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Differences in kinetics and dynamics of endogenous versus exogenous advanced glycation end products (AGEs) and their precursors

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ABSTRACT

Advanced glycation end products (AGEs) and their precursors, referred to as glycation products, are a heterogenous group of compounds being associated with adverse health effects. They are formed endogenously and in exogenous sources including food. This review investigates the roles of endogenously versus exogenously formed glycation products in the potential induction of adverse health effects, focusing on differences in toxicokinetics and toxicodynamics, which appeared to differ depending on the molecular mass of the glycation product. Based on the available data, exogenous low molecular mass (LMM) glycation products seem to be bioavailable and to contribute to dicarbonyl stress and protein cross-linking resulting in formation of endogenous AGEs. Bioavailability of exogenous high molecular mass (HMM) glycation products appears limited, while these bind to the AGE receptor (RAGE), initiating adverse health effects. Together, this suggests that RAGE-binding in relevant tissues will more likely result from endogenously formed glycation products. Effects on gut microbiota induced by glycation products is proposed as a third mode of action. Overall, studies which better discriminate between LMM and HMM glycation products and between endogenous and exogenous formation are needed to further elucidate the contributions of these different types and sources of glycation products to the ultimate biological effects.

1. Introduction

Glycation products are a heterogenous group of compounds which include advanced glycation end products (AGEs) and their precursors such as Amadori products and reactive dicarbonyls. AGEs have been associated with adverse health effects (i.e. chronic diseases, atherosclerosis, inflammation) in both human and animal studies (Nowotny et al., 2018; Gill et al., 2019; Sergi et al., 2020). AGEs can be formed endogenously (i.e. in the host) but are also abundantly present in exogenous sources such as food products and tobacco smoke (Poulsen et al., 2013). Especially in the Western diet AGEs and their precursors are abundant (Uribarri et al., 2010; Piperi, 2017). The question remains however to what extent exogenous glycation products contribute to the endogenous AGE pool and to the associated potential adverse health effects. This review aims to provide a state-of-the-art overview of the toxicokinetics and toxicodynamics of endogenously formed and exogenous dietary AGEs and their precursors in order to evaluate their potential contributions to the adverse effects on human health. Given that the toxicokinetics and toxicodynamics appear to differ depending on the molecular mass of the AGEs and their precursors, the review discriminates not only between exogenous and endogenous but also between free, low molecular mass (LMM) glycation products and dicarbonyl

Abbreviations: ADME, absorption, distribution, metabolism, excretion; AGE, advanced glycation end product; AGE-R1, oligosaccaharyltransferase-48; AGE-R2, 80K-H phosphoprotein; ALE, advanced lipoxidation end product; BSA, bovine serum albumin; CEL, Nε-(carboxyethyl)lysine; CML, Nε-(carboxymethyl)lysine; FL, fructoselysine; HbA1C, glycated hemoglobin; HMF, hydroxymethylfurfural; HMM, high molecular mass; LC-MS/MS, liquid chromatography tandem mass spectrometry; LDL, low density lipoproteins; LMM, low molecular mass; MAPK, mitogen-activated protein kinases; MG-H1, Nδ-(5-hydro-5-methyl-4-imidazolon-2-yl) ornithine; NF-κB, nuclear factor-kappa B; NOD, non-obese diabetic; Nrf2, nuclear factor erythroid 2-related factor 2; PUFA, polyunsaturated fatty acid; RAGE, receptor for AGE; ROS, reactive oxygen species; SCFA, short chain fatty acid; sRAGE, soluble RAGE.

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precursors, and protein-bound, high molecular mass (HMM) glycation products.

First, an overview of the types of glycation products considered in this review will be presented. The second section of this review will give an overview of the toxicokinetics of exogenous and endogenously formed AGEs and their precursors. The third section of the review provides an overview of the toxicodynamics and modes of action in the host. Finally, the findings will be discussed and recommendations for future research will be provided.

2. Endogenous and exogenous glycation products

Exposure to glycation products results from endogenous formation or from intake of glycation products formed exogenously and present in for example food or cigarette smoke. Due to the involvement of various precursors (e.g. dicarbonyls), multiple amino acid residues, and the formation of free and peptide- or protein-bound AGEs, the glycation products formed are a heterogenous group of compounds, consisting of HMM and LMM AGEs and precursors, including cross-linked products (i.e. when two amino acid residues are involved instead of one). In the present review, HMM glycation products refer to products formed by reaction with a protein-bound amino acid residue while LMM glycation products refer to products formed by reaction with a free amino acid residue and/or to dicarbonyl precursors.

2.1. Exogenous formation of AGEs and their precursors

Exogenous AGEs and their precursors present in food products (i.e. bread, milk (powder), processed food products) can be formed at high rates during heating applied to improve the quality and taste of the product, its shelf life, for safety reasons, or to produce the desired food product (Poulsen et al., 2013). During this process, AGEs and their precursors are formed via multiple pathways of the non-enzymatic Maillard reaction (Maillard, 1912; Yaylayan et al., 1994; Buetler et al., 2008; Vistoli et al., 2013; Nguyen et al., 2014). First of all, the carbonyl group of a reducing sugar can bind to the amino group of a free, protein-bound or peptide-bound amino acid, forming a (reversible) Schiff base that spontaneously forms so-called Amadori products. These Amadori products are relevant precursors for AGEs as they can rearrange into AGEs via the Hodge pathway, which is a series of reactions including dehydration, fragmentation, oxidation and cyclization (Yaylayan et al., 1994; Liang et al., 2019). In addition to formation of AGEs via the Hodge pathway, the Schiff base or the covalently-bound Amadori product precursors can also be decomposed via the Namiki pathway into reactive dicarbonyls, also referred to as α-oxoaldehydes (i.e. methylglyoxal, glyoxal, 3-deoxyglucosone) (Yaylayan et al., 1994; Liang et al., 2019; Perrone et al., 2020). These reactive dicarbonyls can react with an unbound or bound amino acid and in this way form AGEs. Among the most abundant and most frequently studied Amadori products and AGEs in food are fructoselysine (FL), which is formed from glucose and lysine (Hegele et al., 2008), and Nε-(carboxymethyl)lysine (CML) (Delgado-Andrade, 2016) which is formed by rearrangement from FL or via a reaction between lysine and the dicarbonyls glyoxal or 3-deoxyglucosone, respectively. Other AGEs include compounds like pyrraline, hydroxymethylfurfural (HMF), Nε-(carboxyethyl)-lysine (CEL) and Nδ-(5-hydro-5-methyl-4-imidazolon-2-yl)-ornithine (MG-H1) (Fig. 1).

Reactive dicarbonyls are involved in the formation of multiple AGEs. The dicarbonyl glyoxal can form CML by reacting with lysine side chains (Glomb and Monnier, 1995). By reacting with a cysteine group, the irreversible end-product S-carboxymethylcysteine can be formed (Zeng and Davies, 2005). If glyoxal reacts with arginine, more complex reactions occur leading to multiple glyoxal-arginine derived AGEs (i.e. carboxymethylarginine, the intermediates G-DH1 (N-(3,4-dihydroxy-1-imidazolidin-2-yl)ornithine) and G-DH2 ((5-(4,5-dihydroxy-2-imino-1-imidazolidinyl)norvaline)) and the subsequent imidazolone-derivatives G-H1, G-H2, G-H3) (Vistoli et al., 2013) (Fig. 1). The dicarbonyl methylglyoxal is also involved in formation of multiple AGEs. Reaction with lysine residues can lead to CEL formation (Ahmed et al., 1997), while reactions with arginine residues can give rise to multiple products depending on the number of nitrogen atoms involved in cyclization and the pH. As such, MG-H1, MG-H2 (2-amino-5-(2--amino-5-hydro-5-methyl-4-imidazolon-1-yl)pentanoic acid) or MG-H3 (2-amino-5-(2-amino-4-hydro-4-methyl-5-imidazolon-1-yl)pentanoic acid) can be formed (Klöpfer et al., 2011)(Fig. 1). The dicarbonyl 3-deoxyglucosone can form the AGEs CML and pyrraline by reacting with lysine residues (Monnier et al., 1996; Miyata, 1997; Niwa et al., 1998; Tsukushi et al., 1999). When 3-deoxyglucosone reacts with arginine residues, multiple products can be formed including 3DG-H1 (N-(5-hydro-5-(2,3,4,-trihydroxybutyl)-4-imidazolon-2-yl)orthinine), 3DG-H2 (5-(2-amino-5-hydro-5-(1,2,3-trihydroxybutyl)-4-imidazolon-1-yl)norvaline) and 3DG-H3 (5-(2-amino-4-hydro-4-(2,3,4-trihydroxybutyl)-5-imidazolon-1-yl)norvaline) (Niwa et al., 1997)(Fig. 1).

When dicarbonyls such as glyoxal, methylglyoxal and 3-deoxyglucosone react with two amino acid residues (both lysine or arginine) this leads to imidazole cross-linked AGEs such as GODIC (N6-(2-{[(4S)-4-ammonio-5-oxido-5-oxopentyl]amino}-3,5-dihydro-4H-imidazol-4-ylidene)-L-lysine) and GOLD (6-{1-[(5S)-5-ammonio-6-oxido-6-oxohexyl]imidazolium-3-yl}-L-norleucine) resulting from reactions with glyoxal, MODIC (2-ammonio-6-({2–[4-ammonio-5-oxido-5-oxopently)amino]-4-methyl-4,5-dihydro-1H-imidazol-5-ylidene}amino)hexanoate) and MOLD (6-{1-[(5S)-5-ammonio-6-oxido-6-oxohexyl]-4-methyl- imidazolium-3-yl}-L-norleucine) with involvement of methylglyoxal and DODIC (N 6 -{2-{[(4S)-4-ammonio-5-oxido-5-oxopentyl]amino}-5 -[(2S,3R)-2,3,4-trihydroxybutyl]-3,5-dihydro-4H-imida-zol-4-ylidene}-L-lysinate) and DOLD (1,3-di(Nε-lysino)-4-(2,3,4-trihydroxybutyl)-imidazolium) involving 3-deoxyglucosone (Vistoli et al., 2013) (Fig. 1). When adduct formation or crosslinking occurs in proteins, HMM AGEs are formed.

In addition to the above mentioned major pathways of AGE formation, dicarbonyls and thus eventually AGEs can also be formed via lipid peroxidation of polyunsaturated fatty acids (PUFAs) (Vistoli et al., 2013) or via autoxidation of monosaccharides (i.e. Wolff pathway) (Ott et al., 2014; Sergi et al., 2020).

2.2. Endogenous formation of AGEs and their precursors

In endogenous formation of AGEs and their precursors, the same pathways as described above that proceed via non-enzymatic reactions are involved, although they occur at lower rates compared to exogenous formation due to the lower physiological temperatures. In addition, specific endogenous AGE formation pathways include glycolysis and the so-called polyol pathway.

General metabolism of glucose or fructose via glycolysis can lead to formation of reactive metabolites including glyceraldehyde and methylglyoxal. Glyceraldehyde 3-phosphate and dihydroxyacetone phosphate, formed via glycolysis, can spontaneously and non-enzymatically degrade to methylglyoxal (Ramasamy et al., 2006; Liu et al., 2013). The formed methylglyoxal can react with (un)bound amino groups resulting in AGE formation. The AGE pentosidine can be formed by rearrangement of pentose-derived Amadori product precursors, but can also be formed in a reaction between lysine or arginine residues with e.g. ascorbate, 3-deoxyglucosone or glyceraldehyde (Vistoli et al., 2013). The polyol pathway is active under hyperglycemic conditions and involves sorbitol formation from glucose. Sorbitol can be oxidized to

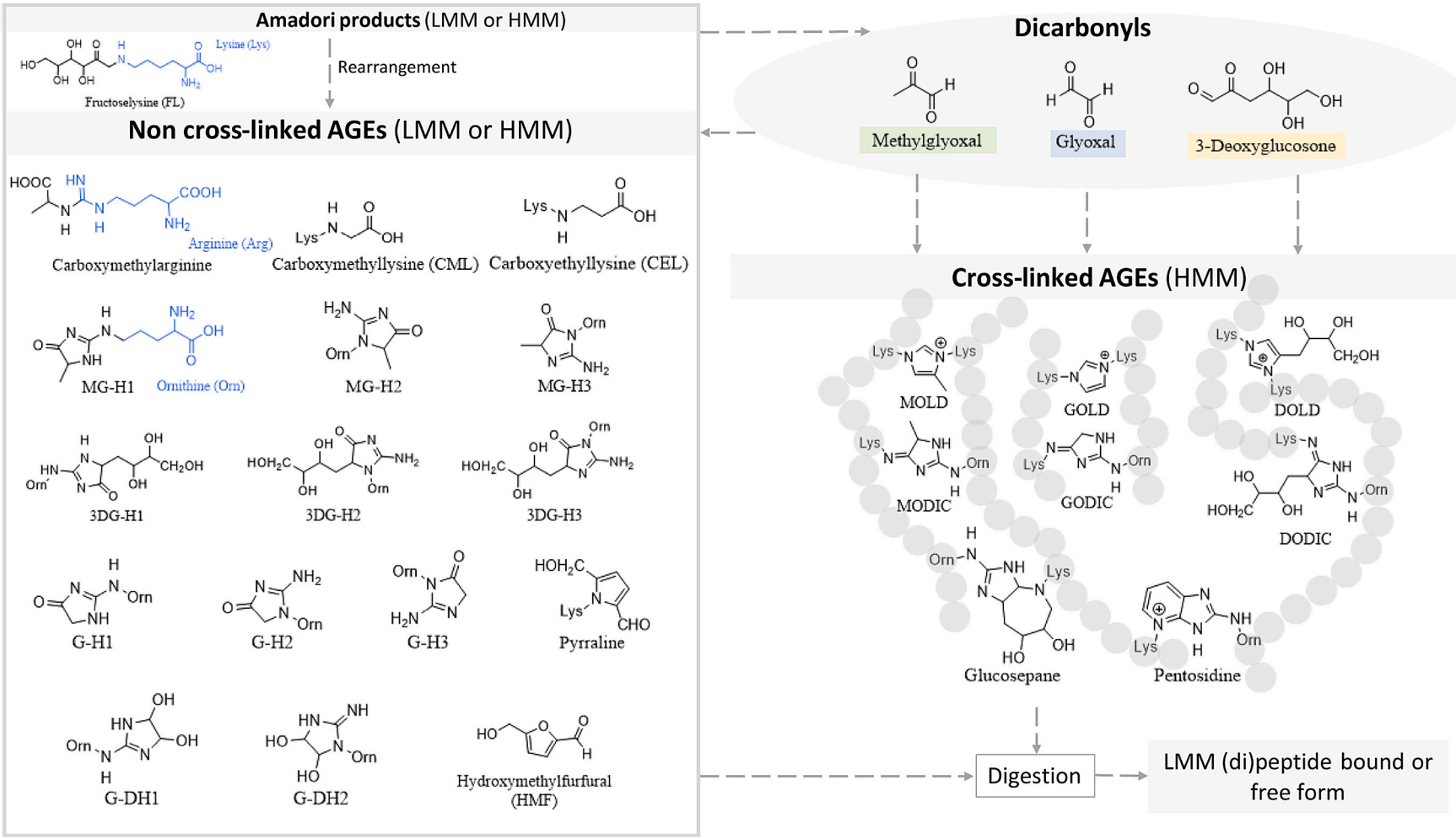

Fig. 1. Structural formulas of AGEs and their precursors mentioned in the text including both non-crosslinked and cross-linked AGEs, Amadori product precursors and dicarbonyl precursors. Part of the structures visualized in blue show the structure of abbreviated side-chains. Abbreviations: AGE = advanced glycation end product; LMM = low molecular mass; HMM = high molecular mass. Structural formulas were compiled with ChemDraw 18. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

fructose via sorbitol dehydrogenase (Tsukushi et al., 1999; Sergi et al., 2020).

Over-activation of this pathway leads to an increase in dicarbonyl formation via accumulation of upstream metabolites such as fructose (Sergi et al., 2020).

Besides the above-mentioned endogenous glycation product formation pathways, endogenous lipid peroxidation, resulting from reactive oxygen species (ROS)-induced lipid peroxidation of PUFAs in biological membranes, can also lead to increased dicarbonyl and subsequent AGE formation (Vistoli et al., 2013). AGEs formed via reactive dicarbonyls produced by lipid peroxidation are also referred to as ALEs (advanced lipoxidation end products), which in some cases can lead to the same reaction products because lipid peroxidation may result in the same reactive dicarbonyls (Vistoli et al., 2013). In this review, we focus on the AGEs while ALEs which are formed exclusively and only following lipid peroxidation are not explicitly included.

Specific for endogenous Amadori product precursor and AGE formation is the formation of glycated albumin and hemoglobin (HbA1C), the latter having a widespread use as a biomarker to monitor glycemic control (Feskens et al., 2020). The Amadori product glucosyllysine can form a cross-linking adduct with arginine side chains, forming glucosepane (Vistoli et al., 2013), which is the most abundant cross-linking AGE found in extracellular matrix related to ageing and diabetic complications (Bieme et al., 2002; Sell et al., 2005). Another example is the AGE pyrraline which can form cross-links with cysteinyl thiol groups or other pyrraline adducts under oxidative conditions.

3. Toxicokinetics

Several studies have reported on toxicokinetics of AGEs and their precursors using either *in vitro,* animal or human based models. One important aspect to consider when evaluating literature studies is which analytical methods were used for quantifying and characterizing the studied glycation products (Hellwig et al., 2019). General methods such as immuno-based methods or methods based on fluorescence which are unable to differentiate between the different glycation products have been frequently used, while more recently the application of liquid chromatography tandem mass spectrometry (LC-MS/MS) methods provides possibilities to quantify and characterize individual AGEs and their precursors. In this section, we provide an overview of toxicokinetic characteristics of AGEs and their precursors published in literature based on the more specific and therefore preferred LC-MS/MS based methods, unless data using these methods were unavailable. Whether the tested and evaluated AGE is in its LMM or HMM form is described when this information was available in the cited literature. First absorption of LMM and HMM glycation products is described, followed by their distribution, metabolism and excretion.

3.1. Absorption

Studies reporting urinary excretion, plasma or tissue levels of AGEs upon their oral administration provide support for the absorption and systemic bioavailability of exogenous AGEs and their precursors (Koschinsky et al., 1997; Vlassara et al., 2002; Uribarri et al., 2003b; Uribarri et al., 2003a; Uribarri et al., 2005; Scheijen et al., 2018). However, these studies often do not quantify the actual levels of LMM glycation products and protein-bound glycation products consumed by the study subjects. Some studies however do characterize whether the AGEs or precursors dosed are given in their LMM or HMM form. These studies reveal that dietary LMM glycation products like free FL are readily absorbed and bioavailable. In rats for example up to 60% of orally administered LMM labelled FL was recovered in urine (Erbersdobler, 1977). In contrast, urinary FL excretion upon oral intake of HMM FL appeared to be substantially lower reported to amount to generally less than 10% of the dose in both rats and adult human, tested 3 up to 10 days upon exposure (Erbersdobler and Faist, 2001; Lee and Erbersdobler, 2005; Somoza et al., 2006). In young children, the excretion of FL upon administration of heat-treated milk protein was reported to be somewhat higher amounting to levels up to 16% of the dose in urine and up to 55% in feces (Niederwieser et al., 1975), but in this study the % of LMM versus HMM FL and/or the potential presence of dicarbonyl precursors in the administered heat treated milk sample remained undefined. The difference in absorption and bioavailability upon oral intake between LMM and HMM forms of the same AGE or precursor can be ascribed to the fact that HMM AGEs themselves cannot be absorbed efficiently but need to be degraded to LMM forms first by host and/or microbiota derived enzymes from the intestinal tract before being absorbed (Erbersdobler, 1977; Poulsen et al., 2013; Xu et al., 2013; Hellwig et al., 2014).

In line with the results for FL and these considerations concerning their LMM or HMM form, also free or dipeptide-bound CML was shown to be readily absorbed *in vitro* and in rats, while HMM CML may be absorbed less efficiently in mice due to insufficient release by the digestive enzymes and/or microbiota derived enzymes (Poulsen et al., 2013; Xu et al., 2013; Hellwig et al., 2014; Li et al., 2015a), with up to 30% of ingested casein-linked CML excreted in urine of rats (Somoza et al., 2006). In another study, 2 week oral exposure of mice to a diet containing 9.4-fold higher levels of total CML (exact form not defined) compared to the control diet, exposure to the diet high in CML did not result in an increase in LMM or HMM CML in the systemic circulation, whilst administration of a single oral dose of free LMM CML to rats resulted in an increase of free LMM CML in plasma reaching a C_{max} at 1 h (Alamir et al., 2012). Another study on the uptake of CML in rats reported comparable recoveries for total CML in urine upon dosing HMM or LMM CML, suggesting that CML in both forms may be absorbed to a similar extent (Poulsen et al., 2016). The limited systemic availability of HMM CML is also supported by the observation that dosing a diet rich in Maillard reaction products to adolescents did not result in an increase in urinary CML levels while fecal CML levels were 2.86 fold higher (Delgado-Andrade et al., 2012). *In vitro* studies using Caco-2 cell layers provided evidence that some free LMM AGEs including CML are most likely transported across the intestinal barrier via passive diffusion (Grunwald et al., 2006), whereas for LMM dipeptide bound AGEs active apical transporters, like the human intestinal peptide transporter (hPEPT1), may play a role, after which intracellular hydrolysis results in release of the free CML transferred via passive diffusion to the systemic circulation (Hellwig et al., 2009, 2011; Stefanie et al., 2010)

For other glycation products the bioavailability may be different although studies using diets with Maillard reaction products cannot be fully conclusive when they do not discriminate between the levels of LMM or HMM AGEs and/or the precursors actually consumed by the volunteers. In the case of exposure to HMM dietary AGEs via consumption of a diet rich in Maillard reaction products, proteolytic breakdown and/or metabolic degradation of the HMM protein-bound AGEs in the intestinal tract may be required to facilitate absorption and subsequent urinary excretion (Förster et al., 2005). The fact however that consumption of a diet free of Maillard reaction products lowers the urinary excretion of free LMM pyrraline and FL by values up to 90% and that of free LMM pentosidine by 40% (Förster et al., 2005) supports that LMM AGEs or LMM AGE precursors originating form dietary exposure are bioavailable and may provide a substantial contribution to endogenous LMM AGEs and their precursors. In a study dosing eight diabetic patients with an AGE rich diet generated by heating chicken egg white with fructose at 90 °C, a substantial increase in crosslinking AGE reactivity in serum and urine was detected a few hours post dosing (Koschinsky et al., 1997) also supporting that at least part of the AGEs and/or their precursors may be bioavailable.

Concerning the bioavailability of the dicarbonyl precursors, it is of interest to note that a study in which 500 micromole of methylglyoxal were ingested by human volunteers did not result in an increase of excreted methylglyoxal in 24 h collected urine, while incubations of methylglyoxal in an *in vitro* simulated gastric and intestinal digestion

model without gut bacteria revealed that only 20% of the initial methylglyoxal could be recovered after 8 h (Degen et al., 2013). Based on these results the authors concluded that dietary methylglyoxal is rapidly degraded during the digestion process in the intestine, and therefore of no influence on the systemic levels of methylglyoxal. A comparable study with 3-deoxyglucosone however led to an increase in urinary excretion of this AGE precursor, supporting that the compound is bioavailable (Degen et al., 2014). It should be noted however, that in other *in vitro* studies with simulated gastrointestinal digestions mimicking the upper part of the gastrointestinal tract including oral, gastric and small intestinal phases reported dicarbonyl compounds and also dietary HMM AGEs to be almost unaltered (Van Der Van Der Lugt et al., 2020; Brighina et al., 2021). Additional small batch fermentations with individual fecal slurries, however, resulted in decreasing concentrations of 3-deoxyglucosone, methylglyoxal and glyoxal (Brighina et al., 2021).

Taken together, it appears that only LMM AGEs and LMM AGE precursors may end up in the systemic circulation and contribute to the endogenous exposure (Poulsen et al., 2013). Zhao et al. (2019) speculated that free AGEs might be less bioavailable than peptide-bound AGEs as uptake of free AGEs via diffusion can be slow and might be rate limiting while peptide-bound AGEs can enter the systemic circulation via multiple routes (e.g. paracellular, via hPEPT1) (Zhao et al., 2019). HMM protein-bound AGEs themselves are not absorbed efficiently but first require degradation to LMM forms, while bioavailability of LMM AGE precursors can contribute to the formation of endogenous LMM and HMM AGEs.

3.2. Distribution

Once absorbed, the LMM AGEs and precursors are detectable in plasma and distributed to various tissues including liver and especially the kidneys where they appear to accumulate. For example upon dosing of casein-bound FL to rats, the levels of protein-bound FL in whole kidneys were increased over 17- and 33-fold above control values (at low dose of 71.4 mg/day and high dose of 474 mg/day, respectively) while those in whole liver increased by only 1.1 and 1.4-fold (Somoza et al., 2006). Upon dosing casein-CML in a low and high dose (40 mg/day and 127.3 mg/day, respectively), concentrations of CML in whole kidney increased 269 and 741-fold and in liver tissue 1.0 and 1.2-fold for low and high dose, respectively (Somoza et al., 2006) pointing at differences between these two model compounds and their major accumulation in the kidney compared to the liver. A high percentage of the FL, amounting to up to 27% of high dose casein FL administered to the rats, appeared to accumulate in the kidneys, while for the casein-CML administered rats this value amounted to only 1.4%. Levels of FL in kidney and liver after the control diet were higher compared to CML levels in the tissues after the control diet, indicating endogenous FL formation as FL content in the control diet was below the limit of detection (0.3 pmol) (Somoza et al., 2006). It is important to note that prior to absorption casein-bound FL and CML were likely degraded to LMM forms in the intestine.

For FL this relatively high level of distribution to the kidney as compared to the liver has been ascribed to the possible involvement of active transporters into the kidney (Erbersdobler and Faist, 2001), while uptake in the liver may proceed be limited to passive diffusion (Finot and Magnenat, 1981). Later studies concluded that macrophage scavenger receptors expressed by liver endothelial cells are involved in uptake and subsequent lysosomal degradation of AGEs in the liver via endocytosis as studied using uncharacterized AGE-BSA (bovine serum albumin) (Sano et al., 1998). However the contribution of this system is debated to be also dependent on the sites and degree of the glycated proteins (Svistounov and Smedsrød, 2004) and occurs slowly and is impaired by AGE-BSA exposure itself (Hansen et al., 2002).

Some studies tested CML individually. In a study with mice, long-term exposure for 30 days to $^{13}C_2$-labelled BSA-bound CML administered through the diet (at a dose of 40 mg/kg bw/day) compared to a low exposure in the control group (0.3 mg/kg bw/day) resulted in high accumulation of $^{13}C_2$-labelled CML in kidney, ileum, colon and lungs, and increased accumulation, although with up to 39-fold lower levels, in brain, testis, heart, muscle and liver tissue (Tessier et al., 2016). However, no distinction was made within this study between protein-bound and free levels of CML accumulating in the tissues as this was not part of the analysis. $^{12}C_2$-CML levels measured in kidney, ileum, colon and lungs – potentially both from exogenous and endogenous origin – were 5 to 9-fold lower compared to the $^{13}C_2$-levels exclusively from dietary origin (Tessier et al., 2016). These results show that dietary, protein-bound HMM CML significantly increased CML levels in multiple tissues, with high accumulation in the kidney, ileum, colon and lungs. In general, relevant to consider for distribution of AGEs to certain tissues is an AGE-exposure induced increase in the permeability of endothelial cells (Dobi et al., 2021). Upon oral administration of free CML (at a dose of 60 mg/kg bw/day) to rats fed a high fat diet for 12 weeks an increase in protein-bound CML levels was reported in the kidney (2.07-fold), heart (1.27-fold), lung (1.19 fold), pancreas (1.70-fold), and muscle (1.48-fold), whereas no statistical increase was found in the liver and spleen (Li et al., 2015a). In a similar study from the same authors, oral administration of free CML (60 mg/kg bw/day for 12 weeks) combined with a regular diet and not a high fat diet as in their other study, a significant increase in protein-bound CML compared to the control was found in kidney (2.06-fold), liver (1.55-fold), heart (1.86-fold) and the lungs (1.41-fold) but not in the spleen, pancreas and serum (Li et al., 2015b). It has to be noted that the dose of free CML administered in these studies is far above the normal estimated total (both free and protein-bound) dietary CML intake of 0.034–0.252 mg/kg bw/day for adults (Tessier and Birlouez-Aragon, 2012). Given these generally less than 2-fold increases in the tissue levels of protein-bound CML upon long term intake of a dose level of free CML that exceeds normal dietary intake 2 to 3 orders of magnitude, this result implies that increases in tissue levels of protein-bound CML upon normal dietary intake of free CML may be negligible.

Other studies reported that higher AGE content of the diet resulted in an increased AGE level in serum (Nowotny et al., 2018). In another study in 20 overweight but healthy individuals a two-week low AGE diet resulted in a decrease in the AGEs MG-H1, CML and CEL in their free form in urine but not in protein-bound levels in serum as measured by LC-MS/MS (de Courten et al., 2016). In a study with 261 adults, no correlation was found between dietary intake as assessed by a dietary recall and serum and urinary CML, quantified using immunobased methods (Semba et al., 2012). The CODAM study included 450 individuals and found a positive correlation between dietary intake of protein-bound CML, CEL and MG-H1 and their free levels in both plasma and urine, but -again- not with their protein-bound form (Scheijen et al., 2018). This indicates that – at least in humans – upon dosing protein-bound HMM AGEs degradation to LMM peptide-bound or free forms is a prerequisite for systemic availability. A recent study in mice did distinguish between protein-bound and free CML, CEL and MG-H1 in both the diet and in tissues and plasma. A heated diet was orally administered for 10 weeks and compared to a standard diet. The heated diet contained increased levels of both free AGEs and protein-bound AGEs, with the latter covering the largest proportion. After 10 weeks of dietary intervention both free and protein-bound CML and CEL were increased in plasma in the mice receiving the heated diet, while MG-H1 was only increased in its free form. In liver only free CML and free MG-H1 were increased, while in kidney CML, CEL and MG-H1 were increased in their free form and only CML was increased in its protein-bound form (van Dongen et al., 2021a). This corroborates that free AGEs might be the preferred form in which protein-bound AGEs become bioavailable. In addition, the results for the three AGEs characterized in the study (i.e. CML, CEL and MG-H1) differed in their responsive patterns in both plasma and tissues, pointing at AGE specific kinetics and the importance of characterizing and measuring individual

AGEs in both protein-bound and free forms.

In a study on the improvement of insulin resistance in human type 2 diabetic patients by restriction of glycation products in the diet it was reported that compared with nondiabetic healthy control individuals, the type 2 diabetic patients showed significantly higher fasting blood glucose, and higher serum levels of CML and the dicarbonyl methylglyoxal before the intervention. In these diabetic subjects a 50% dietary AGE restriction resulted in lower levels of serum CML and methylglyoxal and also of intracellular methylglyoxal compared to the levels before the intervention. Healthy subjects on the AGE restricted diet also showed reduced serum CML and methylglyoxal levels but intracellular levels of CML and methylglyoxal were unaffected. Thus, for both diabetic and healthy subjects there appeared to be a significant association between dietary AGEs and AGE level in serum (Uribarri et al., 2011). A difference in serum CML and methylglyoxal levels upon intake of a diet high or low in total CML and methylglyoxal was also reported in non-obese diabetic (NOD) mice, supporting a correlation between ingested AGEs and AGEs in the systemic circulation (Peppa et al., 2003), although it remains to be established whether the endogenous and exogenous levels refer to the same form of the AGEs. In similar studies in diabetic or apolipoprotein E-deficient (apoE$^{-/-}$) mice a difference in serum and in one of the studies also urinary levels of CML and methylglyoxal-derived AGEs was reported following several weeks of low versus high AGE diet (Hofmann et al., 2002; Lin et al., 2002, 2003; Zheng et al., 2002; Peppa et al., 2003). In all these studies the AGEs were detected by immunological techniques so a differentiation between free or protein-bound AGEs and thus between LMM and HMM AGEs could not be made, which could have been achieved by appropriate sample preparation combined with LC-MS/MS (Hellwig et al., 2019).

3.3. Metabolism

Given the different nature of free LMM and protein-bound HMM glycation products their metabolism also proceeds in a different way. Multiple possibilities of metabolism of AGEs and their precursors *in vivo* have been described in literature and will be discussed in this section. Upon oral intake, protein-bound exogenous HMM AGEs may be subject to enzymatic digestion into LMM AGEs, resulting in systemic exposure to the LMM AGEs, with the heating-induced AGE-mediated change in protein structure potentially to some extent hampering degradation by the digestive enzymes in the gastrointestinal tract (e.g. gut proteases) (Poulsen et al., 2013). Upon oral intake also the LMM AGEs and the LMM AGE precursors may be degraded by the intestinal microbiota, thereby reducing their bioavailability. It was reported for example that 3–10% of orally administered bound Amadori rearrangement products are excreted in urine while only 1–3% appear in feces, indicating that a substantial part (about 80%) can be degraded by the gut microbiota (Tuohy et al., 2006; Zhao et al., 2019). Thus, the majority of orally ingested AGEs may serve as gut bacterial nutrients.

Sofar, some bacterial taxa (i.e. *Bacillus subtilis, Escherichia coli* and *Intestinimonas butyriciproducens* AF211) were shown to (partially) degrade FL with an identified key enzyme being a kinase (encoded by frlD/yhfQ) (Wiame et al., 2002, 2004; Bui et al., 2015). FL can for example be converted into fructoselysine 6-phosphate followed by conversion to lysine and glucose-6-phosphate by *E. coli* (Wiame et al., 2002) and result in further production of the short chain fatty acid butyrate by *I. butyriciproducens* AF211 (Bui et al., 2015). An intracellular enzyme fructosamine 3-kinase found in mammalian but not in bacterial cells can phosphorylate FL into fructosamine 3-phosphate which turns into lysine and the reactive dicarbonyl and AGE-precursor 3-deoxyglucosone (Veiga da-Cunha et al., 2006; Ott et al., 2014). Using anaerobic fecal incubations with different free LMM AGEs or their precursors including FL, CML, pyrraline, and maltosine, it was demonstrated that the level of conversion varies with the glycation product studied, while also showing substantial interindividual variability (Hellwig et al., 2015; van Dongen et al., 2021b). While conversion of FL was complete within a few hours, maltosine was hardly degraded, while the conversion of CML and pyrraline amounted to about 60 and 20% upon 24 h incubation with fecal slurries (Hellwig et al., 2015).

There are also several receptors that play a role in the detoxification of AGEs including oligosaccaharyltransferase-48 (AGE-R1), 80K–H phosphoprotein (AGE-R2) and macrophage scavenger receptors, all known to be present in mammalian cells. AGE-R1 is present on the cell surface of monocytes and macrophages and is able to bind AGEs and induce their endocytosis (Vlassara and Bucala, 1996; Ott et al., 2014). AGEs that have been endocytosed are modified in the cell by lysosomal degradation (Grimm et al., 2010; Ott et al., 2014; Asadipooya and Uy, 2019). The degradation of AGEs likely includes the formation of LMM AGEs from HMM AGEs, while other studies report new intracellular formed AGEs in macrophages (Nagai et al., 2007). The LMM AGEs and their precursors are thought to be soluble in the serum and cleared by the kidney (Semba et al., 2010; Ott et al., 2014) (see section on excretion). It has also been shown that increased activation of AGE-R1 is related to increased turnover of AGEs in plasma and tissues (Poulsen et al., 2013). There are studies where AGE-R1 was found able to inhibit the effects that RAGE activation has on oxidative stress and inflammatory actions by suppressing nuclear factor-kappa B (NF-κB) and mitogen-activated protein kinases (MAPK) phosphorylation. AGE-R1 expression levels can be downregulated by a long-term high AGE burden (Vlassara, 2001; Poulsen et al., 2013). This has also been suggested for AGE-R2, a receptor present on T-lymphocytes (Vlassara, 2001). AGE-R2 is a protein which has not been proven to directly bind AGEs. However, it seems to be involved in the degradation of AGEs by the activation of intracellular signaling. Lastly, the soluble variant of RAGE, sRAGE, is thought to help prevent AGE accumulation. sRAGE is not entirely similar to RAGE as it consists merely of the extracellular parts of the receptor and is present in the circulation. This receptor is thought to bind the same ligands as RAGE (Poulsen et al., 2013; Asadipooya and Uy, 2019). The absence of the intracellular parts cause that the AGE binding to sRAGE does not induce the cellular signaling cascade that would be induced upon binding to RAGE, and sRAGE could thus function as a decoy receptor. The binding of AGEs to sRAGE may potentially prevent the interaction between AGEs and RAGE thus eliminating some of the activity (Asadipooya and Uy, 2019). Possible other functions of sRAGE are still unknown (Steenbeke et al., 2021).

Some studies report on degradation of specific AGEs. Intravenous administration of for example radiolabeled pentosidine to rats resulted in a recovery of 80% of the radioactivity in urine of which only a limited amount (20%) appeared to be intact pentosidine. The authors concluded that free pentosidine is catabolized or modified in the proximal tubule and that the kidney plays a role in pentosidine degradation (Miyata et al., 1998). The nature of the degradation products, whether this process is also relevant for other AGEs and AGE precursors, and whether the products formed present a detoxification or contribute to AGE-associated kidney damage remains to be elucidated.

In addition, conversion by the glutathione dependent glyoxalase system may provide a pathway for detoxification of especially the dicarbonyl AGE precursors such as methylglyoxal and glyoxal. It has been reported that more than 99% of endogenously formed methylglyoxal can be converted by this glyoxalase system into harmless products such as lactate (Rabbani and Thornalley, 2012; Degen et al., 2013). It is of interest to note that the activity of the glyoxalase system is influenced by a genetic polymorphism (Peculis et al., 2013) and operates under control of the nuclear factor erythroid 2-related factor 2 (Nrf2) transcription factor (Xue et al., 2012).

3.4. Excretion

Some HMM AGEs might not be fully hydrolyzed by digestive enzymes or microbiota-derived enzymes, and this may result in substantial fecal excretion. Saturation of these intestinal degradation processes upon increasing dose levels results in increased relative fecal excretion

with increasing dose levels (Somoza et al., 2006). For FL efficient degradation of both its free and protein-bound form by gut microbiota has been established with, depending on the experimental set-up, almost complete degradation within a few hours (Mori et al., 1980; Wiame et al., 2002; Bui et al., 2015; Hellwig et al., 2015; van Dongen, van der Zande, et al., 2021), while degradation of other LMM and HMM AGEs and precursors by intestinal microbiota as well as the pathways involved in these degradations remain to be further characterized. The relatively high fecal excretion of up to 55% of the administered dose of FL in young children (Niederwieser et al., 1975) has been ascribed to their different intestinal microbial communities and activity suggested to result from their lower extent of adaptation to chronic dietary intake of heat-treated proteins (Somoza et al., 2006).

Once in the systemic circulation AGEs and their precursors are mainly excreted via the kidneys into urine. Especially LMM AGEs and LMM AGE precursors are readily eliminated from the body by renal excretion via glomerular filtration (Semba et al., 2010; Ott et al., 2014). The renal clearance of an intravenous dose of free CML or CEL in rats was rapid with over 87% recovery in urine within 2 h (Bergmann et al., 2001). In humans, free pyrraline and pentosidine were recovered in the urine at 50 and 60% of the dietary doses respectively, while consumption of HMM pentosidine resulted in only 2% urinary recovery of pentosidine (Förster et al., 2005), indicating that this excretion via glomerular filtration will be less relevant for HMM AGEs (Semba et al., 2010; Ott et al., 2014). In addition, this limited urinary recovery of the HMM AGE is likely to be (in part) due to the limited bioavailability of HMM AGEs upon dietary intake.

In a study in rats there was a trend of increasing urinary excretion of free CML with increasing dietary levels of heat processed proteins, with 4–19% of the CML present in the diet (actual form not characterized) being recovered in urine. The increasing trend made the authors conclude that the urinary CML was preliminary of dietary origin (Liardon et al., 1987). Another study with rats, already referred to in the section on absorption, concluded that recovery of CML in urine was independent of the molecular mass of the administered CML, suggesting, in contrast to most other data, comparable ADME characteristics between LMM and HMM CML (Poulsen et al., 2016).

Important to note is that some studies reported that upon their excretion by glomerular filtration free CML and pentosidine and especially also peptide bound LMM AGEs could be reabsorbed in the proximal tubule (Horie et al., 1997; Miyata et al., 1998; Asano et al., 2002; Saito et al., 2005). Tissue accumulation and/or binding of LMM AGEs to tissue proteins corroborates to the accumulation of HMM AGEs (Poulsen et al., 2013) as mentioned in the section on distribution.

3.5. Conclusions on ADME characteristics

Altogether, most studies indicate substantial differences in the ADME characteristics of LMM AGEs and AGE precursors versus protein-bound HMM AGEs. These differences result in different kinetics of exogenous versus endogenously formed glycation products, as summarized in Fig. 2. Upon oral intake exogenous HMM AGEs show limited if any bioavailability so that systemic exposure to HMM AGEs is expected to result mainly from endogenously formed AGEs. In the gastrointestinal tract exogenous HMM AGEs are degraded to LMM AGEs which can become systemically available. Once in the systemic circulation especially LMM AGEs and precursors are cleared via urinary excretion. Elimination and clearance of HMM AGEs rather depends on receptor mediated transport into cells where they can be degraded via lysosomal degradation. Endogenous HMM AGEs may result from exposure to endogenously formed or exogenously provided AGE precursors including the reactive dicarbonyls like glyoxal, methylglyoxal, or 3-deoxyglucosone, although one could also argue that these reactive AGE precursors in food may readily react with proteins and amino acids in the food matrix before being ingested. This would leave endogenous production of the reactive AGE precursors and possibly exposure to LMM glycation products as a major source for endogenous HMM AGE formation. The production of these endogenous reactive AGE precursors may be enhanced for example upon exposure to high levels of glucose (Ramasamy et al., 2005), via degradation of FL (Veiga da-Cunha et al., 2006), in individuals with diabetes (Beisswenger et al., 1999; Lu et al., 2011; Scheijen and Schalkwijk, 2014; Rabbani et al., 2016), or upon ageing (Akhter et al., 2021). In general, interspecies and interindividual differences in toxicokinetic properties are likely to exist and remain to be characterized to a further extent.

Based on these toxicokinetic considerations, systemic and tissue levels of HMM AGEs may result mainly from endogenous formation, while LMM AGEs and precursors may originate from both endogenous and exogenous sources. Effects of dietary exogenous HMM AGEs themselves may thus be limited to the intestinal tract and/or result from their LMM intestinal degradation products.

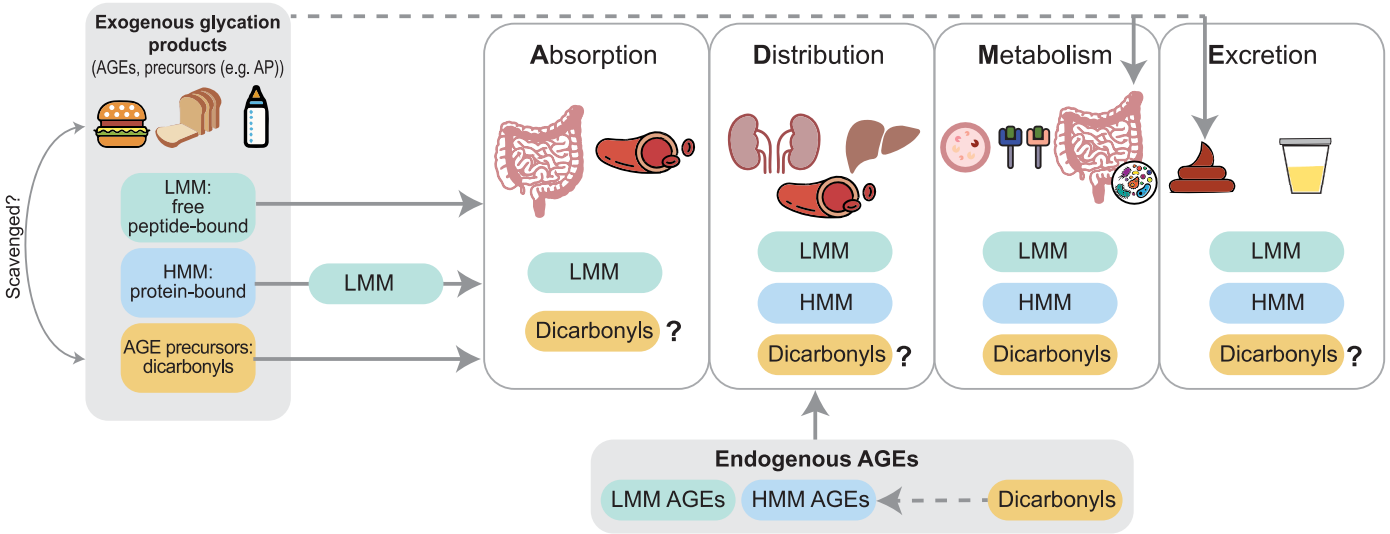

Fig. 2. Overview of toxicokinetic characteristics of exogenous and endogenous glycation products including advanced glycation end products (AGEs) and their precursors such as the Amadori products (AP), and distinguishing between their low molecular mass (LMM) form (green), high molecular mass (HMM) form (blue) and their reactive dicarbonyl precursors (yellow). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

4. Toxicodynamics

The modes of action generally reported to play a role in the ultimate potential adverse health effects of glycation products include 1) dicarbonyl stress resulting in cross-linking and damage to protein structures and functions, and 2) interactions with AGE receptors (RAGEs) inducing pathways leading to adverse effects. These two pathways are of different importance for LMM AGEs and AGE precursors versus HMM AGEs. In addition, 3) toxicodynamic effects of AGEs and their precursors on gut microbiota composition and/or gut barrier integrity provide another potential link between dietary exposure to glycation products and possible pathological consequences.

4.1. Dicarbonyl stress resulting in cross-linking and protein damage

Early in the process of production of glycation products, dicarbonyls can be formed e.g. via decomposition of Amadori products via the Namiki pathway or as products of glycolysis. These dicarbonyls are reactive compounds. Accumulation of such dicarbonyls can not only result in AGE production but also in what is referred to as dicarbonyl stress (Singh et al., 2001), which can have negative effects on health. Dicarbonyls are able to react with body proteins and amino acids, leading to the formation of AGEs and cross-linking of proteins. Baynes and Thorpe (1999) confirmed that increased production of endogenous AGEs in diabetes is linked to increased cross-linking of body proteins (Baynes and Thorpe, 1999). Dicarbonyls have been reported to react with for example amino groups of proteins of the connective tissue matrix and the basement membranes (Raj et al., 2000; Singh Singh Jaggi et al., 2014). The respective components are long-lived proteins so that damage formed may accumulate over time (Sharma et al., 2015). In the case of very high AGE concentrations, short-lived plasma proteins can be affected as well, such as for examples low density lipoproteins (LDL) and immunoglobulins (Sharma et al., 2015).

Cross-linking of body proteins can have many physiological consequences. It results in altered structure and function of the proteins (Zieman and Kass, 2004; Sharma et al., 2015). Additionally, the proteins are less easily degraded (Zieman and Kass, 2004). The AGE cross-linking of proteins such as collagen is related to an increase in stiffness in tissues that are rich in these proteins (Sharma et al., 2015). This includes arterial stiffness, stiffness in lung tissue, joints, and extracellular matrix. Stiffness in these tissues has been associated with diseases including hypertension, cataract, dementia, atherosclerosis, glomerulosclerosis, emphysema and joint pain (Raj et al., 2000). Cross-linking of body proteins is related to complications in diabetes and increased cardiovascular risk (Singh Singh Jaggi et al., 2014).

Dicarbonyl stress has also been associated with damage in the kidney, vascular damage and accelerated atherosclerosis development (Raj et al., 2000; Singh et al., 2001; Bussel et al., 2017). Development of atherosclerosis occurs not only because of cross-linking but also because AGEs formed in the matrix of vessel walls are thought to be able to 'trap' LDL. This leads to decreased uptake and degradation of LDL in the kidney, which in turn promotes the lipoprotein accumulation and atherosclerosis (Singh et al., 2001; Sharma et al., 2015). Raj et al. (2000) also concluded that LDL, when bound to the extracellular matrix as a result of AGE formation, can be oxidized (Raj et al., 2000). This results in the formation of toxic degradation products of LDL. These oxidized LDL particles can lead to the formation of antibodies which bind to AGEs in vessel walls, and thereby contribute to vascular inflammation and atherosclerosis (Lopes-Virella et al., 2013). In addition, dicarbonyl stress can lead to oxidative stress and inflammation and also induce carbonylation of biomolecules such as DNA, and thus damage DNA (Roberts et al., 2003; Rabbani and Thornalley, 2015; Lin et al., 2016).

The reactive dicarbonyls causing protein crosslinking are precursors of AGEs that may originate from both exogenous and endogenous sources. However, given the high reactivity of these dicarbonyls it can also be foreseen that when formed in food upon heating they may be scavenged via reactions with food matrix proteins forming AGEs in the food before the food is actually consumed. Relatively low levels of dicarbonyls (0–40 mg/kg food) were indeed found in certain food products in a recently presented dietary dicarbonyl database where the three major dicarbonyls methylglyoxal, glyoxal and 3-deoxyglucosone were quantified in multiple food products. The presence of relatively lower levels of dicarbonyls in certain food products was explained by the presence of potential scavengers such as polyphenols or protein residues in the food product. However, multiple food products contained relatively high levels of dicarbonyls (40–2990 mg/kg) (i.e. cake, dried fruit, candy bars) (Maasen et al., 2021). It remains to be investigated if these dicarbonyls would be scavenged when these food products are consumed combined with other dietary compounds.

4.2. Interactions with receptors

Circulating AGEs can bind to AGE receptors (RAGEs) on cell surfaces. RAGEs can be found on cells in the cardiovascular system, including heart tissue, endothelial cells, white blood cells, lung tissue, neural tissue and the intestinal tract (Brett et al., 1993; Poulsen et al., 2013). Following the binding of AGE to RAGE, the transcription factor, NF-κB is activated (Poulsen et al., 2013; Perrone et al., 2020). Activation of NF-κB leads to activation of NADPH oxidase, which increases oxidative stress, and activates an inflammatory cascade. This cascade consists of elevated expression of proinflammatory cytokines, growth factor and adhesive molecules, which are molecules that interact with leukocytes (Perrone et al., 2020). Oxidative stress also contributes to endogenous formation of AGEs. ROS involved in oxidative stress can damage proteins, possibly accompanied by the production of more AGEs (Asadipooya and Uy, 2019) and increased infiltration of macrophages (Hulsmans and Holvoet, 2010). Besides the inflammatory response and increased oxidative stress, the activation of NF-κB causes proliferative, fibrotic, angiogenic, thrombogenic and apoptotic reactions. These reactions can contribute to the development of cardiovascular diseases (Singh et al., 2001; Perrone et al., 2020). The combination of chronic inflammation, oxidative stress and high AGE content has been shown to promote chronic kidney disease and kidney damage (Semba et al., 2010). Animal studies suggested that the combination of these factors can even be involved in tumor development (Gebhardt et al., 2008).

It was found that not all AGEs have the same affinity to RAGE. Standards of free CML and CEL were not able to interact with RAGE (Kislinger et al., 1999; Xie et al., 2008) and the presence of a polypeptide backbone was found to be required in order to interact with RAGE as tested with both synthesized peptide-bound CML (~1 kDa) (Xie et al., 2008) and HMM CML (>30 kDa), the latter being synthesized by glycation of BSA or as derived from endogenous sources (Kislinger et al., 1999; Xie et al., 2008; Penfold et al., 2010). In line with this, synthesized HMM MGO-derived AGEs such as MG-H1 in its HMM form and the HMM, cross-linked MOLD were shown to interact with RAGE (Valencia et al., 2004; Xue et al., 2014; Lee et al., 2021). The early Amadori product FL on the other hand, was not able to interact with RAGE at all, not in its LMM or HMM form (Xie et al., 2008). Overall, despite the heterogenous chemical structures, it seems that the presence of at least a polypeptide backbone is a prerequisite for an AGE to interact with RAGE, while early glycation products such as the Amadori product FL do not seem to interact with RAGE at all.

Studies on the effect of dietary AGE exposure and expression of cytokines have reported 3.5-fold increased expression of various cytokines upon providing an AGE rich diet to mice (Sowndhar Sowndhar Rajan et al., 2018). Interestingly, the heated diet induced a stronger inflammatory response than the unheated diet enriched with CML, suggesting that free AGEs may not be the AGEs responsible for induction of the inflammatory response. The involvement of RAGE in these processes was shown in a study in which RAGE knock out mice did not show production of inflammatory cytokines, endothelial dysfunction and aortic stiffening upon 9 months exposure to a diet enriched in HMM

CML-BSA (Grossin et al., 2015).

Finally the RAGE-dependent release of serotonin by human parietal cells *in vitro* was shown to be affected by HMM AGEs whilst free CML showed a RAGE-independent increase in serotonin release (Holik et al., 2018). Another *in vitro* study with RAGE-expressing HEK-293 cells showed a comparable RAGE-dependent effect on cellular p38 MAP kinase activation by free and casein-linked HMM CML, although it should be noted that also non-AGE type products from heating, such as *N*-methylpyridinium, appeared able to induce this effect (Zill et al., 2003).

Other receptors interacting with AGEs include AGE-R1, AGE-R2, macrophage scavenger receptors and the soluble form of RAGE (sRAGE) (Sano et al., 1998; Singh et al., 2001). These receptors have different functions from RAGE. As discussed in Section 3.3, AGE-R1, AGE-R2 and macrophage scavenger receptors are involved in endocytosis and subsequent degradation of AGEs (Poulsen et al., 2013; Asadipooya and Uy, 2019).

It is thought that exogenous HMM AGEs, provided they can reach the systemic circulation, can bind to RAGE similarly as endogenously produced AGEs (Uribarri et al., 2015). However, given the potential limited bioavailability of HMM AGEs their role in activation of the RAGE receptors may be limited compared to that of endogenously formed HMM AGEs, except in the gastrointestinal tract where RAGE expression is generally low (Brett et al., 1993) but is upregulated under pathophysiological conditions (Chen et al., 2012).

4.3. Alterations of gut microbiota composition and/or gut barrier integrity

A third mode of action potentially involved in the toxicodynamics of AGEs includes their effect on the gut microbiota composition and activity. Such effects may result in a decrease or increase of the abundance of specific bacteria, which in turn may have no, positive, or negative health implications, such as for example an effect on inflammation. Increasingly links between alterations in gut microbiota composition and disease have been reported (Carding et al., 2015). Multiple studies showed an effect of exposure to exogenous AGEs on gut microbiota composition, both in experimental animals and humans. Table 1 presents an overview, and reveals that upon dietary exposure to a (heated) diet rich in AGEs several studies reported a decrease in the relative abundance of *Lactobacillus spp*. (Seiquer et al., 2014; Delgado-Andrade et al., 2017; Mastrocola et al., 2020; van Dongen et al., 2021a), while others showed an increase in the genus *Akkermansia* (Han et al., 2018; Snelson et al., 2021) and/or *Allobaculum* (Marungruang et al., 2016; Qu et al., 2017; Han et al., 2018) or *Dubosiella* (van Dongen et al., 2021a). Effects on host health directly linked to these AGE-mediated gut microbial alterations remain to be established and understood. Such effects may potentially result from alterations in gut microbial production of short chain fatty acids (SCFAs) (Table 1)(Delgado-Andrade et al., 2017; Qu et al., 2017, 2018; Han et al., 2018; Yang et al., 2020), or of other fecal bacterial metabolites (Qu et al., 2018; Snelson et al., 2021) although evidence for such an underlying mode of action remains to be substantiated. Nevertheless, and whatever the underlying mode of action, given the important role of the gut microbiota in human health and disease (Round and Mazmanian, 2009) an AGE-mediated effect on the gut microbiota could prove to represent an additional mode of action for AGE-mediated health effects. Obviously, free AGEs and precursors, reactive dicarbonyls, dipeptide bound AGEs and precursors resulting from digestion, and HMM AGEs and precursors may all affect the gut microbiota in different ways. An important condition to further elucidate such effects is to distinguish between all these AGEs and their precursors when characterizing exposure; this information is not always provided in the studies listed in Table 1.

In addition to alterations in gut microbiota profiles (Aljahdali et al., 2017; Yacoub et al., 2017), exposure to exogenous AGEs can induce other effects in the intestine. It was found that intestinal epithelial integrity was affected by exposure to dietary AGEs, as shown by altered gene expression of several tight junction proteins (Qu et al., 2017; Snelson et al., 2021), potentially resulting in increased systemic exposure to exogenous (HMM) AGEs or increased systemic infiltration of bacteria and microbial metabolites or components (Kellow and Coughlan, 2015). Overall, the potential effects of exogenous dietary glycation products on the intestinal microbiota and the potential consequences for metabolite formation, intestinal inflammatory processes and barrier integrity (Gasaly et al., 2021), support the relevance of including the gut microbiota composition, function and dynamic (local) effects combined with intestinal translocation studies in future glycation product exposure studies (Snelson and Coughlan, 2019).

5. Discussion

The present review aimed to provide an overview of the toxicokinetics and toxicodynamics of AGEs and their precursors, in order to evaluate the potential contribution of both endogenous and exogenous dietary glycation products on human health. The overview reveals the important influence of the molecular mass on the toxicokinetics and toxicodynamics of the AGEs and their precursors. Table 2 presents an overview of the major differences in the toxicokinetics and toxicodynamics of endogenously formed versus exogenous glycation products. From this overview it follows that the contribution of exogenous glycation products to the potential adverse health effects may be limited for various reasons.

First of all, the systemic bioavailability of HMM AGEs upon their oral intake may be limited. The extent to which they are degraded in the digestive track remains to be quantified and may vary for each HMM glycation product (Poulsen et al., 2013). In contrast LMM AGEs and precursors present in food may become bioavailable, although for the reactive dicarbonyl precursors this may to some extent be hampered by the fact that upon their formation upon heating of food they may already react and be scavenged by amino acids and proteins present in the food matrix or diet before or when the food is actually consumed. For CML which is known to be a major AGE in heat processed foods, it was demonstrated that exposure to free CML at levels that exceeded an average dietary intake by 2–3 orders of magnitude resulted in an increase in tissue protein-bound CML levels to only a limited extend (less than 2-fold or not at all) (Li et al., 2015a), suggesting that at the much lower average dietary intake levels these increases may be negligible. However, it should be noted that this result may be different upon a life-long dietary exposure to AGEs. Other LMM AGEs or precursors, like for example FL may show higher levels of bioavailability but the extent to which they contribute to formation of endogenous protein-bound HMM AGEs remains to be established.

The limited systemic bioavailability of HMM AGEs may limit the contribution of exogenous glycation products to adverse effects induced via RAGE receptors, since RAGE affinity of AGEs appeared to be mainly dependent on the size of the AGE with protein- or peptide-bound CML or protein- or peptide-bound CEL interacting with RAGE, while free CML or free CEL did not (Kislinger et al., 1999; Xie et al., 2008). Only in the intestinal tract orally ingested HMM AGEs may be able to activate RAGE, while for systemic effects rather endogenous formation of HMM AGEs may dominate the induction of adverse health effects via RAGE.

In addition, AGEs and their precursors, including those in their HMM form, may affect the composition and activity of the gut microbiota. This would provide another mode of action for AGE mediated effects on host health since effects on the gut microbiota are known to influence host health in both beneficial and adverse ways (Round and Mazmanian, 2009; Power et al., 2014; Chen et al., 2021). The importance of this mode of action in the processes underlying the potential health effects of AGEs remains to be studied to a further extent, although various studies already reported an effect of AGEs on the composition and activity of the intestinal microbiota (Table 1). Also, the relative importance of dicarbonyl stress versus the role of RAGE activation remains to be elucidated and may vary for the adverse effect under consideration.

Table 1
Alterations in gut microbial composition and metabolome due to exogenous exposure to glycation products. Abbreviations: AGE = advanced glycation end products; AP = Amadori product; CEL = carboxyethyllysine; CML = carboxymethyllysine; HMF = hydroxymethylfurfural; MG-H1 = Nδ-(5-hydro-5-methyl-4-imidazolon-2-yl)-ornithine; RCT = randomized controlled trial; LMM = low molecular mass; HMM = high molecular mass; PB = protein-bound; SCFA = short chain fatty acid; MGO = methylglyoxal; GO = glyoxal; 3-DG = 3-deoxyglucosone.

Exposure	Subject or system used	Altered bacterial taxa		Altered bacterial metabolites	Reference
		Increased compared to control group	Decreased compared to control group		
***In vivo* human studies**					
Diet high in total CML and HMF, randomized two-period crossover trial for 7 days with wash-out period	20 adolescents, fecal samples		*Lactobacillus* spp., *Enterobacteria*, ratio *Escherichia/Shigella*		Seiquer et al. (2014)
Dietary AGE restriction for one month after habitual high AGE diet	20 peritoneal dialysis patients, RCT, fecal samples	*Alistipes indistinctus, Clostridium hathewayi, Ruminococcus gauvreauii*	*Prevotella copri, Bifidobacterium animalis*		Yacoub et al. (2017)
***In vivo* studies with experimental animals**					
Heated glucose-lysine added to the diet, resulting in increased APs, HMF and CML. Orally exposed for 87 days.	Rats, cecal content		Lactobacilli, total bacteria		Seiquer et al. (2014)
Soluble LMM or HMM AGEs from bread crust added to the diet for 88 days (LMM <5 kDa; HMM >5 kDa)	Rats, cecal content	LMM: *Bacteroides* spp., ratio *Escherichia/Shigella* HMM: total bacteria, ratio *Escherichia/Shigella*	LMM: total bacteria, *Lactobacillus* spp., *E. rectale/C. coccoides*, HMM: *Lactobacillus* spp., *E. rectale/C. coccoides*, *C. leptum*	Total fecal SCFAs increased after both LMM and HMM AGE diets	Delgado-Andrade et al. (2017)
Heated high-fat diet, for 8 weeks	apoE$^{-/-}$ mice, cecal content	*Firmicutes, Allobaculum, Clostridiales*	*Bacteroidetes, Rikenellaceae*		Marungruang et al. (2016)
Glycated fish protein, orally for 14 days	Rats (Spraque-Dawley), cecal content	Actinobacteria, Verrucomicrobia, *Allobaculum, Collinsella, Ruminococcaceae_UCG-014, Lactobacillus animalis, Turicibacter, Akkermansia, Allisonella, Lachnospiraceae_UCG-006*	Fusobacteria, Deferribacteres, *Ruminococcus_gauvreauii_group, Ruminococcaceae_UCG-009, Erysipelatoclostridium*	Total fecal SCFAs were increased; cecal SCFAs were unaffected	Han et al. (2018)
CML, orally for 21 days (1.6 mg/kg bw/day)	Mice, cecal samples	*Bacteroidaceae, Odoribacteraceae, Desulfovibrionaceae, Dorea*	*Lachnospiraceae, Sutterella*		Aljahdali et al. (2017)
High AGE diet (generated by heat treatment), orally for 8 months	Mice, fecal samples	Increased: Actinobacteria, *Porphyromonadaceae, Prevotellaceae, Helicobacteraceae Parabacteroides, Alloprevotella, Helicobacter, Ruminococcaceae_UCG_014,* unclassified *Rhodospirallaceae*	Decreased: Firmicutes, *Rikenellaceae, Lachnospiraceae, Desulfovibrionaceae Desulfovibrio, Rikenellaceae_RC9_gut_group,* unclassified *Lachnospiraceae, Alistipes, Lachnospiraceae_NK4A136_group*	Decrease in fecal acetate and butyrate, increase in fecal isobutyrate and isovalerate. Effects on fecal metabolome by upregulation of 36 metabolites and downregulation of 21 metabolites.	Qu et al. (2018)
AGE-enriched diet (generated by replacing casein with modified, glycated casein), orally for 22 weeks	Mice, fecal samples	*Lachnospiraceae Parabacteroides, Ruminococcus, Lawsonia*	*Muribaculaceae Lactobacillus, Prevotella, Anaerostipes, Candidatus Arthromitus,*		Mastrocola et al. (2020)
High AGE diet (generated by heat treatment), orally up to 18 weeks	Rats, cecal samples	Proteobacteria, *Allobaculum, Bacteroides, Desulfovibrio*	Bacteroidetes, *Alloprevotella, Ruminococcaceae, Lachnospiraceae, Eubacterium, Phascolarctobacterium*	Decrease of the cecal SCFAs acetate and propionate.	Qu et al. (2017)
Heat-treated diet, orally for 24 weeks (measured increased CML, CEL, fructosamine)	Mice, cecal samples	*Helicobacteraceae, Akkermansia,*	*Saccharibacteria, Ruminococcus, Sutterella*	Increased metabolites related to phenylalanine, tryptophan and tyrosine pathways in the cecal metabolome after heat treated diet.	Snelson et al. (2021)
High AGE diet (generated by heat treatment), orally for 16 weeks. Measured increase of free CML and CEL (by ELISA)	Mice (young: 3 months old; old: 15 months old), cecal samples	Young: *Parabacteroides* Old: *Tenericutes*	Young: *Odoribacter*	Cecal total SCFA did not differ between groups. Increased isobutyric and isovaleric acid in young mice compared to control.	Yang et al. (2020)
High AGE diet (generated by heat treatment), orally for 10 weeks. Measured	Mice, fecal samples	*Dubosiella*	*Lactobacillus*, *Bacteroides*		van Dongen et al. (2021a)

(*continued on next page*)

Table 1 (*continued*)

Exposure	Subject or system used	Altered bacterial taxa		Altered bacterial metabolites	Reference
		Increased compared to control group	Decreased compared to control group		
increase of PB CML, CEL, MG-H1, free CEL and MG-H1 and 3-DG, MGO, GO.					

Table 2
Overview of main characteristics for toxicokinetics and toxicodynamics of endogenous and exogenous AGEs. Abbreviations: AGE = advanced glycation end product; LMM = low molecular mass; HMM = high molecular mass.

	Endogenous glycation products	Exogenous glycation products
Toxicokinetics		
Contribute to the AGE level in the systemic circulation.	Yes	Partly, mainly for LMM AGEs and precursors and dicarbonyl precursors and for HMM AGEs and precursors upon digestive degradation to their LMM form
Can be cleared from the systemic circulation.	Yes, HMM via lysosomal degradation and LMM via glomerular filtration	Yes, mainly LMM AGEs and precursors and dicarbonyl precursors via glomerular filtration
Toxicodynamics		
Can cause damage by cross-linking.	Yes, especially the dicarbonyl precursors	Yes, especially the dicarbonyl precursors
Can cause damage by binding to RAGE.	Yes, especially the HMM AGEs	HMM AGEs only in the gastrointestinal tract or upon digestive degradation to LMM AGEs
Can affect gut microbiota composition and/or the intestinal barrier.	No	Yes, differences between LMM and HMM glycation products remain to be established

Overall, considering the significant differences between the HMM and LMM AGEs and precursors in both toxicodynamics and toxicokinetics, the distinction between glycation products based on molecular mass is of importance and should be taken into account when evaluating the potential health effects of AGEs and precursors. However it should also be recognized that only characterizing the molecular mass of the AGEs tested may provide insufficient information, because in addition to molecular mass, other structural characteristics of different glycation products and their precursors may equally well affect their toxicokinetic and toxicodynamic properties (e.g. when comparing cross-linked with non cross-linked AGEs). Given that at present data on only a limited number of well characterized individual AGEs or precursors are available future studies should include testing of more individual AGEs and their precursors and also on better characterization of the material tested. Thus, based on our reviewed findings we identified several research needs for the future. First of all, it is important that future studies invest in better characterization of the glycation product actually tested, and of the urinary, fecal, tissue, or plasma AGE and precursor levels measured, identifying and quantifying the AGEs and precursors by analytical techniques that enable quantification of the different glycation product and of at least the HMM glycation products, LMM glycation products and dicarbonyl precursors. The absence of this information for both the test materials as well as the AGE related biomarkers and endpoints quantified hampers interpretation of the results presented and confuses the discussions on the role of exogenous AGEs as compared to endogenous AGEs in the overall health effects. A recent overview of endogenous versus exogenous sources of putative genotoxins indicated that the endogenous formation of reactive dicarbonyls may be one to two orders of magnitude higher than the estimated intake via food (Rietjens et al., 2022) suggesting that the role of dietary dicarbonyls to the overall exposure may be limited, and illustrating that for these and also other AGEs it is essential to generate this knowledge. This information will prove essential to quantify the respective contributions of exogenous versus endogenous glycation products to the AGE induced health effects. In addition, considering the heterogeneity of the glycation products, as also reflected in different ADME outcomes, AGEs and their precursors cannot be grouped together but specific, individual information is required for a proper evaluation, especially considering ADME properties. The use of *in vitro* models can help to increase the understanding of toxicokinetic and toxicodynamic properties of individual AGEs and precursors as *in vitro* assays provide better possibilities than *in vivo* studies to test multiple individual as well as mixtures of glycation products. LC-MS/MS based analytical techniques, such as proteomics, can be a valuable addition to further elucidate the nature of the HMM AGEs as well as of AGE modified cellular targets. Furthermore, it remains to be elucidated if reactive dietary dicarbonyls are scavenged by for example the food matrix before reaching the systemic circulation, and also to what extent they can actually become systemically available. Given the results of the present overview it seems prudent to conclude that when considering studies focusing on a role of exogenous AGEs and precursors in adverse human health effects to focus on either effects in the gastrointestinal tract (including effects on the gut microbiota) and/or effects induced by exposure to AGEs or their precursors known to be bioavailable and able to increase systemic endogenous AGE levels and/or dicarbonyl stress.

To conclude, based on the current state-of-the-art, the role of exogenous HMM AGEs and precursors seems to be restricted by their limited bioavailability to local effects on the intestine including its microbiota, unless being degraded to their LMM form. An important role is probably left for reactive (endogenously formed) dicarbonyl AGE precursors and as a consequence the endogenously formed AGEs. This implies that an important route for future research could be the role of especially reactive AGE dicarbonyl precursors and the endogenous pathways leading to their bioavailability, formation and detoxification. The direct contribution of reactive dicarbonyl precursors to dicarbonyl stress and their indirect contribution to endogenous HMM AGE formation and subsequent RAGE activation remain to be further studied. Future research on AGEs should better characterize the material tested and quantify the levels originating from endogenous versus exogenous formation.

CRediT authorship contribution statement

Katja C.W. van Dongen: Conceptualization, Writing – original draft, Writing – review & editing, Visualization. **Leonie Kappetein:** Conceptualization, Writing – original draft. **Ignacio Miro Estruch:** Writing – review & editing. **Clara Belzer:** Writing – review & editing. **Karsten Beekmann:** Writing – review & editing. **Ivonne M.C.M. Rietjens:** Conceptualization, Writing – original draft, Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

Ahmed, M.U., Brinkmann Frye, E., Degenhardt, T.P., Thorpe, S.R., Baynes, J.W., 1997. Nε-(Carboxyethyl)lysine, a product of the chemical modification of proteins by methylglyoxal, increases with age in human lens proteins. Biochem. J. 324, 565–570.

Akhter, F., Chen, D., Akhter, A., Yan, S.F., Yan Ss, Du, 2021. Age-dependent accumulation of dicarbonyls and advanced glycation endproducts (AGEs) associates with mitochondrial stress. Free Radic. Biol. Med. 164, 429–438.

Alamir, I., Niquet-Leridon, C., Jacolot, P., Rodriguez, C., Orosco, M., Anton, P.M., Tessier, F.J., 2012. Digestibility of extruded proteins and metabolic transit of N e-carboxymethyllysine in rats. Amino Acids 44, 1441–1449.

Aljahdali, N., Gadonna-Widehem, P., Delayre-Orthez, C., Marier, D., Garnier, B., Carbonero, F., Anton, P.M., 2017. Repeated oral exposure to N ε-carboxymethyllysine, a maillard reaction product, alleviates gut microbiota dysbiosis in colitic mice. Dig. Dis. Sci. 62, 3370–3384.

Asadipooya, K., Uy, E.M., 2019. Advanced glycation end products (AGEs), receptor for AGEs, diabetes, and bone: review of the literature. J. Endocr. Soc. 3, 1799–1818.

Asano, M., Fujita, Y., Ueda, Y., Suzuki, D., Miyata, T., Sakai, H., Saito, A., 2002. Renal proximal tubular metabolism of protein-linked pentosidine, an advanced glycation end product. Nephron 91, 688–694.

Baynes, J.W., Thorpe, S.R., 1999. Role of oxidative stress in diabetic complications: a new perspective on an old paradigm. Diabetes.

Beisswenger, P.J., Howell, S.K., Touchette, A.D., Lal, S., Szwergold, B.S., 1999. Metformin reduces systemic methylglyoxal levels in type 2 diabetes. Diabetes 48, 198–202.

Bergmann, R., Helling, R., Scheunemann, M., Mading, P., Wittrisch, H., Johannsen, B., Henle, T., 2001. Radio fluorination and positron emission tomography (PET) as a new approach to study the in vivo distribution and elimination of the advanced glycation endproducts Nε-carboxymethyllysine (CML) and Nε-carboxyethyllysine (CEL). Food Nahrung 45, 182–188.

Bieme, K.M., Alexander Fried, D., Lederer, M.O., 2002. Identification and quantification of major maillard cross-links in human serum albumin and lens protein: evidence for glucosepane as the dominant compound. J. Biol. Chem. 277, 24907–24915.

Brett, J., Marie Schmidt, A., Du Yan, S., Shan Zou, Y., Weidman, E., Pinsky, D., Nowygrod, R., Neeper, M., Przysiecki, C., Shaw, A., Migheli, A., Stern, D., 1993. Survey of the distribution of a newly characterized receptor for advanced glycation end products in tissues. Am. J. Pathology 143.

Brighina, S., Poveda Turrado, C., Restuccia, C., Walton, G., Fallico, B., Oruna-Concha, M. J., Arena, E., 2021. Detrimental effect on the gut microbiota of 1,2-dicarbonyl compounds after in vitro gastro-intestinal and fermentative digestion. Food Chem. 341, 128237.

Buetler, T.M., Leclerc, E., Baumeyer, A., Latado, H., Newell, J., Adolfsson, O., Parisod, V., Richoz, J., Maurer, S., Foata, F., Piguet, D., Junod, S., Heizmann, C.W., Delatour, T., 2008. Nε-carboxymethyllysine-modified proteins are unable to bind to RAGE and activate an inflammatory response. Mol. Nutr. Food Res. 52, 370–378.

Bui, T.P.N., Ritari, J., Boeren, S., De Waard, P., Plugge, C.M., De Vos, W.M., 2015. Production of butyrate from lysine and the Amadori product fructoselysine by a human gut commensal. Nat. Commun. 6, 1–10.

BCT Van, Bussel, Poll Mcg, Van de, Schalkwijk, C.G., Bergmans, D.C.J.J., 2017. Increased dicarbonyl stress as a novel mechanism of multi-organ failure in critical illness. Int. J. Mol. Sci. 18, 346, 2017, Vol 18, Page 346.

Carding, S., Verbeke, K., Vipond, D.T., Corfe, B.M., Owen, L.J., 2015. Dysbiosis of the gut microbiota in disease. Microb. Ecol. Health Dis. 26.

Chen, P., Zhao, J., Gregersen, H., 2012. Up-regulated expression of advanced glycation end-products and their receptor in the small intestine and colon of diabetic rats. Dig. Dis. Sci. 57, 48–57.

Chen, Y., Zhou, J., Wang, L., 2021. Role and mechanism of gut microbiota in human disease. Front. Cell. Infect. Microbiol. 11.

de Courten, B., de Courten, M.P., Soldatos, G., Dougherty, S.L., Straznicky, N., Schlaich, M., Sourris, K.C., Chand, V., Scheijen, J.L., Kingwell, B.A., Cooper, M.E., Schalkwijk, C.G., Walker, K.Z., Forbes, J.M., 2016. Diet low in advanced glycation end products increases insulin sensitivity in healthy overweight individuals: a double-blind, randomized, crossover trial. Am. J. Clin. Nutr. 103, 1426–1433.

Degen, J., Beyer, H., Heymann, B., Hellwig, M., Henle, T., 2014. Dietary influence on urinary excretion of 3-deoxyglucosone and its metabolite 3-deoxyfructose. J. Agric. Food Chem. 62, 2449–2456.

Degen, J., Vogel, M., Richter, D., Hellwig, M., Henle, T., 2013. Metabolic transit of dietary Methylglyoxal. In: Journal of Agricultural and Food Chemistry. American Chemical Society, pp. 10253–10260.

Delgado-Andrade, C., 2016. Carboxymethyl-lysine: thirty years of investigation in the field of AGE formation. Food Funct. 7, 46–57.

Delgado-Andrade, C., Pastoriza de la Cueva, S., Peinado, M.J., , Rufián-Henares JÁ, Navarro, M.P., Rubio, L.A., 2017. Modifications in bacterial groups and short chain fatty acid production in the gut of healthy adult rats after long-term consumption of dietary Maillard reaction products. Food Res. Int. 100, 134–142.

Delgado-Andrade, C., Tessier, F.É.J., Niquet-Leridon, C., Seiquer, I., Navarro, M.P., 2012. Study of the urinary and faecal excretion of Ne-carboxymethyllysine in young human volunteers. Amino Acids 43, 595–602.

Dobi, A., Rosanaly, S., Devin, A., Baret, P., Meilhac, O., Harry, G.J., d'Hellencourt, C.L., Rondeau, P., 2021. Advanced glycation end-products disrupt brain microvascular endothelial cell barrier: the role of mitochondria and oxidative stress. Microvasc. Res. 133, 104098.

Erbersdobler, H.F., 1977. The biological significance of carbohydrate-lysine crosslinking during heat-treatment of food proteins. Adv. Exp. Med. Biol. 86B, 367–378.

Erbersdobler, H.F., Faist, V., 2001. Metabolic transit of Amadori products. Nahrung-Food 45, 177–181.

Feskens, E., Brennan, L., Dussort, P., Flourakis, M., Lindner, L.M.E., Mela, D., Rabbani, N., Rathmann, W., Respondek, F., Stehouwer, C., Theis, S., Thornalley, P., Vinoy, S., 2020. Potential markers of dietary glycemic exposures for sustained dietary interventions in populations without diabetes. Adv. Nutr.

Finot, P.A., Magnenat, E., 1981. Metabolic transit of early and advanced maillard products. Prog. Food Nutr. Sci. 5, 193–207.

Förster, A., Kühne, Y., Henle, T., 2005. Studies on absorption and elimination of dietary maillard reaction products. Ann. N. Y. Acad. Sci. 1043, 474–481.

Gasaly, N., de Vos, P., Hermoso, M.A., 2021. Impact of bacterial metabolites on gut barrier function and host immunity: a focus on bacterial metabolism and its relevance for intestinal inflammation. Front. Immunol. 1807, 0.

Gebhardt, C., Riehl, A., Durchdewald, M., Németh, J., Fürstenberger, G., Müller-Decker, K., Enk, A., Arnold, B., Bierhaus, A., Nawroth, P.P., Hess, J., Angel, P., 2008. RAGE signaling sustains inflammation and promotes tumor development. J. Exp. Med. 205, 275–285.

Gill, V., Kumar, V., Singh, K., Kumar, A., Kim, J.-J., 2019. Advanced glycation end products (AGEs) may Be a striking link between modern diet and health. Biomolecules 9, 888.

Glomb, M.A., Monnier, V.M., 1995. Mechanism of protein modification by glyoxal and glycolaldehyde, reactive intermediates of the Maillard reaction. J. Biol. Chem. 270, 10017–10026.

Grimm, S., Ernst, L., Grötzinger, N., Höhn, A., Breusing, N., Reinheckel, T., Grune, T., 2010. Cathepsin D is one of the major enzymes involved in intracellular degradation of AGE-modified proteins. Free Radic. Res. 44, 1013–1026.

Grossin, N., Auger, F., Niquet-Leridon, C., Durieux, N., Montaigne, D., Schmidt, A.M., Susen, S., Jacolot, P., Beuscart, J.B., Tessier, F.J., Boulanger, E., 2015. Dietary CML-enriched protein induces functional arterial aging in a RAGE-dependent manner in mice. Mol. Nutr. Food Res. 59, 927–938.

Grunwald, S., Krause, R., Bruch, M., Henle, T., Brandsch, M., 2006. Transepithelial flux of early and advanced glycation compounds across Caco-2 cell monolayers and their interaction with intestinal amino acid and peptide transport systems. Br. J. Nutr. 95, 1221–1228.

Han, K., Jin, W., Mao, Z., Dong, S., Zhang, Q., Yang, Y., Chen, B., Wu, H., Zeng, M., 2018. Microbiome and butyrate production are altered in the gut of rats fed a glycated fish protein diet. J. Funct.Foods 47, 423–433.

Hansen, B., Svistounov, D., Olsen, R., Nagai, R., Horiuchi, S., Smedsrød, B., 2002. Advanced glycation end products impair the scavenger function of rat hepatic sinusoidal endothelial cells. Diabetologia 45, 1379–1388.

Hegele, J., Buetler, T., Delatour, T., 2008. Comparative LC–MS/MS profiling of free and protein-bound early and advanced glycation-induced lysine modifications in dairy products. Anal. Chim. Acta 617, 85–96.

Hellwig, M., Bunzel, D., Huch, M., Franz, C.M.A.P., Kulling, S.E., Henle, T., 2015. Stability of individual maillard reaction products in the presence of the human colonic microbiota. J. Agric. Food Chem. 63, 6723–6730.

Hellwig, M., Geissler, S., Matthes, R., Peto, A., Silow, C., Brandsch, M., Henle, T., 2011. Transport of free and peptide-bound glycated amino acids: synthesis, transepithelial flux at caco-2 cell monolayers, and interaction with apical membrane transport proteins. Chembiochem 12, 1270–1279.

Hellwig, M., Geissler, S., Peto, A., Knütter, I., Brandsch, M., Henle, T., 2009. Transport of free and peptide-bound pyrraline at intestinal and renal epithelial cells. J. Agric. Food Chem. 57, 6474–6480.

Hellwig, M., Humpf, H.-U., Hengstler, J., Mally, A., Vieths, S., Henle, T., 2019. Quality criteria for studies on dietary glycation compounds and human health. J. Agric. Food Chem. 67, 11307–11311.

Hellwig, M., Matthes, R., Peto, A., Löbner, J., Henle, T., 2014. N-ε-fructosyllysine and N-ε-carboxymethyllysine, but not lysinoalanine, are available for absorption after simulated gastrointestinal digestion. Amino Acids 46, 289–299.

Hofmann, S.M., Dong, H.J., Li, Z., Cai, W., Altomonte, J., Thung, S.N., Zeng, F., Fisher, E. A., Vlassara, H., 2002. Improved insulin sensitivity is associated with restricted intake of dietary glycoxidation products in the db/db mouse. Diabetes 51, 2082–2089.

Holik, A.K., Stöger, V., Hölz, K., Somoza, M.M., Somoza, V., 2018. Impact of free Nε-carboxymethyllysine, its precursor glyoxal and AGE-modified BSA on serotonin release from human parietal cells in culture. Food Funct. 9, 3906–3915.

Horie, K., Miyata, T., Maeda, K., Miyata, S., Sugiyama, S., Sakai, H., Van Ypersele De Strihou, C., Monnier, V.M., Witztum, J.L., Kurokawa, K., 1997. Immunohistochemical colocalization of glycoxidation products and lipid peroxidation products in diabetic renal glomerular lesions. Implication for

glycoxidative stress in the pathogenesis of diabetic nephropathy. J. Clin. Invest. 100, 2995–3004.
Hulsmans, M., Holvoet, P., 2010. The vicious circle between oxidative stress and inflammation in atherosclerosis. J. Cell Mol. Med. 14, 70–78.
Kellow, N.J., Coughlan, M.T., 2015. Effect of diet-derived advanced glycation end products on inflammation. Nutr. Rev. 73, 737–759.
Kislinger, T., Fu, C., Huber, B., Qu, W., Taguchi, A., Yan S, Du, Hofmann, M., Yan, S.F., Pischetsrieder, M., Stern, D., Schmidt, A.M., 1999. N(ε)-(carboxymethyl)lysine adducts of proteins are ligands for receptor for advanced glycation end products that activate cell signaling pathways and modulate gene expression. J. Biol. Chem. 274, 31740–31749.
Klöpfer, A., Spanneberg, R., Glomb, M.A., 2011. Formation of arginine modifications in a model system of N α- Tert -butoxycarbonyl (Boc)-arginine with methylglyoxal. J. Agric. Food Chem. 59, 394–401.
Koschinsky, T., He, C.-J., Mitsuhashi, T., Bucala, R., Liu, C., Buenting, C., Heitmann, K., Vlassara, H., 1997. Orally absorbed reactive glycation products (glycotoxins): an environmental risk factor in diabetic nephropathy. Proc. Natl. Acad. Sci. Unit. States Am. 94, 6474–6479.
Lee, H.-W., Gu, M.J., Lee, J.-Y., Lee, S., Kim, Y., Ha, S.K., Lee, H.-W., Gu, M.J., Kim, Y., Ha, S.K., Lee, J.-Y., Lee, S., 2021. Methylglyoxal-lysine dimer, an advanced glycation end product, induces inflammation via interaction with RAGE in mesangial cells. Mol. Nutr. Food Res. 65, 2000799.
Lee, K., Erbersdobler, H.F., 2005. Balance experiments on human volunteers with ε-fructoselysine (FL) and lysinoalanine (LAL). Mail React. Chem. Food Heal. 358–363.
Li, M., Zeng, M., He, Z., Zheng, Z., Qin, F., Tao, G., Zhang, S., Chen, J., 2015a. Effects of long-term exposure to free nε-(carboxymethyl)lysine on rats fed a high-fat diet. J. Agric. Food Chem. 63, 10995–11001.
Li, M., Zeng, M., He, Z., Zheng, Z., Qin, F., Tao, G., Zhang, S., Chen, J., 2015b. Increased accumulation of protein-bound N ε-(carboxymethyl)lysine in tissues of healthy rats after chronic oral N ε-(carboxymethyl)lysine. J. Agric. Food Chem. 63, 1658–1663.
Liang, Z., Chen, X., Li, L., Li, B., Yang, Z., 2019. The fate of dietary advanced glycation end products in the body: from oral intake to excretion. Crit. Rev. Food Sci. Nutr.
Liardon, R., De Weck-Gaudard, D., Philippossian, G., Finot, P.-A., 1987. Identification of N-Carboxymethyllysine: a New Maillard Reaction Product, in Rat Urine, 35, pp. 427–431.
Lin, J.-A., Wu, C.-H., Lu, C.-C., Hsia, S.-M., Yen, G.-C., 2016. Glycative stress from advanced glycation end products (AGEs) and dicarbonyls: an emerging biological factor in cancer onset and progression. Mol. Nutr. Food Res. 60, 1850–1864.
Lin, R.Y., Choudhury, R.P., Cai, W., Lu, M., Fallon, J.T., Fisher, E.A., Vlassara, H., 2003. Dietary glycotoxins promote diabetic atherosclerosis in apolipoprotein E-deficient mice. Atherosclerosis 168, 213–220.
Lin, R.Y., Reis, E.D., Dore, A.T., Lu, M., Ghodsi, N., Fallon, J.T., Fisher, E.A., Vlassara, H., 2002. Lowering of dietary advanced glycation endproducts (AGE) reduces neointimal formation after arterial injury in genetically hypercholesterolemic mice. Atherosclerosis 163, 303–311.
Liu, J., Desai, K., Wang, R., Wu, L., 2013. Up-regulation of aldolase A and methylglyoxal production in adipocytes. Br. J. Pharmacol. 168, 1639–1646.
Lopes-Virella, M.F., Baker, N.L., Hunt, K.J., Cleary, P.A., Klein, R., Virella, G., 2013. Baseline markers of inflammation are associated with progression to macroalbuminuria in type 1 diabetic subjects. Diabetes Care 36, 2317–2323.
Lu, J., Randell, E., Han, Y.C., Adeli, K., Krahn, J., Meng, Q.H., 2011. Increased plasma methylglyoxal level, inflammation, and vascular endothelial dysfunction in diabetic nephropathy. Clin. Biochem. 44, 307–311.
Maasen, K., Scheijen, J.L.J.M., Opperhuizen, A., Stehouwer, C.D.A., Van Greevenbroek, M.M., Schalkwijk, C.G., 2021. Quantification of dicarbonyl compounds in commonly consumed foods and drinks; presentation of a food composition database for dicarbonyls. Food Chem. 339, 128063.
Maillard, L.C., 1912. Action des acides amines sur les sucres; formation des melanoidines par voie methodique. Comptes. R Acad. Sci. 154, 66–68.
Marungruang, N., Fåk, F., Tareke, E., 2016. Heat-treated high-fat diet modifies gut microbiota and metabolic markers in apoe-/- mice. Nutr. Metab. 13, 1–11.
Mastrocola, R., Collotta, D., Gaudioso, G., Le Berre, M., Cento, A.S., Ferreira Alves, G., Chiazza, F., Verta, R., Bertocchi, I., Manig, F., Hellwig, M., Fava, F., Cifani, C., Aragno, M., Henle, T., Joshi, L., Tuohy, K., Collino, M., 2020. Effects of exogenous dietary advanced glycation end products on the cross-talk mechanisms linking microbiota to metabolic inflammation. Nutrients 12, 2497.
Miyata, S., 1997. Accumulation of pyrraline-modified albumin in phagocytes due to reduced degradation by lysosomal enzymes. J. Biol. Chem. 272, 4037–4042.
Miyata, T., Ueda, Y., Horie, K., Nangaku, M., Tanaka, S., de Strihou, C. van Y., Kurokawa, K., 1998. Renal catabolism of advanced glycation end products: the fate of pentosidine. Kidney Int. 53, 416–422.
Monnier, V.M., Nagaraj, R.H., Portero-Otin, M., Glomb, M., Elgawish, A.H., Sell, D.R., Friedlander, M.A., 1996. Structure of advanced Maillard reaction products and their pathological role. In: Nephrology Dialysis Transplantation. Oxford University Press, pp. 20–26.
Mori, B., Kojima, K., Saito, S., 1980. Fructoselysine in urine of rats fed 14C-lysine-labeled casein browned by amino-carbonyl reaction. Agric. Biol. Chem. 44, 1327–1331.
Nagai, R., Fujiwara, Y., Mera, K., Otagiri, M., 2007. Investigation of pathways of advanced glycation end-products accumulation in macrophages. Mol. Nutr. Food Res. 51, 462–467.
Nguyen, H.T., van der Fels-Klerx, H.J., van Boekel, M.A.J.S., 2014. N ε -(carboxymethyl) lysine: a review on analytical methods, formation, and occurrence in processed food, and health impact. Food Rev. Int. 30, 36, 52.
Niederwieser, A., Giliberti, P., Matasovic, A., 1975. N(ε)/1 deoxyfructosyl/lysine in urine after ingestion of a lactose free, glucose containing milk formula. Pediatr. Res. 9, 867, 867.
Niwa, H., Takeda, A., Wakai, M., Miyata, T., Yasuda, Y., Mitsuma, T., Kurokawa, K., Sobue, G., 1998. Accelerated formation of N(ε)-(carboxymethyl) lysine, an advanced glycation end product, by glyoxal and 3-deoxyglucosone in cultured rat sensory neurons. Biochem. Biophys. Res. Commun. 248, 93–97.
Niwa, T., Katsuzaki, T., Ishizaki, Y., Hayase, F., Miyazaki, T., Uematsu, T., Tatemichi, N., Takei, Y., 1997. Imidazolone, a novel advanced glycation end product, is present at high levels in kidneys of rats with streptozotocin-induced diabetes. FEBS Lett. 407, 297–302.
Nowotny, K., Schröter, D., Schreiner, M., Grune, T., 2018. Dietary advanced glycation end products and their relevance for human health. Ageing Res. Rev. 47, 55–66.
Ott, C., Jacobs, K., Haucke, E., Navarrete Santos, A., Grune, T., Simm, A., 2014. Role of advanced glycation end products in cellular signaling. Redox Biol.
Peculis, R., Konrade, I., Skapare, E., Fridmanis, D., Nikitina-Zake, L., Lejnieks, A., Pirags, V., Dambrova, M., Klovins, J., 2013. Identification of glyoxalase 1 polymorphisms associated with enzyme activity. Gene 515, 140–143.
Penfold, S.A., Coughlan, M.T., Patel, S.K., Srivastava, P.M., Sourris, K.C., Steer, D., Webster, D.E., Thomas, M.C., MacIsaac, R.J., Jerums, G., Burrell, L.M., Cooper, M.E., Forbes, J.M., 2010. Circulating high-molecular-weight RAGE ligands activate pathways implicated in the development of diabetic nephropathy. Kidney Int. 78, 287–295.
Peppa, M., He, C., Hattori, M., McEvoy, R., Zheng, F., Vlassara, H., 2003. Fetal or neonatal low-glycotoxin environment prevents autoimmune diabetes in NOD mice. Diabetes 52, 1441–1448.
Perrone, A., Giovino, A., Benny, J., Martinelli, F., 2020. Advanced glycation end products (AGEs): biochemistry, signaling, analytical methods, and epigenetic effects. Oxid. Med. Cell. Longev.
Piperi, C., 2017. Dietary advanced glycation end-products: molecular mechanisms and preventive tools. Curr. Nutr. Rep.
Poulsen, M.W., Andersen, J.M., Hedegaard, R.V., Madsen, A.N., Krath, B.N., Monošík, R., Bak, M.J., Nielsen, J., Holst, B., Skibsted, L.H., Larsen, L.H., Dragsted, L.O., 2016. Short-term effects of dietary advanced glycation end products in rats. Br. J. Nutr. 115, 629–636.
Poulsen, M.W., Hedegaard, R.V., Andersen, J.M., de Courten, B., Bügel, S., Nielsen, J., Skibsted, L.H., Dragsted, L.O., 2013. Advanced glycation endproducts in food and their effects on health. Food Chem. Toxicol. 60, 10–37.
Power, S.E., O'Toole, P.W., Stanton, C., Ross, R.P., Fitzgerald, G.F., 2014. Intestinal microbiota, diet and health. Br. J. Nutr. 111, 387–402.
Qu, W., Nie, C., Zhao, J., Ou, X., Zhang, Y., Yang, S., Bai, X., Wang, Y., Wang, J., Li, J., 2018. Microbiome–metabolomics analysis of the impacts of long-term dietary advanced-glycation-end-product consumption on C57bl/6 mouse fecal microbiota and metabolites. J. Agric. Food Chem. 66, 8864–8875.
Qu, W., Yuan, X., Zhao, J., Zhang, Y., Hu, J., Wang, J., Li, J., 2017. Dietary advanced glycation end products modify gut microbial composition and partially increase colon permeability in rats. Mol. Nutr. Food Res. 61.
Rabbani, N., Thornalley, P.J., 2012. Methylglyoxal, glyoxalase 1 and the dicarbonyl proteome. Amino Acids 42, 1133–1142.
Rabbani, N., Thornalley, P.J., 2015. Dicarbonyl stress in cell and tissue dysfunction contributing to ageing and disease. Biochem. Biophys. Res. Commun. 458, 221–226.
Rabbani, N., Xue, M., Thornalley, P.J., 2016. Dicarbonyls and glyoxalase in disease mechanisms and clinical therapeutics. Glycoconj. J. 33, 513–525.
Raj, D.S.C., Choudhury, D., Welbourne, T.C., Levi, M., 2000. Advanced glycation end products: a nephrologist's perspective. Am. J. Kidney Dis. 35, 365–380.
Ramasamy, R., Vannucci, S.J., Yan, SS Du, Herold, K., Yan, S.F., Schmidt, A.M., 2005. Advanced glycation end products and RAGE: a common thread in aging, diabetes, neurodegeneration, and inflammation. Glycobiology 15, 16R–28R.
Ramasamy, R., Yan, S.F., Schmidt, A.M., 2006. Methylglyoxal comes of AGE. Cell.
Rietjens, I.M.C.M., Michael, A., Bolt, H.M., Siméon, B., Andrea, H., Nils, H., Christine, K., Angela, M., Gloria, P., Daniel, R., Natalie, T., Gerhard, E., 2022. The role of endogenous versus exogenous sources in the exposome of putative genotoxins and consequences for risk assessment. Arch. Toxicol. 1, 1–56.
Roberts, M.J., Wondrak, G.T., Laurean, D.C., Jacobson, M.K., Jacobson, E.L., 2003. DNA damage by carbonyl stress in human skin cells. Mutat. Res. Mol. Mech. Mutagen. 522, 45–56.
Round, J.L., Mazmanian, S.K., 2009. The gut microbiota shapes intestinal immune responses during health and disease. Nat. Rev. Immunol. 9, 313–323.
Saito, A., Takeda, T., Sato, K., Hama, H., Tanuma, A., Kaseda, R., Suzuki, Y., Gejyo, F., 2005. Significance of proximal tubular metabolism of advanced glycation end products in kidney diseases. In: Annals of the New York Academy of Sciences. New York Academy of Sciences, pp. 637–643.
Sano, H., Higashi, T., Matsumoto, K., Melkko, J., Jinnouchi, Y., Ikeda, K., Ebina, Y., Makino, H., Smedsrød, B., Horiuchi, S., 1998. Insulin enhances macrophage scavenger receptor-mediated endocytic uptake of advanced glycation end products. J. Biol. Chem. 273, 8630–8637.
Scheijen, J.L.J.M., Hanssen, N.M.J., van Greevenbroek, M.M., Van der Kallen, C.J., Feskens, E.J.M., Stehouwer, C.D.A., Schalkwijk, C.G., 2018. Dietary intake of advanced glycation endproducts is associated with higher levels of advanced glycation endproducts in plasma and urine: the CODAM study. Clin. Nutr. 37, 919–925.
Scheijen, J.L.J.M., Schalkwijk, C.G., 2014. Quantification of glyoxal, methylglyoxal and 3-deoxyglucosone in blood and plasma by ultra performance liquid chromatography tandem mass spectrometry: evaluation of blood specimen. Clin. Chem. Lab. Med. 52, 85–91.

Seiquer, I., Rubio, L.A., Peinado, M.J., Delgado-Andrade, C., Navarro, M.P., 2014. Maillard reaction products modulate gut microbiota composition in adolescents. Mol. Nutr. Food Res. 58, 1552–1560.
Sell, D.R., Biemel, K.M., Reihl, O., Lederer, M.O., Strauch, C.M., Monnier, V.M., 2005. Glucosepane is a major protein cross-link of the senescent human extracellular matrix. J. Biol. Chem. 280, 12310–12315.
Semba, R.D., Ang, A., Talegawkar, S., Crasto, C., Dalal, M., Jardack, P., Traber, M.G., Ferrucci, L., Arab, L., 2012. Dietary intake associated with serum versus urinary carboxymethyl-lysine, a major advanced glycation end product, in adults: the Energetics Study. Eur. J. Clin. Nutr. 66, 3–9.
Semba, R.D., Nicklett, E.J., Ferrucci, L., 2010. Does accumulation of advanced glycation end products contribute to the aging phenotype? J. Gerontol. - Ser. A Biol. Sci. Med. Sci. 65, 963–975.
Sergi, D., Boulestin, H., Campbell, F.M., Williams, L.M., 2020. The role of dietary advanced glycation end products in metabolic dysfunction. Mol. Nutr. Food Res., 1900934
Sharma, C., Kaur, A., Thind, S.S., Singh, B., Raina, S., 2015. Advanced glycation End-products (AGEs): an emerging concern for processed food industries. J. Food Sci. Technol.
Singh Jaggi, A., Parkash Singh, V., Bali, A., Singh, N., 2014. Advanced glycation end products and diabetic complications. KOREAN J. PHYSIOL. PHARMACOL. 18, 1–14.
Singh, R., Barden, A., Mori, T., Beilin, L., 2001. Advanced glycation end-products: a review. Diabetologia 44, 129–146.
Snelson, M., Coughlan, M.T., 2019. Dietary advanced glycation end products: digestion, metabolism and modulation of gut microbial ecology. Nutrients.
Snelson, M., Tan, S.M., Clarke, R.E., De Pasquale, C., Thallas-Bonke, V., Nguyen, T.V., Penfold, S.A., Harcourt, B.E., Sourris, K.C., Lindblom, R.S., Ziemann, M., Steer, D., El-Osta, A., Davies, M.J., Donnellan, L., Deo, P., Kellow, N.J., Cooper, M.E., Woodruff, T.M., Mackay, C.R., Forbes, J.M., Coughlan, M.T., 2021. Processed foods drive intestinal barrier permeability and microvascular diseases. Sci. Adv. 7, 1–15.
Somoza, V., Wenzel, E., Weiß, C., Clawin-Rädecker, I., Grübel, N., Erbersdobler, H.F., 2006. Dose-dependent utilisation of casein-linked lysinoalanine, N(epsilon)-fructoselysine and N(epsilon)-carboxymethyllysine in rats. Mol. Nutr. Food Res. 50, 833–841.
Sowndhar Rajan, B., Manivasagam, S., Dhanusu, S., Chandrasekar, N., Krishna, K., Kalaiarasu, L.P., Babu, A.A., Vellaichamy, E., 2018. Diet with high content of advanced glycation end products induces systemic inflammation and weight gain in experimental mice: protective role of curcumin and gallic acid. Food Chem. Toxicol. 114, 237–245.
Steenbeke, M., Bruyne, S De, Buyzere, M De, Lapauw, B., Speeckaert, R., Petrovic, M., Delanghe, J.R., Speeckaert, M.M., 2021. The role of soluble receptor for advanced glycation end-products (sRAGE) in the general population and patients with diabetes mellitus with a focus on renal function and overall outcome. Crit. Rev. Clin. Lab Sci. 58, 113–130.
Stefanie, G., Michael, H., Madlen, Z., Fritz, M., Thomas, H., Matthias, B., 2010. Transport of the advanced glycation end products alanylpyrraline and pyrralylalanine by the human proton-coupled peptide transporter hPEPT1. J. Agric. Food Chem. 58, 2543–2547.
Svistounov, D., Smedsrød, B., 2004. Hepatic clearance of advanced glycation end products (AGEs)—myth or truth? J. Hepatol. 41, 1038–1040.
Tessier, F.J., Birlouez-Aragon, I., 2012. Health effects of dietary Maillard reaction products: the results of ICARE and other studies. Amino Acids 42, 1119–1131.
Tessier, F.J., Niquet-Léridon, C., Jacolot, P., Jouquand, C., Genin, M., Schmidt, A.-M., Grossin, N., Boulanger, E., 2016. Quantitative assessment of organ distribution of dietary protein-bound ^{13}C-labeled N$^{\epsilon}$-carboxymethyllysine after a chronic oral exposure in mice. Mol. Nutr. Food Res. 60, 2446–2456.
Tsukushi, S., Katsuzaki, T., Aoyama, I., Takayama, F., Miyazaki, T., Shimokata, K., Niwa, T., 1999. Increased erythrocyte 3-DG and AGEs in diabetic hemodialysis patients: role of the polyol pathway. Kidney Int. 55, 1970. –1976.
Tuohy, K.M., Hinton, D.J.S., Davies, S.J., Crabbe, M.J.C., Gibson, G.R., Ames, J.M., 2006. Metabolism of Maillard reaction products by the human gut microbiota – implications for health. Mol. Nutr. Food Res. 50, 847–857.
Uribarri, J., Cai, W., Ramdas, M., Goodman, S., Pyzik, R., Xue, C., Li, Z., Striker, G.E., Vlassara, H., 2011. Restriction of advanced glycation end products improves insulin resistance in human type 2 diabetes: potential role of AGER1 and SIRT1. Diabetes Care 34, 1610–1616.
Uribarri, J., Cai, W., Sandu, O., Peppa, M., Goldberg, T., Vlassara, H., 2005. Diet-derived advanced glycation end products are major contributors to the body's AGE pool and induce inflammation in healthy subjects. Ann. N. Y. Acad. Sci. 1043, 461–466.
Uribarri, J., del Castillo, M.D., de la Maza, M.P., Filip, R., Gugliucci, A., Luevano-Contreras, C., Macías-Cervantes, M.H., Markowicz Bastos, D.H., Medrano, A., Menini, T., Portero-Otin, M., Rojas, A., Sampaio, G.R., Wrobel, K., Wrobel, K., Garay-Sevilla, M.E., 2015. Dietary advanced glycation end products and their role in health and disease. Adv. Nutr. 6, 461–473.
Uribarri, J., Peppa, M., Cai, W., Goldberg, T., Lu, M., Baliga, S., Vassalotti, J.A., Vlassara, H., 2003a. Dietary glycotoxins correlate with circulating advanced glycation end product levels in renal failure patients. Am. J. Kidney Dis. 42, 532–538.
Uribarri, J., Peppa, M., Cai, W., Goldberg, T., Lu, M., He, C., Vlassara, H., 2003b. Restriction of dietary glycotoxins reduces excessive advanced glycation end products in renal failure patients. J. Am. Soc. Nephrol. 14, 728–731.
Uribarri, J., Woodruff, S., Goodman, S., Cai, W., Chen, X., Pyzik, R., Yong, A., Striker, G. E., Vlassara, H., 2010. Advanced glycation end products in foods and a practical guide to their reduction in the diet. J. Am. Diet Assoc. 110, 911–916.e12.
Valencia, J.V., Weldon, S.C., Quinn, D., Kiers, G.H., DeGroot, J., TeKoppele, J.M., Hughes, T.E., 2004. Advanced glycation end product ligands for the receptor for advanced glycation end products: biochemical characterization and formation kinetics. Anal. Biochem. 324, 68–78.
Van Der Lugt, T., Venema, K., Van Leeuwen, S., Vrolijk, M.F., Opperhuizen, A., Bast, A., 2020. Gastrointestinal digestion of dietary advanced glycation endproducts using an: in vitro model of the gastrointestinal tract (TIM-1). Food Funct. 11, 6297–6307.
van Dongen, K.C.W., Linkens, A.M.A., Wetzels, S.M.W., Wouters, K., Vanmierlo, T., van de Waarenburg Mph, L.J.M., Scheijen, J., de Vos, W.M., Belzer, C., Schalkwijk, C.G., 2021a. Dietary advanced glycation endproducts (AGEs) increase their concentration in plasma and tissues, result in inflammation and modulate gut microbial composition in mice; evidence for reversibility. Food Res. Int. 147, 110547.
van Dongen, K.C.W., van der Zande, M., Bruyneel, B., Vervoort, J.J.M., Rietjens, I.M.C. M., Belzer, C., Beekmann, K., 2021b. An in vitro model for microbial fructoselysine degradation shows substantial interindividual differences in metabolic capacities of human fecal slurries. Toxicol. Vitro 72, 105078.
Veiga da-Cunha, M., Jacquemin, P., Delpierre, G., Godfraind, C., Théate, I., Vertommen, D., Clotman, F., Lemaigre, F., Devuyst, O., van Schaftingen, E., 2006. Increased protein glycation in fructosamine 3-kinase-deficient mice. Biochem. J. 399, 257.
Vistoli, G., De Maddis, D., Cipak, A., Zarkovic, N., Carini, M., Aldini, G., 2013. Advanced glycoxidation and lipoxidation end products (AGEs and ALEs): an overview of their mechanisms of formation. Free Radic. Res. 47, 3–27.
Vlassara, H., 2001. The AGE-receptor in the pathogenesis of diabetic complications. Diabetes Metab. Res. Rev. 17, 436–443.
Vlassara, H., Bucala, R., 1996. Recent progress in advanced glycation and diabetic vascular disease: role of advanced glycation end product receptors. Diabetes 45, 65–66.
Vlassara, H., Cai, W., Crandall, J., Goldberg, T., Oberstein, R., Dardaine, V., Peppa, M., Rayfield, E.J., 2002. Inflammatory mediators are induced by dietary glycotoxins, a major risk factor for diabetic angiopathy. Proc. Natl. Acad. Sci. U. S. A. 99, 15596–15601.
Wiame, E., Delpierre, G., Collard, F., Van Schaftingen, E., 2002. Identification of a pathway for the utilization of the Amadori product fructoselysine in Escherichia coli. J. Biol. Chem. 277, 42523–42529.
Wiame, E., Duquenne, A., Delpierre, G., Van Schaftingen, E., 2004. Identification of enzymes acting on α-glycated amino acids in *Bacillus subtilis*. FEBS Lett. 577, 469–472.
Xie, J., Reverdatto, S., Frolov, A., Hoffmann, R., Burz, D.S., Shekhtman, A., 2008. Structural basis for pattern recognition by the receptor for advanced glycation end products (RAGE). J. Biol. Chem. 283, 27255–27269.
Xu, H., Wang, Z., Wang, Y., Hu, S., Liu, N., 2013. Biodistribution and elimination study of fluorine-18 labeled nε-carboxymethyl-lysine following intragastric and intravenous administration. PLoS One 8, e57897.
Xue, J., Ray, R., Singer, D., Böhme, D., Burz, D.S., Rai, V., Hoffmann, R., Shekhtman, A., 2014. The receptor for advanced glycation end products (RAGE) specifically recognizes methylglyoxal-derived AGEs. Biochemistry 53, 3327–3335.
Xue, M., Rabbani, N., Momiji, H., Imbasi, P., Anwar, M.M., Kitteringham, N., Park, B.K., Souma, T., Moriguchi, T., Yamamoto, M., Thornalley, P.J., 2012. Transcriptional control of glyoxalase 1 by Nrf2 provides a stress-responsive defence against dicarbonyl glycation. Biochem. J. 443, 213–222.
Yacoub, R., Nugent, M., Cai, W., Nadkarni, G.N., Chaves, L.D., Abyad, S., Honan, A.M., Thomas, S.A., Zheng, W., Valiyaparambil, S.A., Bryniarski, M.A., Sun, Y., Buck, M., Genco, R.J., Quigg, R.J., He, J.C., Uribarri, J., 2017. Advanced glycation end products dietary restriction effects on bacterial gut microbiota in peritoneal dialysis patients; a randomized open label controlled trial. PLoS One 12, e0184789.
Yang, S., Wang, G., Ma, Z feei, Qin, L., Zhai, Y., Yu, Z., Xue, M., Zhang, Y., Wan, Z., 2020. DietaryAdvancedGlycationEnd products–InducedCognitive impairment in aged ICR mice: protective role of quercetin. Mol. Nutr. Food Res. 64, 1901019.
Yaylayan, V.A., Huyghues-Despointes, A., Feather, M.S., 1994. Chemistry of Amadori rearrangement products: analysis, synthesis, kinetics, reactions, and spectroscopic properties. Crit. Rev. Food Sci. Nutr. 34, 321–369.
Zeng, J., Davies, M.J., 2005. Evidence for the formation of adducts and S-(Carboxymethyl)cysteine on reaction of r-dicarbonyl compounds with thiol groups on amino acids, peptides, and proteins. Chem. Res. Toxicol. 18.
Zhao, D., Sheng, B., Wu, Y., Li, H., Xu, D., Nian, Y., Mao, S., Li, C., Xu, X., Zhou, G., 2019. Comparison of free and bound advanced glycation end products in food: a review on the possible influence on human health. J. Agric. Food Chem.
Zheng, F., He, C., Cai, W., Hattori, M., Steffes, M., Vlassara, H., 2002. Prevention of diabetic nephropathy in mice by a diet low in glycoxidation products. Diabetes Metab. Res. Rev. 18, 224–237.
Zieman, S.J., Kass, D.A., 2004. Advanced Glycation Endproduct Crosslinking in the Cardiovascular System: Potential Therapeutic Target for Cardiovascular Disease. Drugs.
Zill, H., Bek, S., Hofmann, T., Huber, J., Frank, O., Lindenmeier, M., Weigle, B., Erbersdobler, H.F., Scheidler, S., Busch, A.E., Faist, V., 2003. RAGE-mediated MAPK activation by food-derived AGE and non-AGE products. Biochem. Biophys. Res. Commun. 300, 311–315.