Mini Review

HORMONE RESEARCH IN PÆDIATRICS

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Dietary Advanced Glycation End Products and Their Potential Role in Cardiometabolic Disease in Children

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Key Words
Obesity · Children · Insulin resistance · Metabolic syndrome · Advanced glycation end products · Receptor of advanced glycation end products

Abstract
The rising incidence of obesity and metabolic diseases such as diabetes mellitus and cardiovascular disease in adolescents and young adults is of grave concern. Recent studies favor a role of lifestyle factors over genetics in the perpetuation of inflammation, insulin resistance and oxidative stress, which are pathophysiologic processes common to the above diseases; furthermore, the importance of dietary factors in addition to calories and physical activity in these processes is being increasingly recognized. Advanced glycation end products (AGEs) belong to a category of dietary oxidants which have been implicated in the pathogenesis of inflammation, oxidative stress, insulin resistance, β-cell failure and endothelial dysfunction. This paper reviews the studies of AGEs with a focus on their role in cardiometabolic disease in children. A Medline search was performed using the key words 'childhood obesity', 'metabolic syndrome' and 'advanced glycation end products'. Articles published in English between 1975 and 2015 and their references were reviewed. While most studies were performed in adults, a few studies also demonstrated a role of AGEs in obesity and associated cardiometabolic comorbidities in the younger population. Available evidence suggests an involvement of AGEs in the pathogenesis of adiposity and β-cell failure in children. Potential areas for further research to investigate underlying mechanisms are proposed.

Introduction

There is a worldwide worsening epidemic of obesity, diabetes mellitus (DM) and cardiovascular disease (CVD) with an increasing onset in children and young adults [1]. However, the knowledge of mechanisms underlying the progression to DM and CVD particularly in children is still limited; this represents a barrier for further progress in this field. Strategies to identify the child at risk, mechanisms involved and how to prevent/treat these conditions in their early stages of development, are needed urgently and are vital in effectively preventing or halting the progression of DM and CVD.

These multifactorial diseases are known to be associated with low-grade inflammation, insulin resistance (IR)

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and oxidative stress (OS) across the age spectrum [2]. An increasing number of studies point to a pathogenic role of dietary factors in obesity-associated chronic inflammation, particularly with regard to their pro-oxidant properties. Advanced glycation end products (AGEs) belong to one such category of oxidants, which may cause β-cell failure, IR and endothelial dysfunction. AGEs are traditionally known to be produced endogenously as a result of hyperglycemia and increased OS. Recently, accumulated data additionally indicate that exogenous AGEs ingested with food or smoking represent a major contributor to the pool of AGEs in the body. In this article, we will review experimental and human studies looking at the role of AGEs in causing DM and CVD with special emphasis on dietary AGEs and on studies in children. We will also review studies evaluating the role of AGEs and their receptor variants in children with a focus on cardiometabolic risk. Finally, we will delineate the challenges of research in the field and present some insights into future directions, particularly in relation to children and adolescents.

What Are AGEs and What Are Their Pathogenic Mechanisms?

Reducing sugars such as glucose and fructose undergo spontaneous reactions with free amino groups on proteins, peptides or amino acids, lipids and nucleic acids to form a heterogeneous group of compounds known as AGEs; this is the classical Maillard reaction. The term AGEs, as currently used, broadly encompasses products of both glycoxidation and lipid peroxidation such as intermediate reactive precursors [1-deoxyglyoxal (1-DG), 3-DG and methylglyoxal (MG)] as well as terminal nonreactive AGEs [carboxymethyllysine (CML) and pentosidine]. These reactions increase in the presence of hyperglycemia and OS in vivo. In addition, all these reactions also occur in the environment and accelerate in the presence of high temperatures. For example, cooking food under dry conditions with the application of high heat significantly increases the formation of AGEs.

AGEs, endogenous or exogenous, can produce tissue damage by two main mechanisms. First, AGEs can covalently crosslink proteins and, therefore, directly alter protein structure and function. Second, through a variety of receptor and non-receptor mechanisms, AGEs can activate several intracellular pathways that increase generation of reactive oxygen species (ROS) and inflammatory cytokines.

The receptor for AGEs [membrane-bound receptor of AGE (mRAGE)] is a well-studied membrane-bound receptor that binds AGEs, initiating a cascade of intracellular events leading to inflammation and OS [3]. Other receptors of AGEs such as advanced glycation end product receptor-1, -2 and -3 (AGE-R1, AGE-R2 and AGE-R3) and scavenger receptors are considered to be endocytic in nature and also involved in the clearance of AGEs. Moreover, AGE-R1 has been shown to participate in pathways that decrease intracellular OS [4]. It has been proposed that chronic AGE overload results in unbalanced activation of downstream proinflammatory and pro-oxidative pathways. There is also a circulating pool of RAGE, collectively known as soluble RAGE (sRAGE), whose role still remains controversial. sRAGE consists of the isoform derived from membrane-bound RAGE by the proteolytic action of metalloproteases [such as a disintegrin and metalloprotease-10 (ADAM-10) and matrix metalloprotease-9] and a minor, alternatively spliced, isoform of RAGE known as endogenously secreted RAGE (esRAGE) [5]. In animal studies, administration of sRAGE prevented and stabilized established atherosclerosis [6, 7] and ameliorated retinal neuronal dysfunction in experimental diabetic retinopathy [8]. Therefore, sRAGE has been suggested to act as a decoy receptor that binds and eliminates circulating AGEs. A contrary view that has been proposed is that sRAGE may be a marker of tissue RAGE expression and represent disease activity [9]. The exact pathophysiological role of these soluble variants remains controversial and is a matter of active investigation. More recently, it has been shown that AGEs also activate intracellular pathways through Toll-like receptor-4 in addition to RAGE [10]. Figure 1 shows possible actions of major receptors as a result of interaction with AGEs during normal cellular homeostasis.

Dietary AGEs

Food and tobacco are two major environmental sources of AGEs. The dietary content of AGEs depends on the protein, lipid and carbohydrate content of the food as well as on the temperature and conditions of cooking, especially moisture. Animal-derived foods cooked at high temperature, for a prolonged time and under dry conditions have the highest content of AGEs [11]. Dietary sources of AGEs contain both highly reactive intermediate precursors such as carbonyl derivatives as well as terminal AGEs such as CML. The gastrointestinal absorption of dietary AGEs has been confirmed by the oral administration of double-labeled single-protein AGEs, with or without specific AGE inhibitors, such as aminoguani-

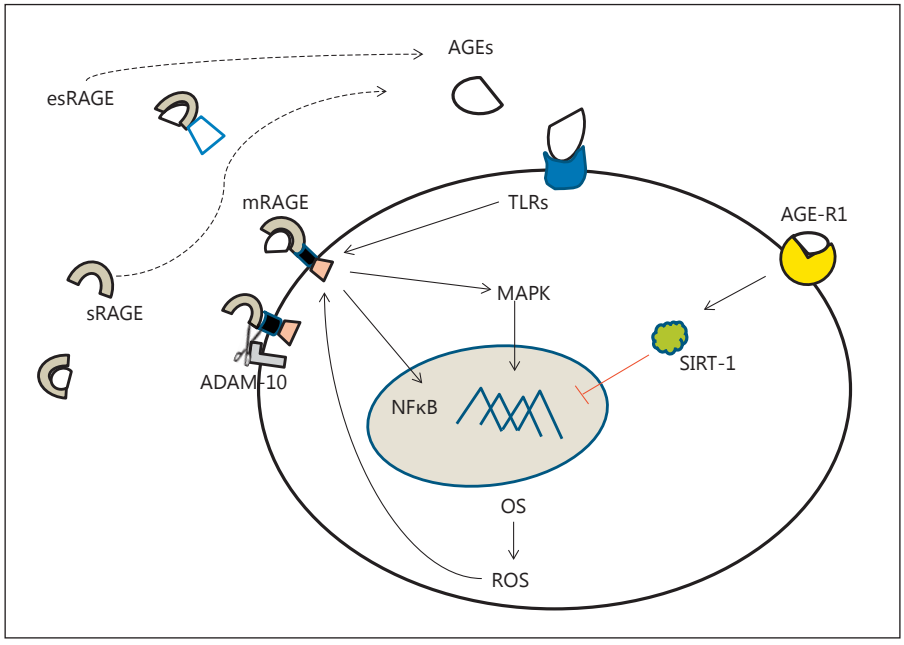

Fig. 1. AGEs and their major receptors. AGEs bind to mRAGE and cause activation of inflammatory pathways (MAPK, NFκB) or are endocytosed and cleared by AGE-R1. AGE-R1 activates sirtuins, a group of deacetylases that suppress NF-κB. ADAM-10 is a metalloprotease that cleaves mRAGE and releases it into the circulation as sRAGE. esRAGE is an alternatively spliced form that constitutes approximately 15% of the circulating RAGE pool. TLR-4 is another receptor implicated in mediating the action of AGEs. AGE-R1 = Advanced glycation end product receptor (OST-48); MAPK = mitogen-activated protein kinase; NFκB = nuclear factor κ light-chain enhancer of activated B cells; SIRT-1 = survival factor sirtuin 1; TLR = Toll-like receptor.

dine in rats, or the enrichment of low-AGE experimental diets with specific AGEs in mice [4, 12]. Chronic studies involving dietary AGE modification have also confirmed an association between dietary AGE burden and circulating AGE levels. An estimated 10% of ingested AGEs are absorbed into the circulation and about 70% of those absorbed are retained in the body and contribute to the AGE pool in the body, where they become indistinguishable from endogenous AGEs both structurally and functionally; kinetic studies in rats have shown that dietary AGEs are bioreactive molecules capable of covalently crosslinking tissue proteins and causing glycoxidative damage similar to glycotoxins produced endogenously [13]. AGEs are further metabolized by detoxifying enzymes such as glyoxalases in different tissues as well as excreted by the kidneys. Therefore, AGEs may accumulate with decreased availability of glyoxalases [14] or in conditions of decreased renal clearance.

In vitro Studies Linking AGEs and Metabolically Active Tissues

Adipose Cells

Incubation with AGEs prevented the differentiation of 3T3-L1 adipocytes, a commonly studied adipose cell line. In addition, the cells demonstrated a decreased glucose uptake activity and increased ROS in the presence of AGEs. Glucose uptake activity perturbation was reversed by blocking RAGE as well as by N-acetylcysteine, an antioxidant. This suggests that AGE action on glucose uptake is mediated by RAGE-generated intracellular OS. Furthermore, AGEs increased the expression of monocyte chemoattractant protein-1, an inflammatory marker involved in adipose tissue macrophage infiltration and IR [15].

Islet Cells

Incubation of two insulin-secreting cell lines (HIT-T15 and INS-1) with AGEs enhanced cell apoptosis and inhibited insulin secretion in cell culture models [16, 17]. It was also suggested that AGEs might bind to insulin and decrease its biologic activity. The apoptotic effects of AGEs were shown to be mediated via mitochondrial electron transport chain inhibition as well as the NADPH oxidase-mediated increase in ROS [17]. Further, studies in rat islets showed that RAGE blockade could reverse the apoptotic effects of AGEs, although the impact of AGEs on glucose-stimulated insulin secretion could not be reversed. Interestingly, the addition of glucagon-like peptide-1 reversed apoptosis and impaired glucose-stimulated insulin secretion in the islets, suggesting that it has a protective action against AGEs [18]. It is not known, however, if this glucagon-like peptide-1 effect is at the receptor-binding site or at a post-receptor level. This suggests that AGEs might act via different receptors to exert their actions on insulin secretion as well as apoptosis.

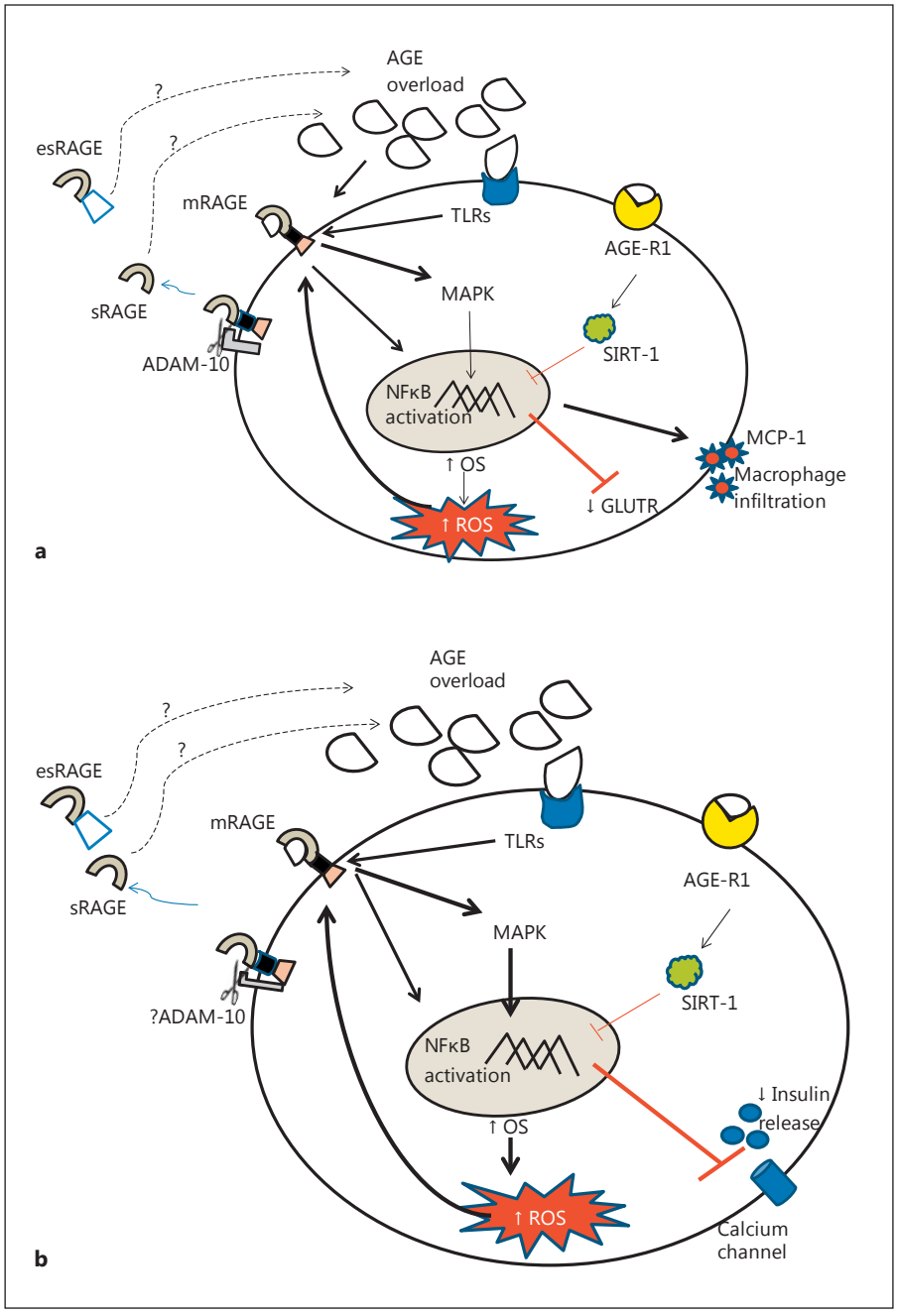

Fig. 2. Chronic AGE overload leads to increased mRAGE expression, leading to OS. In addition, the AGE-R1 level is decreased. This is manifested as increased macrophage infiltration and IR in the fat cell (**a**) and as decreased insulin secretion in the β cell (**b**). AGE-R1 = Advanced glycation end product receptor (OST-48); GLUTR = glutamyl-tRNA reductase; MAPK = mitogen-activated protein kinase; MCP-1 = monocyte chemoattractant protein-1; NFκB = nuclear factor κ light-chain enhancer of activated B cells; SIRT-1 = survival factor sirtuin 1; TLR = Toll-like receptor.

Hepatic Cells

The liver is a major clearing house for AGEs with 85% of intravenously injected AGEs being cleared by sinusoidal cells and Kupffer cells and less than 15% by hepatocytes. AGEs, on the contrary, impair the scavenger function of rat hepatic sinusoidal endothelial cells [19]. Furthermore, hepatic stellate cells are activated when exposed to triglyceraldehyde-derived AGEs and demonstrate an increased expression of RAGE as well as of genes involved in inflammation and fibrogenesis [20]. These findings, coupled with elevated levels of triglyceride-derived AGEs in patients with nonalcoholic steatohepatitis, suggest a role of AGEs in nonalcoholic steatohepatitis and cirrhosis of the liver [21]. In addition, AGEs may cause IR and upregulate inflammation [as evidenced by increased C-reactive protein levels (CRP)] in hepatocytes. Both of the

Table 1. Studies in various animal models assessing the impact of a lower dietary AGE intake

Animal	Animal model	Age at start	Intervention	Duration	Observed effects	Ref.
Mouse	db/db C57/BL-6J	Adult (4 weeks)	LAGE vs. HAGE chow 10-fold	20 weeks	Lower AGE levels, improved insulin sensitivity, glucose tolerance in the LAGE diet group, better preserved islet architecture	26
Mouse	C57BL6	Adult (6 weeks)	LAGE-HF vs. HAGE-HF diet 2.4-fold	6 months	HAGE-HF-fed mice were heavier, hyperinsulinemic and diabetic compared to the LAGE-HF or control diet	25
Mouse	NOD	Adult/neonatal	LAGE vs. HAGE 5-fold	44 weeks	LAGE diet decreased autoimmune diabetes 3-fold in F0 females and 5-fold in their first- and second-generation offspring when kept on a LAGE diet	31
Mouse	NOD, db/db mice	Adult	LAGE vs. HAGE 6-fold	4 or 11 months	LAGE diet mitigated DM nephropathy in both models, increased survival in NOD mice	29
Mouse	DM Apo $E^{-/-}$	Adult (6–8 weeks)	LAGE vs. HAGE 4-fold	2 months	Reduced atherosclerotic lesions with no change in lipids	27
Mouse	Apo $E^{-/-}$ with intimal injury	Adult (12 weeks)	HAGE vs. LAGE 10-fold followed by arterial injury	5 weeks	Decreased neointimal area, intima/media ratio, number of macrophages, lower AGE levels in blood and endothelial cells and macrophages in the neointimal lesions	28
Mice	C57/BL6J	Adult/F3 offspring	MG added to LAGE diet	18 months	Increased adiposity, AGE, leptin and insulin level, insulin resistance earlier in F3 vs. F0, decreased AGER-1 and SIRT-1 levels in adipose tissue, skeletal muscle and liver	32
Rats	Sprague-Dawley	Adult	Aminoguanidine after AGE albumin	Single dose	Aminoguanidine increased urinary excretion of AGEs and decreased AGE deposits in the kidney and liver	12

LAGE = Low AGE; HAGE = high AGE; HF = high fat; NOD = non-obese diabetic; F0, F1, F3 = successive generations; AGER-1 = advanced glycation end product receptor-1; SIRT-1 = survival factor sirtuin 1.

above effects are thought to be mediated by the activation of Rac-1 kinases followed by IκB kinase and c-Jun N-terminal kinase activation and downstream insulin receptor substrate-1 (IRS-1) serine phosphorylation in the hepatocyte and adjacent hepatic stellate cells [22].

Muscle Cells

Exposure of L6 skeletal muscle cells to human glycated albumin induced IR (decreased insulin-stimulated glucose uptake and decreased glycogen synthase activity) via protein kinase Cα-mediated serine and threonine phosphorylation of IRS-1 and IRS-2 [23].

Endothelial Cells

A study with human umbilical vein endothelial cells confirmed that food-derived AGEs induce significant tumor necrosis factor α activation as well as cell-oxidative and crosslink formation activities and that these actions are mediated by RAGE and non-receptor mechanisms [24].

Figure 2 demonstrates the hypothesized impact of AGE ligand excess in the fat cell (fig. 2a) and the β cell (fig. 2b) in the pathogenesis of cardiometabolic risk.

Experimental Studies Linking Dietary AGEs and Disease

Studies of various animal models of diabetes, atherosclerosis and kidney disease have demonstrated a negative impact of a high-AGE diet and benefits of dietary intervention with a low-AGE diet. For example, in both control C57/Bl-6 [25] and spontaneously diabetic db/db mice [26], restriction of AGE intake decreased serum AGE levels and improved insulin sensitivity. This suggests that dietary AGEs induce and exacerbate IR both under genetic and environmentally acquired conditions that predispose to IR. Furthermore, Lin et al. [27, 28] have shown that apolipoprotein-E-deficient mice develop atherosclerotic lesions in the presence and absence of diabetes when exposed to a high dietary AGE intake. Interestingly, the lesions decreased significantly by lowering of dietary AGEs, suggesting a link of dietary AGEs with atherosclerosis. Glycation of low-density lipoprotein cholesterol and endothelial dysfunction are some of the proposed mechanisms for AGE-mediated atherosclerosis.

Table 2. Human studies assessing the impact of AGEs on healthy subjects as well as various diseases

Study design	Humans	n	Age, years	Diet type; duration	Impact on chronic inflammation/disease	Ref.
Observational						
Cross-sectional	Healthy young and elderly	325	19–90		Dietary AGE intake and serum AGE levels correlate with CRP and mononuclear TNFα, VCAM-1 and isoprostane level	38
Cross-sectional	Adults with MS Adults without MS	130 137	49–75 52–85		Dietary AGE intake and CML level higher in those with MS compared to those without MS	39
Longitudinal	Healthy subjects	49			Change in AGE intake correlates with change in AGE level	38
Cross-sectional	Obese vs. lean children	18 obese 18 lean	5–10 4–17		CML and FL-AGE levels are lower in obese children despite worse CRP, IL-6 and HOMA-IR	36
Cross-sectional	Obese children	88 (51 male)	11–15		CML levels correlate inversely with waist z-score, IL-6 as well as isoprostane, TNFα and VCAM-1	37
Interventional						
Randomized parallel	Healthy	30	18–45, >60	Low AGE vs. standard diet; 4 months	↓ CML and RAGE expression, ↑ AGER-1	38
	CKD stage 3	9		Low AGE vs. standard diet; 4 months		
Nonrandomized one arm	Healthy	64	18–24	Heat-processed high AGE diet; 1 month	↓ CML, improved HOMA-IR	46
Crossover	DM	11	32–52	Low AGE vs. high AGE diet; 2 weeks	↓ Serum AGE levels corresponded with ↓ in dietary AGE	47
Randomized parallel	DM	13	~62	Low AGE vs. high AGE diet; 6 weeks	↑ TNFα and CRP on HAGE and ↓ on LAGE diet	47
Randomized parallel	T2DM	20	41–71	Single high and low AGE diet meal	↓ Endothelial dysfunction and reactive hyperemia impairment after LAGE diet, also lower markers of endothelial dysfunction and OS	49
Nonrandomized one arm	T2DM	13	51.3–62.5	Single high AGE meal	Endothelial dysfunction improved after benfotiamine treatment prior to a high-AGE meal	50

↑ = Increased; ↓ = decreased; CKD = chronic kidney disease; TNFα = tumor necrosis factor α; VCAM-1 = soluble vascular cell adhesion molecule-1; MS = metabolic syndrome; FL = fructose lysine; IL-6 = interleukin-6; HOMA-IR = homeostatic model assessment of insulin resistance.

A low-AGE diet prevented further progression of diabetic nephropathy in both db/db mice and high-fat-fed mice models [29], suggesting a pathogenic role of AGEs in renal dysfunction. This was further reinforced by the finding that a high-AGE diet administered for a 6-week period increased proteinuria in 5/6 nephrectomized rats [30].

Interestingly, in a model of autoimmune diabetes, when female non-obese diabetic mice were maintained on an AGE-restricted diet, the incidence of diabetes dropped from 90 to 30% with reduced insulitis and lower antigenic response [31]. It is possible that a low-AGE environment prevented the onset of type 1 DM (T1DM) possibly by decreasing the T-cell stimulus or by inhibiting direct β-cell damage. Furthermore, the impact of a dietary restriction of AGEs continued in the next two generations with the incidence of diabetes being less than 15% as long as the dams and their offspring were continued on the low-AGE diet. This suggests that avoidance of AGEs during critical developmental periods can prevent their detrimental effects. The preserved transgenerational protective effect of the restricted AGE intake points to a strong likelihood of reduced transplacental transfer of AGEs with involvement of an epigenetic mechanism. In another study, the F3 offspring of female mice fed an otherwise low-AGE diet supplemented with MG showed an earlier onset of adiposity and IR [32], further reinforcing the possibility of an epigenetic transmission of the effects of AGEs in offspring. The data from animal studies are summarized in table 1.

Human Studies Linking Dietary AGEs and Disease

Most studies assessing dietary AGEs have involved a modification of diet or supplementation with anti-AGE agents and have been performed in adults. Recently, a few studies have examined dietary AGEs in children either directly or indirectly by measuring receptors of AGEs, especially the soluble form. Table 2 presents a summary of observational and interventional studies of AGEs in children and adults.

Studies in Children/Adolescents

Dietary AGEs in Children

To date, there have been very few studies assessing AGEs in children/adolescents, and they have shown mixed results. A study of mother-infant pairs demonstrated a strong correlation of maternal levels of serum AGEs (represented by CML and MG) with those of the neonates. Further, the introduction of processed infant foods increased the dietary AGE consumption, which was also reflected in higher serum AGE levels in the infants. In addition, levels of serum AGEs correlated inversely with levels of adiponectin, an antiinflammatory adipokine in the infants [33]. A recent study by another research group confirmed differences in insulin sensitivity based on AGE levels in breastfed versus formula-fed infants, although these differences disappeared at follow-up at age 12–14 months [34]. Boor et al. [35] recently examined the interaction of AGEs in diet and RAGE gene polymorphisms in infants by comparing formula-fed and breastfed infants, although dietary AGE was not measured directly. Breastfed infants carrying the major allele of the –374A/T RAGE gene polymorphism were noted to be most insulin sensitive, while insulin sensitivity improved in formula-fed infants carrying the same major allele. Thus, they concluded that the –374A/T RAGE gene polymorphism impacted glucose metabolism and insulin sensitivity in a diet-dependent manner.

The above studies suggest a possible relationship of dietary AGEs and insulin sensitivity in infancy. Also, they raise important questions about the possible postnatal programming effects of AGEs when considered in conjunction with the animal studies discussed previously that span multiple generations [31, 32], although a causal effect cannot be yet established.

Observational Studies of Serum AGEs in Children

A study comparing obese and lean children showed lower serum AGE levels in children with obesity than in lean children despite their higher levels of CRP and interleukin-6 and comparable renal function. The authors suggested renal hyperfiltration of AGEs as a compensatory mechanism that might explain these results [36]. A similar negative correlation of CML with adiposity and inflammatory markers has been reported in a cross-sectional study of middle-school children with obesity [37]. These findings are contrary to those in adults [38, 39] and need further investigation for underlying mechanisms. An interesting explanation that has been suggested is trapping of AGEs in adipose-tissue macrophages, but this needs further confirmation.

Another study of population-based and twin cohorts of children with T1DM showed elevated serum CML levels to be a strong predictor of T1DM. Genetic model fitting suggested CML levels to be an environmentally acquired risk factor for diabetes [40]. These results combined with studies of animal models suggest an important role of AGEs in autoimmune diabetes that needs to be further investigated. Further, children and adolescents with type 2 DM (T2DM) [41] lose their β cells at a faster pace compared to adults [42] for reasons that are not yet clear. An important consequence to consider is the adverse impact of AGEs on the glucose metabolism in obese children predisposed to develop T2DM; dietary AGEs can provide a further hit to the already stressed β-cell burdened to produce extra insulin in order to compensate for the obesity-associated IR. Therefore, it would be important to study the effect of a low-AGE dietary intervention in this population as a potential approach to mitigate the epidemic of T2DM that threatens future generations.

AGE Receptor Variants in Children with Obesity

A common approach in previous studies has been to measure levels of circulating sRAGE instead of actual serum AGE levels and trying to correlate them with the severity of different diseases. An important problem here is that the exact role which these circulating forms of RAGE play in the AGE-RAGE axis remains elusive. A study of prepubertal children with obesity demonstrated a significant negative correlation of sRAGE and esRAGE levels with birth weight; children born small and large for gestational age had lower sRAGE and esRAGE levels compared to their appropriate for gestational age counterparts [43]. Whether these observations are related to genetic factors or point to an epigenetic phenomenon is yet to be determined. In addition, sRAGE and esRAGE had a negative correlation with IR independent of birth weight. Other studies in prepubertal obese children showed a significant negative correlation of sRAGE and

esRAGE levels with carotid intima-media thickness [44] as well as presence of hepatic steatosis, independent of body mass index [45]. In the previously mentioned study of middle-school children with obesity [37], the authors reported a significant negative correlation of sRAGE with adiposity and of both sRAGE and esRAGE with acute insulin response, which is consistent with observations in adults with diabetes.

Interventional Studies

Healthy adults habitually consuming 'high normal' dietary AGEs were randomized to either continuing their high intake of AGEs or to a low-AGE diet. Those on the low-AGE diet were noted to have significant reductions in circulating AGE levels after 4 months of intervention with a parallel decrease in markers of OS and inflammation. Of note, there were no changes in energy or nutrient consumption during the study [38]. In another trial of 62 healthy adults, utilizing a randomized crossover design with two diets, one with a high amount of Maillard reaction products (MRPs) and another milder diet incorporating steam-based cooking, Birlouez-Aragon et al. [46] demonstrated a decrease in insulin sensitivity but an increase in triglycerides and cholesterol after 1 month on the high-MRP diet. While CML levels correlated strongly with cholesterol and triglycerides, they did not correlate with insulin sensitivity, suggesting a possible involvement of other MRPs.

Studies in patients with DM have also shown a significant decrease in CRP, vascular cell adhesion molecule-1 and AGE levels as early as after 6 weeks [47] as well as a decrease in IR after 4 months of intervention with a low-AGE diet [48]. In addition, in patients with T2DM, a low-AGE meal was noted to be associated with less impairment of macrovascular and microvascular endothelial function than a similar meal enriched with AGEs by cooking with heat [49]. Interestingly, pretreatment with benfotiamine (a liposoluble vitamin B1) prevented the increase in serum levels of AGEs and markers of OS as well as endothelial dysfunction associated with a high-AGE diet in diabetic patients [50].

Interventional Studies in Children

A recent study in prepubertal obese children with hepatic steatosis demonstrated an increase in esRAGE levels in response to a daily supplementation with 600 mg of vitamin E [51]. Serum or dietary AGE levels were not measured in this study. Future studies will be needed to elucidate the mechanism underlying the improved esRAGE level in response to vitamin E and its significance in the pathogenesis of hepatic steatosis. As mentioned previously, although not interventional in design, studies by Mericq et al. [33] and Boor et al. [35] have suggested effects of RAGE polymorphisms and AGEs in the diet on the glucose metabolism in infants.

The above studies suggest that circulating AGEs and RAGE variants are perhaps affected by both genetic and environmental factors and may be markers of cardiometabolic disease risk. One interesting possibility that has not been studied so far is that AGEs derived from the diet may contribute to the changes in levels of circulating RAGE variants since AGEs stimulate RAGE directly. These studies further support the hypothesis that AGE-RAGE axis alterations occur in early childhood, although many issues remain undefined.

Conclusions

In summary, we believe there are enough data suggesting a role for dietary AGEs in inducing low-grade chronic inflammation, OS, IR and vascular dysfunction in adults, although similar studies in younger populations are lacking. In view of the rising incidence of obesity and the associated comorbidities of DM and CVD in children and the potential role of AGEs in adiposity and β-cell damage, further studies to help define whether dietary AGEs play a similar role in children and adolescents are definitely warranted. Several research gaps remain to be addressed. Given the challenges of recruitment in children and the sample size needed, a collaborative multicenter effort by investigators interested in studying this field can provide a useful strategy towards achieving meaningful results with the following common goals: (1) to characterize the response of serum AGE levels to dietary AGE intake in healthy and obese children; (2) to determine if serum AGEs are associated with measures of inflammation or IR in children with obesity independent of energy intake as they are in adults; (3) to investigate if general dietary counseling practices adequately modify dietary AGE content and intake in this population as previously shown in adults; (4) to study the impact of changes in other antioxidant nutrients on AGE levels, and finally (5) to clearly define the relationship between AGE levels in the diet and serum and RAGE variants including sRAGE, esRAGE and RAGE at a cellular level as well as RAGE gene polymorphisms in children, both healthy and those with obesity.

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References

1 Olshansky SJ, Passaro DJ, Hershow RC, Layden J, Carnes BA, Brody J, Hayflick L, Butler RN, Allison DB, Ludwig DS: A potential decline in life expectancy in the United States in the 21st century. New Engl J Med 2005;352:1138–1145.
2 Berenson GS, Wattigney WA, Tracy RE, Newman WP 3rd, Srinivasan SR, Webber LS, Dalferes ER Jr, Strong JP: Atherosclerosis of the aorta and coronary arteries and cardiovascular risk factors in persons aged 6–30 years and studied at necropsy (the Bogalusa Heart Study). Am J Cardiol 1992;70:851–858.
3 Yan SF, Ramsamy R, Schmidt AM: The RAGE axis: a fundamental mechanism signaling danger to the vulnerable vasculature. Circ Res 2010;106:842–853.
4 Cai W, He JC, Zhu L, Chen X, Striker GE, Vlassara H: AGE-receptor-1 counteracts cellular oxidant stress induced by AGEs via negative regulation of p66shc-dependent FKHRL1 phosphorylation. Am J Physiol Cell Physiol 2008;294:C145–C152.
5 Kalea AZ, Schmidt AM, Hudson BI: RAGE: a novel biological and genetic marker for vascular disease. Clin Sci (Lond) 2009;116:621–637.
6 Park L, Raman KG, Lee KJ, Lu Y, Ferran LJ Jr, Chow WS, Stern D, Schmidt AM: Suppression of accelerated diabetic atherosclerosis by the soluble receptor for advanced glycation endproducts. Nat Med 1998;4:1025–1031.
7 Bucciarelli LG, Wendt T, Qu W, Lu Y, Lalla E, Rong LL, Goova MT, Moser B, Kislinger T, Lee DC, Kashyap Y, Stern DM, Schmidt AM: RAGE blockade stabilizes established atherosclerosis in diabetic apolipoprotein E-null mice. Circulation 2002;106:2827–2835.
8 Barile GR, Pachydaki SI, Tari SR, Lee SE, Donmoyer CM, Ma W, Rong LL, Buciarelli LG, Wendt T, Horig H, Hudson BI, Qu W, Weinberg AD, Yan SF, Schmidt AM: The RAGE axis in early diabetic retinopathy. Invest Ophthalmol Vis Sci 2005;46:2916–2924.
9 Yamagishi S, Matsui T: Soluble form of a receptor for advanced glycation end products (sRAGE) as a biomarker. Front Biosci (Elite Ed) 2010;2:1184–1195.
10 Chen YJ, Sheu ML, Tsai KS, Yang RS, Liu SH: Advanced glycation end products induce peroxisome proliferator-activated receptor γ down-regulation-related inflammatory signals in human chondrocytes via Toll-like receptor-4 and receptor for advanced glycation end products. PLoS One 2013;8:e66611.
11 Goldberg T, Cai W, Peppa M, Dardaine V, Uribarri J, Vlassara H: Advanced glycoxidation end products in commonly consumed foods. J Am Diet Assoc 2004;104:1287–1291.
12 He C, Sabol J, Mitsuhashi T, Vlassara H: Dietary glycotoxins: inhibition of reactive products by aminoguanidine facilitates renal clearance and reduces tissue sequestration. Diabetes 1999;48:1308–1315.
13 Koschinsky T, He CJ, Mitsuhashi T, Bucala R, Liu C, Buenting C, Heitmann K, Vlassara H: Orally absorbed reactive glycation products (glycotoxins): an environmental risk factor in diabetic nephropathy. Proc Natl Acad Sci USA 1997;94:6474–6479.
14 Wu JC, Li XH, Peng YD, Wang JB, Tang JF, Wang YF: Association of two glyoxalase I gene polymorphisms with nephropathy and retinopathy in type 2 diabetes. J Endocrinol Invest 2011;34:e343–e348.
15 Unoki H, Bujo H, Yamagishi S, Takeuchi M, Imaizumi T, Saito Y: Advanced glycation end products attenuate cellular insulin sensitivity by increasing the generation of intracellular reactive oxygen species in adipocytes. Diabetes Res Clin Pract 2007;76:236–244.
16 Luciano Viviani G, Puddu A, Sacchi G, Garuti A, Storace D, Durante A, Monacelli F, Odetti P: Glycated fetal calf serum affects the viability of an insulin-secreting cell line in vitro. Metabolism 2008;57:163–169.
17 Lin N, Zhang H, Su Q: Advanced glycation end-products induce injury to pancreatic β cells through oxidative stress. Diabetes Metab 2012;38:250–257.
18 Puddu A, Storace D, Durante A, Odetti P, Viviani GL: Glucagon-like peptide-1 counteracts the detrimental effects of advanced glycation end-products in the pancreatic β cell line HIT-T 15. Biochem Biophys Res Commun 2010;398:462–466.
19 Hansen B, Svistounov D, Olsen R, Nagai R, Horiuchi S, Smedsrød B: Advanced glycation end products impair the scavenger function of rat hepatic sinusoidal endothelial cells. Diabetologia 2002;45:1379–1388.
20 Fehrenbach H, Weiskirchen R, Kasper M, Gressner AM: Up-regulated expression of the receptor for advanced glycation end products in cultured rat hepatic stellate cells during trans-differentiation to myofibroblasts. Hepatology 2001;34:943–952.
21 Hyogo H, Yamagishi S, Iwamoto K, Arihiro K, Takeuchi M, Sato T, Ochi H, Nonaka M, Nabeshima Y, Inoue M, Ishitobi T, Chayama K, Tazuma S: Elevated levels of serum advanced glycation end products in patients with non-alcoholic steatohepatitis. J Gastroenterol Hepatol 2007;22:1112–1119.
22 Hyogo H, Yamagishi H: Advanced glycation end products (AGEs) and their involvement in liver disease. Curr Pharm Des 2008;14:969–972.
23 Miele C, Riboulet A, Maitan MA, Oriente F, Romano C, Formisano P, Giudicelli J, Beguinot F, Van Obberghen E: Human glycated albumin affects glucose metabolism in L6 skeletal muscle cells by impairing insulin-induced insulin receptor substrate (IRS) signaling through a protein kinase C α-mediated mechanism. J Biol Chem 2003;278:47376–47387.
24 Cai W, Gao QD, Zhu L, Peppa M, He C, Vlassara H: Oxidative stress-inducing carbonyl compounds from common foods: novel mediators of cellular dysfunction. Mol Med 2002;8:337–346.
25 Sandu O, Song K, Cai W, Zheng F, Uribarri J, Vlassara H: Insulin resistance and type 2 diabetes in high-fat-fed mice are linked to high glycotoxin intake. Diabetes 2005;54:2314–2319.
26 Hofmann SM, Dong HJ, Li Z, Cai W, Altomonte J, Thung SN, Zeng F, Fisher EA, Vlassara H: Improved insulin sensitivity is associated with restricted intake of dietary glycoxidation products in the db/db mouse. Diabetes 2002;51:2082–2089.
27 Lin RY, Choudhury RP, Cai WJ, Lu M, Fallon JT, Fisher EA, et al: Dietary glycotoxins promote diabetic atherosclerosis in apolipoprotein E-deficient mice. Atherosclerosis 2003;168:213–220.
28 Lin RY, Reis ED, Dore AT, Lu M, Ghodsi N, Fallon JT, Fisher EA, Vlassara H: Lowering of dietary advanced glycation endproducts (AGE) reduces neointimal formation after arterial injury in genetically hypercholesterolemic mice. Atherosclerosis 2002;163:303–311.
29 Zheng F, He CJ, Cai WJ, Hattori M, Steffes M, Vlassara H: Prevention of diabetic nephropathy in mice by a diet low in glycoxidation products. Diabetes Metab Res Rev 2002;18:224–237.

30 Sebekova K, Fais V, Hofmann T, Schinzel R, Heidland A: Effects of a diet rich in advanced glycation end products in the rat remnant kidney model. Am J Kidney Dis 2003;41:S48–S51.
31 Peppa M, He C, Hattori M, McEvoy R, Zheng F, Vlassara H: Fetal or neonatal low-glycotoxin environment prevents autoimmune diabetes in NOD mice. Diabetes 2003;52:1441–1448.
32 Cai WJ, Ramdas M, Zhu Li, Chen X, Striker GE, Vlassara H: Oral advanced glycation endproducts (AGEs) promote insulin resistance and diabetes by depleting the antioxidant defenses AGE receptor-1 and sirtuin-1. Proc Natl Acad Sci USA 2012;109:15888–15893.
33 Mericq V, Piccardo C, Cai W, Chen X, Zhu L, Striker GE, Vlassara H, Uribarri J: Maternally transmitted and food-derived glycotoxins: a factor preconditioning the young to diabetes? Diabetes Care 2010;33:2232–2237.
34 Klenovics KS, Boor P, Somoza V, Celec P, Fogliano V, Sebekova K: Advanced glycation end products in infant formulas do not contribute to insulin resistance associated with their consumption. PLoS One 2013;8:e53056.
35 Boor P, Celec P, Klenovicsová K, Vlková B, Szemes T, Minárik G, Turna J, Sebeková K: Association of biochemical parameters and RAGE gene polymorphisms in healthy infants and their mothers. Clin Chim Acta 2010;411:1034–1040.
36 Sebekova K, Somoza V, Jarcuskova M, Heidland A, Podracka L: Plasma advanced glycation end products are decreased in obese children compared with lean controls. Int J Pediatr Obes 2009;4:112–118.
37 Accacha S, Rosenfeld W, Jacobson A, Michel L, Schnurr FJ, Shelov S, Ten S, Boucher-Berry C, Carey DE, Speiser PW, Lowell B, Conroy R, Klein M, Fennoy I, Rapaport R, Rosenbaum M: Plasma advanced glycation end products (AGEs), receptors for AGEs and their correlation with inflammatory markers in middle school-age children. Horm Res Paediatr 2013;80:318–327.
38 Vlassara H, Cai W, Goodman S, Pyzik R, Yong A, Chen X, Zhu L, Neade T, Beeri M, Silverman JM, Ferrucci L, Tansman L, Striker GE, Uribarri J: Protection against loss of innate defenses in adulthood by low advanced glycation end products (AGE) intake: role of the antiinflammatory AGE receptor-1. J Clin Endocrinol Metab 2009;94:4483–4491.
39 Uribarri J, Cai W, Woodward M, Tripp E, Goldberg L, Pyzik R, Yee K, Tansman L, Chen X, Mani V, Fayad ZA, Vlassara H: Elevated serum advanced glycation endproducts in obese indicate risk for the metabolic syndrome: a link between healthy and unhealthy obesity? J Clin Endocrinol Metab 2015;100:1957–1966.
40 Beyan H, Riese H, Hawa MI, Beretta G, Davidson HW, Hutton JC, Burger H, Schlosser M, Snieder H, Boehm BO, Leslie RD: Glycotoxin and autoantibodies are additive environmentally determined predictors of type 1 diabetes: a twin and population study. Diabetes 2012;61:1192–1198.
41 TODAY Study Group: Effects of metformin, metformin plus rosiglitazone, and metformin plus lifestyle on insulin sensitivity and β-cell function in TODAY. Diabetes Care 2013;36:1749–1757.
42 UK Prospective Diabetes Study (UKPDS) Group: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837–853.
43 de Giorgis T, D'Adamo E, Giannini C, Chiavaroli V, Scarinci A, Verrotti A, Chiarelli F, Mohn A: Could receptors for advanced glycation end products be considered cardiovascular risk markers in obese children? Antioxid Redox Signal 2012;17:187–191.
44 Chiavaroli V, D'Adamo E, Giannini C, de Giorgis T, De Marco S, Chiarelli F, Mohn A: Serum levels of receptors for advanced glycation end products in normal-weight and obese children born small and large for gestational age. Diabetes Care 2012;35:1361–1363.
45 D'Adamo E, Giannini C, Chiavaroli V, de Giorgis T, Verrotti A, Chiarelli F, Mohn A: What is the significance of soluble and endogenous secretory receptor for advanced glycation end products in liver steatosis in obese prepubertal children? Antioxid Redox Signal 2011;14:1167–1172.
46 Birlouez-Aragon I, Saavedra G, Tessier FJ, Galinier A, Ait-Ameur L, Lacoste F, Niamba CN, Alt N, Somoza V, Lecerf JM: A diet based on high heat treated foods promotes risk factors for DM and CVD. Am J Clin Nutr 2010;91:1220–1226.
47 Vlassara H, Cai W, Crandall J, Goldberg T, Oberstein R, Dardaine V, Rayfield EJ: Inflammatory mediators are induced by dietary glycotoxins, a major risk factor for diabetic angiopathy. Proc Natl Acad Sci USA 2002;99:15596–15601.
48 Uribarri J, Cai W, Ramdas M, Goodman S, Pyzik R, Chen X, Zhu L, Striker GE, Vlassara H: Restriction of advanced glycation end products improves insulin resistance in human type 2 diabetes: potential role of AGER1 and SIRT1. Diabetes Care 2011;34:1610–1616.
49 Negrean M, Stirban A, Stratmann B, Gawlowski T, Horstmann T, Götting C, Kleesiek K, Mueller-Roesel M, Koschinsky T, Uribarri J, Vlassara H, Tschoepe D: Effects of low- and high-advanced glycation endproduct meals on macro- and microvascular endothelial function and oxidative stress in patients with type 2 diabetes mellitus. Am J Clin Nutr 2007;85:1236–1243.
50 Stirban A, Negrean M, Stratmann B, Gawlowski T, Horstmann T, Götting C, Kleesiek K, Mueller-Roesel M, Koschinsky T, Uribarri J, Vlassara H, Tschoepe D: Benfotiamine prevents macro- and microvascular endothelial dysfunction and oxidative stress following a meal rich in advanced glycation end products in individuals with type 2 diabetes. Diabetes Care 2006;29:2064–2071.
51 D'Adamo E, Marcovecchio ML, Giannini C, de Giorgis T, Chiavaroli V, Chiarelli F, Mohn A: Improved oxidative stress and cardio-metabolic status in obese prepubertal children with liver steatosis treated with lifestyle combined with vitamin E. Free Radic Res 2013;47:146–153.