reduced ammonia and indole production (52). The intake of glycated fish protein in high-fat fed rats also decreased relative abundance of *Ruminiclostridium* and *Desulfovibrio*, as well as dose-dependent effects, including increased *Ruminococcus* and *Roseburia* abundance in low glycated protein diet and decreased *Helicobacter* and Lachnospiraceae upon high-dose glycated protein intake. Moreover, the observed AGE-induced modulation of gut microbiota composition was associated with a significant reduction of systemic proinflammatory cytokine (IL-1β and IL-6) levels and lipid profile improvement, thus indicative of the potential beneficial effects on gut and metabolism (53).

It has been also demonstrated that the glycation of the milk proteins, β-lactoglobulin and casein, significantly increased fermentability of the proteins by *Lactobacillus* and *Bifidobacterium* thus promoting their growth, although the effect was more profound at the initial steps of Maillard reaction (54). β-lactoglobulin-galactose conjugate was also shown to promote *Clostridium coccoides-Eubacterium* rectal group growth, as well as increase bacterial acetate production (55). Notably, the modification of β-lactoglobulin by glycation and ultrasonication has been shown to reduce milk protein allergenicity, which may be mediated by lower digestibility, modification of allergenic epitopes on the protein molecule, as well as modulation of gut microbiota composition (56).

The administration of glycated whey proteins to aged male non-obese diabetic mice with autoimmune prostatitis significantly increased mice survival, reduced prostatic inflammation, as well as an increased abundance of *Allobaculum*, *Anaerostipes*, *Bacteroides*, *Parabacteroides* and *Prevotella* and reduced abundance *Adlercreutzia* and *Roseburia*, whereas the population of *Bacteroides acidifaciens* significantly correlated with the observed effects, indicative of the role of gut microbiota modulation in protective effects of glycated whey proteins (57). Similarly, a beneficial effect on the gut microbiota was demonstrated for glycated pea protein which increased *Bacteroides*, *Lactobacillus*/*Enterococcus* and *Bifidobacterium* growth as well as short chain fatty acids (SCFAs), acetate, propionate, lactate, and butyrate production (58).

The dietary restriction of AGEs was shown to reduce systemic CML and MG levels, as well as affect the gut microbiota by increasing the relative abundance of *Alistipes indistinctus*, *Clostridium citroniae*, *Clostridium hathewayi*, and *Ruminococcus gauvreauii*, in parallel with a decrease in *Prevotella copri* and *Bifidobacterium animalis* in peritoneal dialysis patients (59). Concomitantly, in another study, a reduction in dietary AGEs intake did not have a significant effect on the most abundant gut bacteria in healthy obese subjects. As compared to the group with a high AGE intake, the low dietary AGE group was characterized by a greater abundance of *Tyzzerella*, Family_XII_UCG-001 and Christensenellaceae_R-7 Group, as well as a lower abundance of *Negativibacillus*, *Oscillibacter* and *Anaerostipes* (60).

An insight into the distinct effects of various AGEs on the gut microbiota. As clearly detailed in previous studies, the effects of dietary AGEs on the gut microbiota vary significantly, depending on their characteristics, including both the dose, source and chemical properties. The study by Cao *et al* (61) proposed that the observed inconsistencies in the reported effects of AGE intake on the gut microbiota and overall health were dependent on the dose of the glycated protein in the diet. The intake of low levels of glycated fish proteins for 15 weeks in mice resulted not only in an increased abundance of the butyrate-producing bacteria, Lachnospiraceae and *Allobaculum*, but also increased intestinal tight junction protein expression (occludin and Zonula occludens-1), reduced pro-inflammatory cytokine production (IL-1β and IL-6) and improved insulin sensitivity. By contrast, inverse effects were observed upon exposure to high-dose glycated fish protein in parallel with a reduction in *Bifidobacterium* and *Lactobacillus* abundance (61). It has been posited that free AGEs, such as carboxymethyllysine have detrimental

effects on the composition and functions of the gut microbiota, whereas bound AGEs have a more beneficial effect, although certain detrimental effects may be also observed (62). It was hypothesized that the positive effects of glycated proteins, namely fish proteins on the gut microbiota are due to the use of such proteins as a slow fermentable protein source or carbonyl donors providing additional energy to gut microbiota (46). In addition, free and protein-bound AGEs in the diet have distinct effects on the gut microbiota due to differences in digestibility (63). In addition to the AGE species, the molecular weight of the ligand has a significant impact on digestibility. Specifically, in a previous study, in a model of glyoxal-glycated casein digests, CML was degraded predominantly in the low molecular weight fraction (38.7%) followed by medium (21.7%) and high molecular weight fractions (9.6%) which may be mediated by the lower activity of proteases (64).

4. Involvement of AGE-gut microbiota interplay in disease pathogenesis

Type 2 diabetes mellitus. The understanding of the pathogenesis of diabetes mellitus sheds light onto the toxicological effects of AGEs and their role in metabolic diseases (10). Although the dysfunction of the gut microbiota has been known to play a significant role in diabetogenesis (65), the potential interplay between gut microbiota dysfunction and excessive protein glycation in diabetes has been studied only recently. Wu *et al* (66) demonstrated that dietary AGE exposure significantly affected the gut microbiota, with an irreversible increase in *Bacteroidetes* populations and a decrease in *Firmicutes* abundance at the phylum level, whereas at the genera level, a high-AGE diet stimulated *Helicobacter*, *Bacteroides*, *Rikenella*, *Alistipes*, *Bifidobacterium*, *Candidatus Saccharimonas*, *Faecalibaculum*, Clostridiales, *Erysipelatoclostridium* and *Intestinimonas*, and decreased unidentified Lachnospiraceae, *Roseburia*, *Oscillibacter*, *Anaerotruncus*, *Blautia*, *Mucispirillum*, *Angelakisella*, *Lachnoclostridium*, *Lachnospira*, *Ruminiclostridium*, *Acetatifactor*, and *Desulfovibrio*. These perturbations were shown to contribute to diabetes pathogenesis through the modulation of glyceraldehyde and pyruvate production with the subsequent aggravation of insulin resistance and other alterations in carbohydrate and lipid metabolism, as well as inflammation due to higher systemic lipopolysaccharide (LPS) levels (66). A comparative analysis demonstrated that despite a significant increase in circulating AGEs and the induction of insulin resistance in mice exposed to both an AGE-rich diet or purified methylglyoxal-bovine serum protein (exogenous AGE), profound alterations of intestinal permeability and microbiota structure were observed only upon exogenous AGE intake. A high AGE intake was shown to reduce the abundance of *Bacteroidales*_S24-7, Bacteroidaceae, Porphyromonadaceae, Odoribacteraceae, Lachnospiraceae, Rikenellaceae, and Erysipelotrichaceae in parallel with an increase in Desulfovibrionaceae abundance (67). It was proposed that a decrease in butyrate production by butyrate-producing bacteria may promote the impairment of the intestinal epithelial barrier and induce inflammation, thus contributing to systemic insulin resistance (67). The observed increase in *Desulfovibrio* abundance generally corresponds to the early observed positive association between these bacteria with blood glucose indices (68) and Parkinson's disease (69), although the results of the Guangdong Gut Microbiome Project demonstrated that the abundance of *Desulfovibrio* may be inversely associated with body mass index and triglyceride levels (70). Moreover, earlier findings in diabetic db/db mice exposed to high levels of dietary AGEs demonstrated in a significant increase in gut permeability, as well as an elevation of the *Firmicutes*-to-*Bacteroidetes* ratio, altogether being associated with kidney damage and albuminuria, whereas the administration of resistant starch ameliorated these effects (71). It is also notable that the formation of Maillard reaction products with subsequent protein aggregation in bacterial species shares certain similarity to that observed in Parkinson's and Alzheimer's disease (72). Therefore, preliminary data demonstrate that AGE-induced alterations in the gut microbiota can contribute to the aggravation of insulin resistance through a number of mechanisms, including the impairment of the intestinal epithelial barrier and subsequent increase in circulating LPS levels.

Ageing-associated diseases. Recent studies have demonstrated that alterations in the gut microbiota, as well as increased levels of AGEs are associated with aging, contributing to the development of age-related diseases (73,74). Age-related changes in the gut microbiota characterized by a reduced *Firmicutes*-to-*Bacteroidetes* ratio at the phylum level, as well as by the increased abundance of *Turibacter*, *Alloprevotella*, *Parasutterella*, *Bifidobacterium*, *Macellibacteroides*, *Alistipes* sensu stricto 1, *Peptostreptococcaceae incertae sedis* and *Parabacteroides*, and the lower abundance of *Pantoea*, *Anoxybacillus*, *Lachnospiraceae incertae sedis*, *Cutrobacterium* and *Acetatifactor* at the genera level, were shown to contribute to the accumulation of N^6-carboxymethyllysine in microglia and subsequent oxidative stress and mitochondrial dysfunction by increasing intestinal permeability, whereas germ-free mice brain microglia were characterized by lower oxidative stress and mitochondrial damage (75). In corroboration, the translocation of fecal microbiota from aged to young rats impaired cognition, induced synaptic dysfunction, along with oxidative stress and inflammation, which may be at least partially mediated by an increased AGE production and RAGE expression (76). Correspondingly, the antibiotic treatment of 5xFAD mice, a model of Alzheimer's disease that is known to be age-related, resulted in a significant decrease in intestinal Lactobacillaceae abundance, being also associated with reduced hippocampal plaque formation, antidiabetic effect and decreased RAGE expression (77). Taken together, even these limited data demonstrate that age-related alterations of the gut microbiota may contribute to AGE accumulation, particularly in brain tissues, indicating the gut microbiota-AGE interplay in age-related neurodegeneration.

Other diseases. A recent study in ethanol-fed mice demonstrated an increased abundance of *Bacteroidetes* and a decrease in *Firmicutes* numbers, which was associated with an elevation in AGE and RAGE levels in colonic tissues, and considered a potential mechanism of ethanol-related colorectal cancer pathogenesis (78).

5. Effects of gut microbiota modulation on AGE metabolism and toxicity

Probiotics. Several studies have demonstrated that the modulation of the gut microbiota using probiotics is also associated with reduced AGE accumulation and toxicity, thus also supporting the role of the gut microbiota in AGE toxicity. Specifically, in a previous study, in a model of Alzheimer's disease, the modulation of the gut microbiota through the administration of SLAB51 probiotic significantly reduced brain AGE accumulation and tau phosphorylation, and also improved insulin signaling through the Akt/AMPK pathway (79). In another laboratory *in vivo* study, the administration of probiotic *Lactobacillus paraplantarum* BGCG11 significantly reduced AGE accumulation in parallel with inhibiting hyperglycemia, oxidative stress, DNA damage, liver and kidney fibrosis in rats with streptozotocin-induced diabetes (80). In another study, the administration of the commercial probiotic, Protexin®, in Cd-exposed rats significantly reduced the serum MGO levels, as well as decreased tissue Cd accumulation and Cd-induced oxidative stress (81). *Lactococcus lactis* KF140 supplementation has also been shown to reduce serum CML levels and hepatic CML accumulation that may be at least partially mediated by activity of bacteria-derived β-galactosidase (82).

In addition to probiotics, it has been demonstrated that treatment with prebiotics may also modulate AGE accumulation and toxicity. Specifically, the administration of the prebiotic, resistant dextrin, has been shown to significantly reduce carboxymethyl lysine, soluble RAGE, as well as several other cardiometabolic risk factors in adult women (83).

At the same time, additional studies, including clinical trials are required to address the impact of microbiota modulation by probiotics and prebiotics on AGE toxicity and RAGE signaling, as well as the clinical validity of these interventions.

Phytochemicals. Polyphenols have also been shown to have a significant beneficial effect on gut microbiota and glycative stress, and these effects appear partially interrelated (84). Specifically, the administration of *Physalis alkekengi* L. fruit polysaccharide to AGE-fed mice was shown to modulate gut microbiota by increasing the abundance of Rikenallaceae, *Alistipes*,Nocardiaceae,*Rhodococus*,*Bacilli*,Lactobacillaceae, Bacteroidaceae and Burkholderiaceae, improving the *Bacteroidetes*/*Firmicutes* ratio, as well as decreasing LPS production. Treatment with *Physalis alkekengi* polysaccharide also improved the bacterial production of SCFAs, namely acetic and propionic acids, which may at least partially mediate the treatment-induced reduction of insulin resistance (85). It has also been demonstrated that the administration of quercetin to AGE-fed mice significantly ameliorated cognitive dysfunction through the reduction of tau phosphorylation, cathepsin B and neuroinflammation, as well as increased gut microbiota biodiversity and reduced the abundance of *Verrucomicrobia* phylum, and *Blautia* and *Anaerotruncus* genera (86). In addition, it has been proposed that an increase in *Lactobacteria* and particularly *Bifidobacteria* by *Geranium dielsianum* extract may at least partially mediate antiglycative effect of the extract (87). These data demonstrate that the protective effects of phytochemicals against AGE toxicity are mediated by its influence on the composition of the gut microbiota.

6. Role of lipopolysaccharide in the interplay between microbiota and AGE toxicity

LPS, also known as endotoxin, is a cell wall component of Gram-negative bacteria. In the human gut microbiota, *Bacteroidetes*, and to a lesser extent, *Proteobacteria* phyla, are considered as key sources of LPS production (88). LPS mediates a substantial part of the effects of altered microbiota on the host, including the regulation of systemic inflammation (89).

Several studies have demonstrated the significant effect of LPS on cellular production and the accumulation of AGEs or their precursors. Specifically, a previous study demonstrated that the stimulation of RAW264.7 murine macrophages with LPS resulted in a significant increase in intracellular methylglyoxal generation upon high-glucose conditions in parallel with HIF-1 downregulation and pyroptosis (90). A similar effect was observed in LPS-stimulated J774A.1 macrophages and N11 microglia (91). Correspondingly, long-term LPS treatment was shown to increase aortal AGE accumulation (92). In turn, in rat aortic smooth muscle cells, MGO treatment was shown to inhibit LPS-stimulated inducible nitric oxide synthase expression by inhibiting Akt phosphorylation that may be involved in diabetic vascular dysfunction (93). These findings generally corroborate recent data obtained by Kitaura *et al* (94), demonstrating that AGEs may reduce LPS uptake by RAW264.7 macrophages, which may be at least partially mediated by RAGE activation, resulting in altered immune response in diabetes (94).

LPS is a potent pro-inflammatory agent that induces an inflammatory response through a number of mechanisms. It has been shown that AGEs potentiate the pro-inflammatory effects of LPS on gingival fibroblasts under high-glucose conditions, as evidenced by an elevated IL-8 secretion (95). The potentiation of the pro-inflammatory effects of LPS and AGEs may be mediated by the activation of mitogen-activated protein kinases and NF-κB activation in endothelial cells (96).

One of the mechanisms underlying the pro-inflammatory effects of LPS and its impact on NF-κB signaling is the modulation of RAGE signaling (97) (Fig. 3). The activation of RAGE signaling has been shown to mediate certain effects of glucotoxicity, as well as the toxic effects of environmental factors (98,99).

Given the role of AGEs as ligands for RAGE, the modulation of RAGE signal transduction by LPS may also be considered as one of the aspects of microbiota-AGE interplay. Specifically, in human umbilical vein endothelial cells, LPS treatment has been shown to increase both RAGE expression and NF-κB activation, as well as p65 nuclear translocation, whereas anti-RAGE antibody ameliorated the LPS-induced NF-κB activation and subsequent endothelial barrier dysfunction, thus being indicative of the role of RAGE in the LPS-induced inflammatory reaction (100). Anti-RAGE antibody has also been shown to reduce LPS-induced acute lung injury in a neonatal rat model (101). Concomitantly, tje inhibition of NF-κB signaling significantly decreases LPS-induced RAGE expression in alveolar type I epithelial cells, whereas RAGE knockdown inhibits both basal and LPS-induced NF-κB activation (102).

A previous study demonstrated that LPS may directly bind RAGE with a subsequent NF-κB-dependent inflammatory

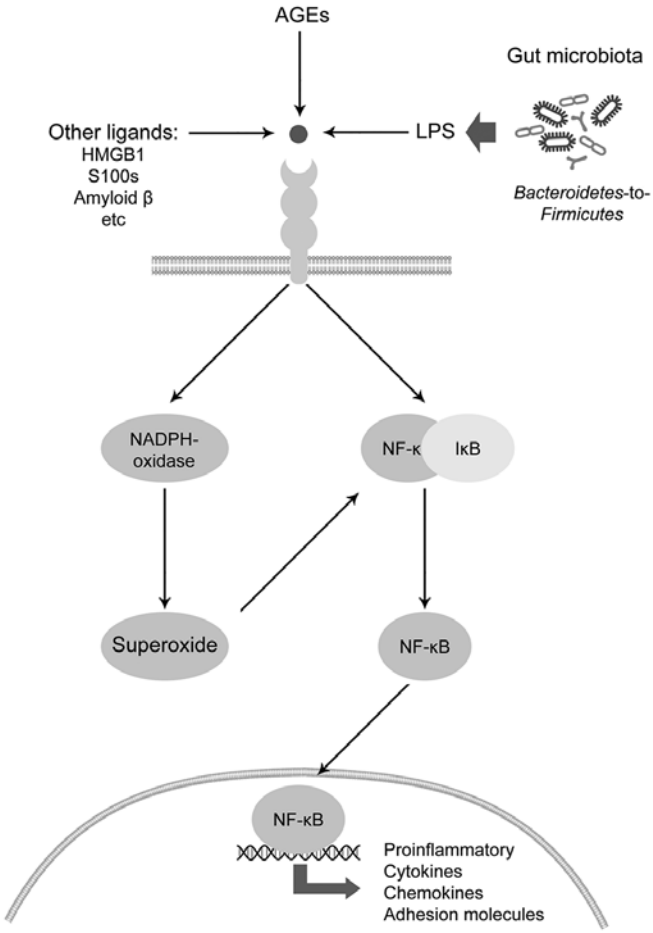

Figure 3. Role of AGEs and LPS in RAGE signaling. AGEs, advanced glycation end-products; LPS, lipopolysaccharide; RAGE, receptor for advanced glycation end products; HMGB1, high mobility group box 1.

response in a murine model of septic shock, whereas the injection of soluble RAGE significantly reduced LPS-induced proinflammatory cytokine expression and tissue damage (103). It has been proposed that the ratio between cell surface RAGE and soluble RAGE (sRAGE) may significantly mediate inflammatory response to bacterial molecules (103). Additional research has demonstrated that the direct interaction between LPS, high mobility group box 1 (HMGB1) and AGEs results in the formation of a triplet complex and subsequent increase in HMGB1 mobility, altogether leading to increased TNF-α mRNA expression in RAW264.7 macrophages through Toll-like receptor 4 (TLR4) and RAGE activation (104).

Another study demonstrated that the inhibition of RAGE signaling thwarted the LPS-induced upregulation of HMGB1 and IL-6 expression through a NF-κB-mediated mechanism (105). Accordingly, the inhibition of RAGE activation has been considered as one of the mechanisms underlying the protective effects of certain agents including β-caryophyllene and perindopril against LPS-induced liver injury (106) and amyloidogenesis (107), respectively. In agreement with this, the phytochemicals, icariin and icaritin, have been found to significantly reduce LPS-induced hippocampal neuroinflammation through the downregulation of HMGB1-RAGE signaling (108). Concomitantly, preconditioning with HMGB1 has been shown to induce LPS tolerance in a RAGE-dependent manner (109).

In addition to the role of RAGE signaling in LPS-induced inflammation, this mechanism may also trigger the adverse effects of LPS on the cytoskeleton and tight junction proteins. Specifically, RAGE signaling has been shown to be involved in LPS-induced cytoskeletal alterations in mouse pulmonary microvascular endothelial cells, as demonstrated in RAGE-knockout pulmonary microvascular endothelial cells, which did not develop F-actin rearrangement and stress fiber formation upon LPS stimulation (110). In another study, RAGE-deficient mice were also found to be resistant to LPS-induced leukocyte infiltration and proinflammatory cytokine secretion, as well as alteration of lung Zonula occludens-1, sodium-potassium ATPase (Na, K-ATPase), and epithelial sodium channel expression. Moreover, in patients with infection-induced acute respiratory distress syndrome, bronchial alveolar lavage fluid sRAGE levels were increased, being associated with pro-inflammatory cytokine levels and pulmonary vascular permeability (111). In line with these observations, it was previously demonstrated that the inhibition of RAGE signaling not only reduced pro-inflammatory cytokine expression in a model of LPS-induced acute lung injury, but also prevented the downregulation of claudin-2 and occludin expression (112). While discussing the role of AGE signaling and LPS in the alteration of cell contacts, it is important to note that glycated caseinate hydrolysate has been shown to possess significantly lower barrier-protective effects in LPS-exposed intestinal IEC-6 cells as compared to unmodified caseinate hydrolysate (113).

The activation of LPS-RAGE signaling has also been shown to mediate carcinogenesis. Specifically, the upregulation of HMGB1/RAGE signaling has been found to be responsible for LPS-induced inflammation and the subsequent malignant transformation of normal cervical epithelial cells (114). Moreover, a previous study demonstrated that the breast tumor microbiota was enriched with Gram-negative bacteria producing LPS. *In vitro* LPS treatment was shown to upregulate S100A7 expression in breast cancer cells, resulting in the upregulation of RAGE expression along with a reduced TLR4 expression that may contribute to tumor growth progression (115).

At the same time, it has been proposed that RAGE signaling may mediate the inflammatory response to bacteria through reactions to other bacterial molecules than LPS (116).

Taken together, these findings demonstrate that AGEs can modulate the pro-inflammatory effects of bacterial LPS, that is normally released by gut microbiota, whereas the pro-inflammatory signals of LPS are mediated by RAGE activation, which is also activated by AGEs.

7. Conclusions and future perspectives

The existing data demonstrate a bilateral association between gut microbiota and the effects of AGEs. Such an association may be summarized by the following aspects: i) Dietary AGEs may have a significant impact on the richness and diversity of the gut microbiota; ii) the gut microbiota may metabolize dietary AGEs; iii) the composition of the gut microbiota is tightly associated with AGE accumulation in the host organism; iv) certain effects of AGE accumulation in the organism may be mediated by the modulation of the gut microbiota; v) the

alteration of the gut microbiota may mediate the development of comorbidities associated with ageing and diabetes; vi) LPS may be considered as the molecule mediating the association between the gut microbiota and AGEs, and particularly, RAGE signaling; vii) dietary interventions aimed at the improvement of the gut microbiota may exert protective effects against AGEs toxicity. Given a mutual interaction between AGE toxicity and dysbiosis, it can be hypothesized that exposure to dietary AGEs may induce gut dysbiosis that further promotes AGE production, thus composing a vicious circle involved in disease pathogenesis. This vicious circle may be involved in the development of opportunistic infections and systemic inflammation in diabetic patients characterized by high levels of endogenous AGE. Therefore, the modulation of the gut microbiota with probiotics or other nutrients may be considered as a potential protective strategy against AGE-induced glycative stress and systemic inflammation. However, further studies on the molecular aspects of the interaction between gut microbiota and AGE metabolism and toxicity are required.

Acknowledgements

Not applicable.

Funding

The present study was performed with the financial support of the Russian Science Foundation (project No. 20-16-00078).

Availability of data and materials

Not applicable.

Authors' contributions

MA and AAT were involved in the conceptualization of the study. MA, AVS, VAG, OLK, AS, JBTR, IPZ, AT and AAT were involved in the investigation of the literature and in the curation of data for inclusion in the review. VAG, OLK, IPZ and AAT were involved in the writing and preparation of the original draft. MA, AVS, AS, JBTR, DAS and AT were involved in the writing, reviewing and editing of the manuscript. AAT was involved in visualization. MA, AVS, AS, JBTR, DAS and AT supervised the study. AAT was involved in funding acquisition. All authors have read and agreed to the published version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

DAS is the Editor-in-Chief for the journal, but had no personal involvement in the reviewing process, or any influence in terms of adjudicating on the final decision, for this article. The other authors declare that they have no competing interests.

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