Review

Dietary advanced glycation endproducts (AGEs) and their health effects – PRO

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Thermal processing of food results in the formation of various novel compounds, among others advanced glycation endproducts (AGEs). AGEs result from nonenzymatic glycation reactions between reducing sugars and free amino groups of proteins, peptides, or amino acids. Due to their potential noxious effects, alimentary AGEs are also called glycotoxins. This review provides a summary of the available evidence on the health effects of exaggerated intake of thermally treated food. Data from experimental studies in rodents and from clinical studies in healthy volunteers and in patients suffering from selected diseases in which AGEs are of pathogenetic importance (diabetes, chronic renal failure) are summarized. It is concluded that, an exaggerated intake of thermally processed foods may exert *in vivo* diabetogenic and nephrotoxic effects, induce low-grade inflammation, enhance oxidative stress, and promote atherosclerosis.

Keywords: Advanced glycation endproducts / Chronic renal insufficiency / CML / Diabetes / Proteinuria

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This article focuses on pro arguments about "Dietary AGEs are a risk to human health".
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1 Introduction

Thermal processing of food leads to the formation of various novel compounds. Among these, heterocyclic amines, acrylamide, and advanced glycation endproducts (AGEs) are well-known compounds hypothesized to cause harmful health effects. Recently, it has been demonstrated, that AGEs are at least partially absorbed into circulation [1]. Several lines of evidence favor the concept that exaggerated intake of thermally processed food might induce pathogenic pathways, or aggravate a pre-existing pathology, *in vivo*. In this paper, data from experimental and clinical studies supporting the potential deleterious effects of the intake of thermally modified diets are reviewed.

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Abbreviations: AGEs, advanced glycation endproducts; **BC,** bread crusts; **CML,** N^{ε}**-carboxymethyllysine; CRI,** chronic renal insufficiency; **HA,** high-AGE; **HF,** high fat; **MG,** methylglyoxal; **NOD,** non-obese diabetic; **TGF-β_1,** transforming growth factor β_1; **VCAM-1,** vascular cell adhesion molecule-1

2 Effects of exaggerated intake of thermally processed food in health

Observed deleterious effects of high-AGE diets on health in healthy animals or human studies are summarized in Table 1.

2.1 Animal studies

Two studies are reviewed. In the first one, male Wistar rats were pair-fed during 6 wk with AGEs-poor (content: 50% w/w commercial rat food Altromin, 25% w/w wheat starch, 23% w/w casein, 2% w/w cellulose) or AGEs rich diet (BC, wheat starch replaced by bread crusts [2, 3]. Average daily intake of AGE-N^{ε}-carboxymethyllysine (CML) in BC diet was about 11 mg/kg body weight/day, while in the AGEs-poor diet, CML contents were below the LOD (analyzed by GS-MS method) [4]. Consumption of BC diet resulted in increase of plasma levels of CML (by 32.9%), carboxyethyllysine (CEL, by 24.5%) (GS-MS method, both) and

Table 1. Biological effects of exaggerated intake of highly thermally processed food

Effects	Health effect			Diabetes effect			CRI effect		
	Slight	Moderate	Intense	Slight	Moderate	Intense	Slight	Moderate	Intense
Metabolic effects									
Gain in body weight	A[5], H[6]	A[3]			A[12]			A[3]	
Gain in organ weight		A[3]					A[3]		
Diabetogenic effects	H[6,7,8]		A[5]	H[17]	A[12]				
Potentiation of inflammation	H[7,8]			A[15,16,] H[17]					
Enhanced oxidative stress		A[4]	A[5]				A[4]	A[19]	
Nephrotoxic effects									
Proteinuria	H[6]	A[3]			A[14,15]	A[13]		A[19]	A[3]
Renal pathology	A[3]					A[13]		A[3]	A[19]
Potentiation of diabetic complications									
Delayed wound healing					A[15]				
Atherogenic effects				A[16]					
Vascular dysfunction					H[18]				
Other effects in diabetes									
Higher incidence of diabetes						A[14]			
Shorter survival					A[14]	A[13]			
Pathology of pancreas				A[12]		A[14]			

A, Effects observed in experimental studies on rodents; H, effects observed in clinical studies; numbers refer to citations.

pentosidine (by 82.4%, $p < 0.01$, HPLC method), and significantly higher renal excretion of CML if compared with the group on AGE-poor diet [4]. Rats on BC diet gained more weight, without changes in glycemia, albuminemia, or lipid profile. Moreover, their kidney, heart, liver, and lung weight was higher, while that of spleen, intestine, and brain remained unaffected. BC fed animals showed signs of increased lipid peroxidation, as reflected by higher plasma levels and kidney content of malondialdehyde–lysine [4]. Nephrotoxic effects of BC diet was reflected by increased proteinuria (1.8-fold, $p < 0.05$) and urinary excretion of transforming growth factor β_1 (TGF-β_1, the most prominent profibrotic cytokine, 3.1-fold), while plasma creatinine and urea levels and creatinine clearance remained unaffected [3].

In the different study, C57/BL6 mice were fed with an isocaloric high fat (HF, 35% w/w, PicoLab Rodent diet D12492, Purina Mills, St. Luis, USA) either low AGEs (LA, 329.6 U AGEs/mg), or HF high-AGE diet (HA, 995.4 U AGE/mg, obtained by heating at 120°C/30 min) for a total period of 6 months. Daily food consumption was comparable throughout the study. Plasma AGE levels reached in the HF–HA animals concentrations 1.5-times higher ($p < 0.01$) than in the HF–LA counterparts. HF–HA group gained significantly more weight, and the amount of visceral fat as well as its AGE-content was approximately 50% higher than in the HF–LA group (both $p < 0.01$). Contrary to HF-LA group, HF–HA animals developed diabetes: they had two-fold higher fasting glucose ($p < 0.01$) and seven-fold higher fasting insulin ($p < 0.01$) levels; and displayed markedly impaired glucose and insulin responses during intravenous glucose tolerance test, euglycemic and hyperglycemic clamps. Plasma 8-isoprostane (marker of lipid peroxidation) was also higher ($p < 0.01$) [5].

2.2 Human studies

In a crossover study, 21 healthy volunteers consumed either heated or unheated high protein (3 g/kg/day) diet, 1 wk each, with 1 wk wash-out period. Both diets were comparable in regard of energy, protein, and carbohydrate intake. In the heated diet daily intake of CML was estimated to vary between 51–66 mg and that of fructoselysine (Fl) to 839–1012 mg. In the unheated diet, CML daily intake was negligible and that of Fl was about seven-times lower. If compared with baseline, fasting serum CML levels (determined by ELISA with monoclonal antibodies, Roche diagnostics, Penzberg, Germany) and its urinary excretion increased significantly on high-AGE diet. On high-AGE diet volunteers gained more weight, and impairment in insulin sensitivity was observed (higher plasma fasting insulin levels without changes in glycemia). Renal effects comprised significant rise in albumin excretion rate. However, it is to be noticed that a marked increase in proteinuria to microalbuminuric range was recorded in only about 1/3 of the volunteers, while in the 1/3 negligible changes within the normal range were recorded. This effect was independent of blood pressure [6].

In a different study, the association between mean daily alimentary AGEs intake (calculated on the basis of 3 days

food records) to serum AGE levels, indicators of microinflammation and insulin resistance was investigated in 90 healthy subjects. Mean daily dietary AGEs intake correlated with (i) plasma AGE levels ($r = 0.40$, $p < 0.007$); (ii) plasma AGE-modified low density lipoprotein apo B concentration ($r = 0.44$, $p < 0.01$), fasting insulin concentration ($r = 0.33$, $p < 0.03$), and high sensitive C-reactive protein levels ($r = 0.36$, $p < 0.02$) [7, 8].

3 Effects of exaggerated intake of thermally processed food on the progression of diabetes mellitus (DM) and chronic renal insufficiency (CRI)

DM and CRI are characterized by an accumulation of AGEs in body fluids and tissues. This rise in AGE levels is of pathogenic importance in development and progression of both diseases (for review see ref. [9, 10]). Except for endogenous mechanisms leading to enhanced AGEs formation (persisting hyperglycemia, enhanced oxidative and carbonyl stress, decreased renal function), dietary intake of food-derived AGEs has to be taken into account. In the mentioned diseases, AGEs-induced pathology results also from the interaction of AGEs with their specific receptors on cells, from among which the receptor for AGEs – RAGE (proatherogenic and proinflammatory receptor) seems to be of crucial importance [11]. Expression of RAGE is low in homeostatsis, but increases dramatically in tissues where AGEs accumulate. This condition may render enhanced vulnerability of tissues to dietary AGEs.

3.1 Diabetes

Biological effects of high dietary intake of thermally modified food in diabetes are summarized in Table 1.

3.1.1 Animal studies

In insulin resistant db/db mice (model of type 2 diabetes) fed for 20 wk with either high-AGE (PicoLab rodent diet 20, Labdiet, Purina Mills; AGE content: 718.5 U/mg, determined by ELISA using 4G9 mAb) or low-AGE diet (AIN-93G, Bio-Serv, Frenchtown, USA, 209.7 U AGEs/mg), representing 3.4-fold difference in AGE content. High-AGE diet intake resulted in higher plasma AGE levels (2.1-fold, $p < 0.05$) and higher body weight gain ($p < 0.005$). The progression of diabetes was aggravated in high-AGE diet group, as reflected by higher fasting insulin concentration ($p < 0.05$), lower glucose and insulin tolerance ($p < 0.05$), and increase in total and HDL-cholesterol levels ($p < 0.0001$). Proteinuria increased (1.9-fold *vs.* low-AGE diet), but statistical significance was not reached, due to high interindividual variability [12].

Furthermore, effects of the high-AGE diet on the development of diabetic nephropathy was investigated in type 1 (nonobese diabetic, NOD) and type 2 (db/db, $^{+}/^{+}$) diabetic mice. High-AGE diet was prepared by heating (100°C for 20–60 s and 125°C for 20–30 min) of AIN-93G standard chow (Bio-Serv), while the identical chow not subjected to the second step of heat exposure represented the low AGE diet. Composition of the diet (total calories: 3.9 kcal/g, 18.4% proteins, 7.2% lipids, 58.6% carbohydrate, 15.8% fiber and moisture, as well as the content of micronutrients) met the daily requirements. Diets differed six-fold in AGEs (determined by ELISA using monoclonal anti-AGE-KHL antibody 4G9 reactive with CML, Alteon, Northvale, USA) and five-fold in methylglyoxal (MG, ELISA, by mAb) content, and were administered for 4 or 14 months. Plasma AGEs concentration, urinary excretion, and kidney tissue AGEs were significantly higher in high-AGE fed animals. In both studies, the high-AGE diet aggravated diabetic nephropathy, as reflected by higher protein excretion ($p < 0.05$), glomerular hypertrophy ($p < 0.05$), mesangial expansion ($p < 0.05$), and estimated fractional mesangial volume ($p < 0.01$). Renal cortex showed higher expression of TGF-β1 ($p < 0.05$) and laminin mRNA ($p < 0.01$) in NOD mice, as well as higher TGF-β1 ($p < 0.05$) and α1 type collagen ($p < 0.01$) mRNA levels in db/db mice. Consistently with mRNA changes, increased glomerular laminin B1 and α1 type collagen expression was confirmed by immunofluorescent microscopy [13].

Different studies addressed the question whether the incidence of diabetes and survival of diabetic NOD mice is influenced by an early exposure to a high-AGE-diet. This was prepared by additional heating of standard mice chow (AIN-93G, Bio-Serv) at 125°C for 20–30 min, resulting in five-fold higher CML-like AGEs and 4.5-fold higher MG content. Comparable food intake resulted in higher plasma AGE levels and their urinary excretion in high-AGE diet group. Feeding of the high-AGE diet markedly influenced the cumulative incidence of diabetes: during 56 wk 94% mice on high-AGE diet developed diabetes, but only 33% in low-AGE diet group ($p < 0.0001$). Moreover, in the first and second generation of offsprings from mothers fed with high- *versus* low-AGE diet, cumulative incidence of diabetes represented 61 *vs.* 14% and 62 *vs.* 13%, respectively. Moreover, onset of the disease was delayed in low-AGE diet group (4-month lag time). High-AGE diet consumption resulted in a shorter survival of diabetic mice: none of high-AGE diet assigned mice survived beyond 44 wk, while 76% of animals on low-AGE diet was alive up to 56 wk ($p < 0.0001$). In high-AGE diet fed mice, higher fasting plasma glucose and insulin concentration with impaired glycemic response to intravenous glucose tolerance test was observed. This was associated with severe inflammatory infiltration in pancreata, marked rise in total number of pancreatic lymphocytes (pLy) ($p < 0.001$) and CD4+ pLy ($p < 0.0001$). Moreover, cytokine profile of CD4+ pLy differed between the groups as well: high-AGE diet group displayed higher proportion of positivity for INF-γ and lower for IL-4

($p < 0.009$ both). PLy from high-AGE-fed mice showed a greater proliferative response to insulin ($p < 0.005$) [14].

Feeding of a high-AGE diet was also shown to influence the development of complications of diabetes, such as (i) wound healing, or (ii) atherosclerosis.

(i) Insulin resistant db/db ($^{+}/^{+}$) mice were assigned either to high-AGE (autoclavable PicoLab rodent diet heated for 30 min at 121.5°C) or same untreated low-AGE diet, yielding a five-fold difference in CML and MG content [15]. High-AGE diet animals exhibited higher plasma CML and MG levels (independently of glycemia), and deterioration of renal function, as reflected by decreased urinary CML and MG excretion and higher albumin excretion rate. To study the course of wound healing, full thickness skin incision was induced. Mice consuming a high-AGE diet exhibited higher AGE skin deposits, decreased epithelisation, angiogenesis, inflammation, granular tissue deposition as well as decreased collagen organization compared with low-AGE group. While re-epitelisation was the dominant mode of wound healing in high-AGE mice, wound contraction prevailed in the low-AGE group. Thus, intake of high amounts of strong heated foods significantly alters the time and quality of wound healing in db/db $^{+}/^{+}$ diabetic mice model [15].

(ii) Effects of dietary AGEs on the development of atherosclerotic lesions in the aorta was studied in genetically hypercholesterolemic apolipoprotein E-deficient (apoE$^{-}/^{-}$) mice with streptozotocin (STZ)-induced diabetes. Mice were fed either a high- or a low-AGE diet (AIN-93G, Bioserve, Frenchtown, USA: 18% protein, 58% carbohydrate, 7.5% fat, 3.73 kcal/g). Both diets were heated at 100°C for 20 s, while high-AGE diet was additionally subjected to 125°C for 30 min, resulting in approximately five-fold difference in AGEs (CML: 2700 ± 830 AGE U/mg *vs.* 12500 ± 700; MG: 2.5 ± 0.32 nmol/mg *vs.* 0.65 ± 0.07) [16]. After processing, vitamin content in both diets was in excess of daily requirements. After a feeding period of 2 months, animals on the high-AGE diet displayed two-fold higher plasma AGE levels than the low-AGE group, while glycemia and dislipidemia remained unaffected. Atherosclerotic lesions at the aortic root of the high-AGE fed animals were 50% bigger than in the corresponding low-AGE group. Lesions in the high-AGE fed animals exhibited significantly higher degree of tissue AGE accumulation (within macrophages, foam cells, endothelial, and smooth muscle cells), enhanced AGE-receptor-1,2 and RAGE expression, higher number of inflammatory cells, and higher tissue staining for vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and monocyte chemoattractant protein-1 (MCP-1) [16].

3.1.2 Human studies

Studies on diabetic patients assigned to consume diets with similar content of calories, proteins, carbohydrate, and fat, but differing five-fold in the AGE content (assessed by ELISA using 4G7 mAb), revealed that high-AGE diet intake resulted in significantly higher plasma AGE levels (MG, AGE-modified LDL), as well as inflammatory marker-plasma CRP, and mediators of vascular dysfunction: plasma VCAM-1 concentration and TNF-α mRNA expression in monocytes [17]. Thus, in type 2 diabetic patients, the effects of AGE-rich meal on acute vascular dysfunction, as quantified by decreased flow-mediated vasodilation (FMD) of the brachial artery, was investigated. In a cross-over study with single meal differing 5.5-fold in AGE content, high-AGE meal induced more profound and longer lasting impairment in FMD (changes at 2, 4, and 6 h *vs.* baseline: $-30^{*,+}$, $-46^{*,+}$, $-21\%^{*,+}$; $^{*}p < 0.05$ *vs.* baseline, $^{+}p < 0.005$ *vs.* low-AGE meal) in comparison with low-AGE meal (changes at 2, 4, and 6 h *vs.* baseline: -13^{*}, -20^{*}, -2%, respectively) [18].

4 CRI

Effects of thermally modified food administration in CRI are summarized in Table 1.

4.1 Animal studies

In male Wistar rats, CRI was induced by subtotal nephrectomy (5/6 NX). Rats were pair fed over 6 wk with low *vs.* high bread crust diet [3]. Plasma levels of pentosidine (+77%, $p < 0.01$) and urinary excretion of CML (+85%, $p < 0.01$) were higher in the high BC group if compared with low BC animals. As in the corresponding experiment with healthy animals [3], rats on high BC diet gained significantly more body weight, their organs were heavier. Kidney hypertrophy was reflected by increased renal cortex protein to DNA ratio and a rise in kidney malondialdehyde content was observed [3, 4]. Creatininemia and creatinine clearance remained unaffected, but renal effects regarding proteinuria and TGF-β1 urinary excretion (3- and 3.6-fold rise *vs.* control diet, respectively) were even more pronounced than in the healthy animals. In a similar study, 5/6NX Sprague–Dawley rats were fed either 50% BC, 50% bread core, or control diet for 4 wk. The BC diet group displayed 1.5-fold higher plasma and 1.6-fold higher kidney CML contents if compared with control diet animals. Renal pathology was reflected by significantly increased proteinuria, increased deposition of collagens I and IV, greater degree of interstitial fibrosis, and macrophage infiltration, as well as upregulation of MCP-1 and TGF-β1 mRNA and protein expression in renal tissue. Moreover, enhanced oxidative stress was reflected by increased plasma concentrations of advanced oxidation protein products and thiobarbituric acid reaction substances, and decreased plasma and renal tissue glutathione peroxidase activity [19].

4.2 Human studies

Eighteen chronic renal failure patients treated with dialysis were assigned to a 4-wk either low- or high-AGE diet [20]. Low AGEs intake resulted in a significant decrease of plasma AGEs, CRP, and plasminogen activator inhibitor-1 (PAI-1) concentrations (by 35, 44, and 17%, respectively, $p < 0.03$). In the high-AGE diet group, only plasma AGEs increased significantly. VCAM-1 and TNF-a levels, similar at baseline, became significantly lower ($p < 0.05$) in patients on low-AGE diet at the end of the study.

5 Discussion

It has been recently demonstrated in a well controlled rat study that, dietary AGEs are absorbed by the intestines since they appear in plasma, and are eliminated from the organism, as reflected by the increase in their kidney content and urinary excretion [1]. In healthy humans, urinary excretion of AGEs is considered to be strictly dependent on daily diet, but the variety concerning the excretion rate of individual AGEs point to different resorption and metabolic pathways [21]. Studies on the effects of dietary intake of chemically characterized AGEs in humans are lacking. As follows from the reviewed data, diets used in aforementioned settings differ substantially by their composition, heat treatment conditions, and duration of administration. The dietary AGEs load in different settings is feasible to compare, since different analytical methods were used to determine foods AGE content. Moreover, data on concentration of other bioactive compounds occurring during heat-processing are not available. It is accepted that CML represents a ligand for RAGE [22], and is suggested to be involved in various pathologies [9 – 11]. Heat processed foods intake represent high load of dietary AGEs, including CML. However, available data allow us only to derive general conclusions on biological effects of the consumption of heat-processed foods, which cannot be yet linked to a particular chemical compound.

It is to be underlined that our knowledge on AGEs-rich diet effects is based predominantly on data from experimental studies in rodents. However, it is widely disputed that rats and mice are phyllogenetically not accustomed to the intake of heated food, thus do not represent a plausible model to study the effects of thermally processed food. On the other hand, during 1000 years of evolution since humans started to heat process their food, neighboring rats and mice might gradually become accustomed to consume these human leftovers. Thus, it might be assumed that at least the urban rodents regularly consume some heated foods. Taking into account that the observed effects of exaggerated heated food intake in humans and rodents studies are similar, data from experimental studies might be with caution extrapolated to potential general conclusions.

Highly thermally modified food may exert various metabolic and nephrotoxic effects, aggravate inflammation, and oxidative stress. The observed deleterious effects of intake of high-AGE diet were very similar in rodents and humans, either in health or reviewed disease states. Animal studies suggest a potential different susceptibility of various tissues to load of heated food, as reflected by differences in organs weight gain [3]. Wittmann's study [6] raises the question of potential interindividual differences with respect to the susceptability to the dietary intake of AGEs: high-AGEs load may be potentially noxious in some virtually healthy sensitive or predisposed individuals, and probably not in general. Strikingly, at least in experimental animals, high consumption of heat treated foods may promote the manifestation of diabetes, substantially contribute to the acceleration of the development of diabetic complications – even in the absence of other metabolic aggravating factors – as well as the survival of diabetic animals. In addition, first evidence was given that a single high-AGE meal may acutely aggravate vascular dysfunction *in vivo*. Animal data suggests that feeding a AGE-rich diet may accelerate chronic kidney disease progression and renal fibrosis *via* a redox-sensitive inflammatory pathway. The virtual discrepancy between the potent proinflammatory effects of high-AGE diet in rodent models and the mentioned *in vivo* study reflects the fact that, in the end stage renal disease patients on renal replacement therapy, uremic state itself is a primary cause of oxidative and carbonyl stress. Correspondingly, the beneficial effects of AGEs restriction are more markedly pronounced. The rat model of CRI (5/6NX) reflects the period of mild to moderate kidney damage, thus much less severe kidney damage than in the investigated patients' group. It might be anticipated that the high dietary intake of heavily thermally modified food may trigger the proinflammatory and pro-oxidant pathways and contribute to acceleration of kidney deterioration during early phases of renal insufficiency. Thus, the recommendation of a restriction of high intakes of severely thermally treated foods may be of clinical relevance in selected patient groups.

6 References

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