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ORIGINAL CONTRIBUTION

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Plasma levels of advanced glycation end products in healthy, long-term vegetarians and subjects on a western mixed diet

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Summary *Background* Evidence indicates that food-derived Maillard's reaction products are absorbed and yet can be detected in the circulation. *Aim of the study* We postulated that consumption of the heat-treated food by omnivores could be reflected by higher plasma levels of advanced glycation end products (AGEs) in comparison with vegetarians, who in cooking (by keeping away from meat) use lower temperatures and less time for heating. *Methods* Plasma fluorescent AGEs (350/450 nm) and N^{ε}-(carboxymethyl)lysine (CML, competitive ELISA) levels were investigated in 3 groups of healthy vegetarians (9 vegans-V, 19 lacto-ovo-vegetarians – VLO and 14 semi-vegetarians – VS) and compared with those of age-matched omnivores (O, n=19). Mean duration of vegetarian diet was V: 7.2±1.0, VLO: 8.2±0.8 and VS: 7.9±1.1 years. *Results* Both fluorescent AGE (O: 9.9±0.5; V: 10.8±0.7, LO: 13.1±0.8* and SV: 11.6±1.2 x10^3 AU), and CML levels (O: 427.1±15.0, V: 514.8±24.6*, LO: 525.7±29.5**, SV: 492.6±18.0* ng/ml) were significantly lower in omnivores than in vegetarians. Plasma glucose, parameters of renal function (plasma concentration of creatinine and cystatin C, calculated glomerular filtration rate – GFR) as well as C-reactive protein levels were within the normal range and did not differ significantly between the groups. Thus, neither decline of kidney function nor inflammatory processes contributed to the rise in plasma AGEs. *Conclusion* Enhanced plasma AGE levels in vegetarians in comparison to omnivores are herein presented for the first time. Mechanisms of AGE elevation and potential pathophysiological relevance of this finding are to be elucidated in prospective studies.

Key words vegetarian diet – advanced glycation end products – carboxymethyllysine – kidney function

Introduction

As described at the turn of the 20th century by the French food chemist, Maillard, protein glycation products are formed during the heat treatment of foods [1]. Later, it was recognized that advanced glycation end products (AGEs) are also formed *in vivo* [2]. Enhanced tissue and plasma levels of AGEs are reported with increasing age and in the course of various diseases, such as diabetes, acute and chronic renal failure and liver cirrhosis [2–7]. The kidney plays a key role in the disposal of AGEs [8–9]. Due to their toxic effects, AGEs are considered as a new class of uremic toxins [10–12], but they are also of pathophysiological relevance in other diseases [13–15].

It is accepted that food-derived Maillard products are

absorbed, at least partially, into the circulation [16–19]. However, their fate in the organism still remains largely unclear.

The traditional domestic processing of meat (cooking, frying, and baking) requires higher temperatures and longer heating times in comparison to culinary treatment of vegetables. Therefore, we postulated that, if dietary protein glycation products contribute substantially to plasma AGE levels, their levels should be higher in omnivores in comparison to subjects on a long-term vegetarian diet. In the present study, we investigated plasma AGE levels (determined as fluorescent AGEs and N^{ε}-carboxymethyllysine) in subjects on three different forms of vegetarian diets (semi-vegetarians, lacto-ovo-vegetarians and vegans) in comparison with those found in a corresponding age-matched group on a traditional Western mixed diet.

Pathophysiological relevance of enhanced AGE levels in healthy vegetarians should be further investigated in aimed prospective studies.

Material and methods

The study was carried out in accordance with the Declaration of Helsinki and reviewed and approved by the Institutional Ethics Committee. All participants gave their written consent.

The investigated groups on the vegetarian diets consisted of healthy adults: 9 vegans (V, exclusively plant food), 19 lacto-ovo-vegetarians (VLO, plant food, milk, eggs, dairy products) and 14 semi-vegetarians (VS, as VLO, fish). The group on a traditional Western mixed diet (O, omnivores) consisted of 19 subjects. All participants were non-smokers. They were free of any medication for at least 3 months prior to the start of the study. Characteristics of the groups are listed in Table 1.

Venous blood was collected into K_2EDTA tubes after overnight fasting. Separated plasma was stored in aliquots at –20 °C, and analyzed for creatinine, glucose, total proteins and C-reactive protein (CRP) concentration (standard methods, Vitros 250 analyzer, J&J, Rochester, USA), and cystatin C levels – a new marker for estimation of glomerular filtration rate (GFR) (immunonephelometrically, Dade Behring, Marburg, Germany). For evaluation of GFR, the nomogram of Randers et al. [20] was used.

Fluorescence measurement of 50-fold diluted plasma samples (corrected for background) was performed in duplicate on a Fluorite 1000 (Dynatech, USA) analyzer at 350/450 nm [5].

The levels of N^{ε}-(carboxymethyl)lysine (CML) in plasma were analyzed after proteinase K digestion in triplicate by competitive ELISA using monoclonal antibodies 4G9 (Alteon Inc., New York) [21] against CML developed by ROCHE Diagnostics (Penzberg, Germany) [22]. N^{ε}-(carboxymethyl)-amino-caproic acid served as a standard.

In addition to blood sample analysis and anthropometric characteristics, the nutritional regimen was inspected by a skilled dietician (by means of dietary interviews) and a food frequency questionnaire on the intake of 102 food items, food groups and recipes. Food groups and recipes involved soups, gravies, sauces, canned vegetables and fruits, as well as jams. Information from the food frequency questionnaire was used to determine the intake of proteins, carbohydrates, milk products and food groups containing predominantly fructose in comparison to glucose (vegetables, fruit, apples – fresh and dried, fruit juices, citrus fruit, honey) employing Alimenta dbase (Food Research Institute, Bratislava, Slovakia).

Statistical analysis was performed using Statgraphics Version 5 Statistical Program. Means were compared by Analysis of Variance; if ANOVA indicated a significant difference between the means, the Least Square Difference test was used to localize the difference. Correlation and regression analysis was performed. $P < 0.05$ was considered as significant.

Table 1 Group characteristics and biochemical parameters in human subjects on a standard western mixed diet and in vegetarians

	Omnivores	Semi-veg.	Lactoovoveg.	Vegans
n	19	14	19	9
Age (years)	30.5±1.6	35.4±2.7	36.1±2.5	39.6±3.0
BMI (kg/m^2)	23.8±0.4	23.1±0.4	22.0±0.5**	20.6±0.8***
Δ veget. diet (y)	–	7.9±1.1	8.2±0.8	7.2±1.0
Glu (umol/l)	4.18±0.10	4.19±0.09	4.21±0.09	4.11±0.13
Crea (µmol/l)	72.3±1.8	79.6±5.1	76.4±5.6	75.5±5.5
Cyst. C (mg/dl)	0.83±0.02	0.83±0.03	0.84±0.04	0.87±0.06
GFR (ml/min/1.73m^2)	103.2±4.4	102.9±6.0	104.9±5.9	99.3±11.2
CRP (mg/dl)	0.0±0.0	0.008±0.008	0.04±0.04	0.0±0.0
TP (g/l)	76.75±1.15	70.61±1.45**	69.24±1.16**	71.10±2.30*

Results are expressed as mean±SEM, *BMI* body mass index, *Δ veget diet* mean time on vegetarian diet, *Glu* plasma glucose, *Crea* plasma creatinine, *Cyst C* plasma cystatin C, *GFR* glomerular filtration rate, *CRP* plasma C-reactive protein, *TP* plasma total proteins, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs. omnivores

Results

The groups were comparable by age. Vegetarians were on their diet regimen for a comparable time period. Mean body mass index (BMI) was lower in V and VLO groups. Although the plasma total protein (TP) concentration was within the normal range in all subjects, in groups on vegetarian diets mean values were lower (by 7–10 %) when compared to O (Table 1). Plasma glucose, creatinine, cystatin C and C-reactive protein concentrations were within the normal range and did not differ significantly between the groups (Table 1).

Overall AGE levels as estimated by plasma fluorescence tended to be higher in all three groups on a vegetarian diet if compared to O, but significance was reached for VLO only. However, if fluorescence was calculated per g of total plasma proteins, the mean in both VLO and VS groups was significantly higher than that in omnivores (Fig. 1). The mean plasma CML level as well as the CML/TP ratio were found to be the lowest in omnivores, and was significantly elevated in all groups of vegetarians. Again, the highest values (though statistically not different from VS and V) were observed in the VLOs (Fig. 2). There was no correlation of fluorescent AGE or CML levels and age, the duration of the vegetarian diet, plasma glucose, GFR, creatinine, and cystatin C concentration, as well as calculated GFR.

From the dietary protocols it was calculated that, in comparison to the omnivores, all of the vegetarian groups consumed less protein, even if the protein intake was adjusted to the individual body weight (Table 2). However, the recommended daily allowance (RDA) [23] was fulfilled (O: 155 %, VS: 120 %, VLO: 110 % and V: 113 %). Relative intake of animal proteins represented 48 % in omnivores, while it was lower in VS (26 %) and VLO (20 %) (Table 4). Absolute carbohydrate intake hardly differed between the groups (Table 2), RDA: O: 105 %, VS: 103 %, VLO: 99 % and V: 101 %, and after the adjustment to the individual body weight it tended to be even slightly higher in all vegetarian groups. Vegetarians consumed less milk and dairy products but more apples, dried apples, citrus fruits and honey. In these food items

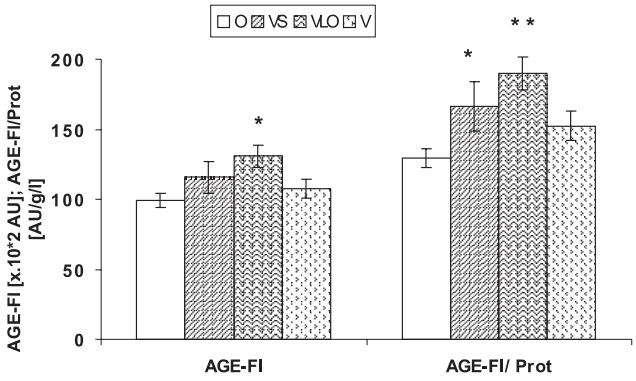

Fig. 1 Plasma fluorescent advanced glycation end product levels in omnivores and vegetarians (*AGE-FI* fluorescent advanced glycation end products, *Prot* plasma total proteins, *O* omnivores, *VS* semi-vegetarians, *VLO* lacto-ovo-vegetarians, *AU* arbitrary units, *: $p < 0.05$ vs. O, **: $p < 0.01$ vs. O).

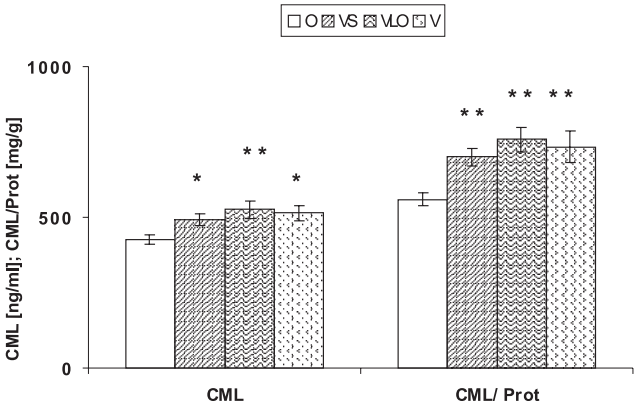

Fig. 2 Plasma N^{ε}-(carboxymethyl)lysine concentration (*CML* N^{ε}-(carboxymethyl)lysine, *Prot* plasma total proteins, *O* omnivores, *VS* semi-vegetarians, *VLO* lacto-ovo-vegetarians, *V* vegans, *: $p < 0.05$ vs. O, **: $p < 0.01$ vs. O).

Table 2 Daily intake of proteins, carbohydrates, fruits and vegetables (g/day) with higher fructose (F) content as compared to glucose (G) content

	Omnivores	Semi-veg.	Lactoovoveg.	Vegans
Proteins (g)	88.6±5.2	68.4±2.9**	63.8±4.2***	64.5±5.6**
Prot/BW (g/kg)	1.26±0.07	1.03±0.04**	1.02±0.07*	1.03±0.09*
Carbohydrates	415.3±23.6	404.2±22.8	392.8±17.7	399.0±28.9
Carb/BW (g/kg)	5.90±0.33	6.05±0.34	6.26±0.26	6.38±0.44
Vegetab (F > G)	75.3±8.7	106.5±10.8*	117.5±11.9***	137.3±14.0***
Veget (F > G)/BW (g/kg)	1.06±0.12	1.59±0.16**	1.87±0.13***	2.20±0.22***
Fruits (F > G)	339.6±36.0	426.5±53.7	600.8±31.8***	696.0±84.1**
Fruits (F > G)/BW (g/kg)	4.82±0.49	6.38±0.74	9.58±0.48***	11.14±1.22***
Apples (5.6 g F; 3.0 g G)[1]	140.1±22.5	222.5±26.0*	395.7±22.9***	359.8±57.4***
Dried apples (20.1 g F; 11.0 g G)[1]	3.1±0.6	10.5±1.5***	11.8±1.5***	12.5±1.6***
Fruit juices (F > G)	167.0±22.2	89.7±20.5*	105.7±45.2	200.8±50.7***
Citrus fruits (F > G)	14.1±3.5	94.0±12.5***	66.8±10.5***	106.0±22.2***
Honey (37.9 g F, 31.4 g G)[1]	2.2±0.4	14.2±3.5**	8.4±1.5***	10.5±1.7***

[1] per 100 g edible food, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

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(especially in apples and honey) fructose is the predominant source of carbohydrates (Table 3). Consumption of legumes/pulses in our groups of vegetarians was roughly 4-times higher than in omnivores (Table 4). The total amount of the consumed grain products was comparable in all investigated groups (Table 4). However, the intake of technologically processed grain products (such as muesli and oat flakes), and whole grain products (dark bread, baked grains, whole grain pasta) was 3 to 6 times higher in vegetarians if compared with omnivores (Table 4).

Discussion

Studies in rats and healthy volunteers have demonstrated the oral bioavailability of certain ingested Amadori compounds from various heated foods [16–18]. Depending on the kind of diet, elevation in serum AGE levels occur in direct proportion to the amount of ingested AGEs [16]. In general, about 10 % is consistently absorbed, while only 30 % of this is excreted in the urine. According to animal experiments using ^{14}C-tracer isotopes, the absorbed radioactivity which appeared in the urine ranged from 16–30 % of low and 1–5 % of high molecular weight Maillard reaction products (MRPs) (reviewed by [18]). In rats, dietary intake of AGE CML – one of the most prominent AGEs [12] – was shown to enhance its endogenous burden and to cause specific biological effects, both at the tissue and cellular level [23]. In healthy subjects, consumption of milk with a controlled content of lactuloselysine was followed by a rapid excretion of furosine via the kidney [24]. Furthermore, an impairment of renal [16, 19] or liver [6] function might result in a further increase of the AGE load in the blood and tissues.

In contrast to the working hypothesis of the present study, as the traditional domestic processing of meat, requiring higher temperatures and longer heating times, should lead to higher levels of plasma AGEs than does a long-term vegetarian diet, it was surprising that the AGE levels in subjects on three different vegetarian diets were not decreased. In fact, overall AGE levels determined spectrofluorimetrically or, analyzed by a CML-specific ELISA were found to be slightly higher than in omnivores.

Now, the arising question is, how can the elevated AGE levels in the vegetarians be explained? In the healthy organisms, plasma and tissue AGE levels reflect the rate of their endogenous production, their removal (by degradation in macrophages, and clearance by the kidney and liver), as well as the dietary intake [2–4, 6, 8, 9, 22, 25].

First of all, we considered the potential non-alimentary factors that could contribute to the observed rise of AGEs in the vegetarians.

Age. AGE levels rise with age [2]. Although ANOVA did not show significant differences between the mean age in the investigated groups, the vegans tended to be slightly older. However, our former investigations on the effects of the age on plasma CML level and fluorescent AGE compounds did not show significant differences in the age bracket of 30–60 years [26].

Smoking [27]. Since all of the included subjects were non-smokers, this putative factor of influence could be excluded.

Diabetes mellitus. An enhanced AGE formation due to diabetes was also excluded, since all subjects were normoglycemic and reported a negative history of diabetes in their parents and siblings.

Renal function. In our study, the rise of the AGE levels in the vegetarians was not due to a decline in renal function because plasma creatinine as well as cystatin C concentrations were within normal range and did not differ

Table 3 Intake of animal proteins, legumes/pulses and grain products

	Omnivores	Semi-veg.	Lactoovoveg.	Vegans
Milk	193.2±18.9	77.0±11.0**	91.5±11.9**	0
Yogurt	171.3±15.0	41.6±4.4**	74.4±5.7**	0
Cream	28.1±3.0	2.3±0.3**	11.6±1.8**	0
Cheese	65.9±7.5	28.6±3.7**	41.9±2.5*	0

* $p < 0.01$; ** $p < 0.001$

Table 4 Intake of animal proteins, legumes/pulses and grain products

	Omnivores	Semi-veg.	Lactoovoveg.	Vegans
Animal proteins	42.5±2.7	17.6±0.9*	12.8±0.5*	0*
Legumes (Pulses)	6.8±0.5	26.2±1.2*	30.2±1.7*	28.7±1.4*
Grain sprouts	0	1.22±0.04*	2.48±0.09*	3.66±0.19*
Grain products[a]	30.2±2.2	98.7±3.6*	155.2±3.1*	184.0±6.1*
Grain products[b]	366.0±8.8	282.7±9.0*	238.6±8.2*	212.6±10.7*
Whole grain products (g/d)	77.6±3.1	138.3±5.2*	239.6±10.8*	282.9±17.1*

* $p < 0.001$
[a] Unheated, but technologically processed
[b] Cooked and baked

between the groups. Also the baseline calculated GFR from serum creatinine and cystatin C levels displayed normal values. However, in the omnivores the postprandial GFR could be higher due to a protein-induced glomerular hyper filtration [28]. As is discussed later, the protein intake in omnivores was much higher than in vegetarians. Thereby, the renal removal of food-derived AGEs could be elevated for several hours after a meal.

Micro-inflammation. A micro-inflammatory process seems unlikely since CRP levels were within the normal range in all participants.

Enhanced oxidative stress. In a similar manner, oxidative stress could be excluded as a possible cause of elevated AGE levels [29, 30]. As in previous investigations in these vegetarian groups, we could show that their plasma antioxidant levels (such as vitamins C, E, A, β-carotene) were higher, while parameters characterizing lipid peroxidation (such as conjugated dienes) were lower in comparison with the age-matched group of omnivores [31–33]. Hence other factors, associated with the long-term implementation of vegetarian diet, have to be taken into account.

Intake of carbohydrates

Intake of carbohydrates (both absolute and relative to body weight) was comparable among all groups. However, a typical difference of vegetarian in comparison to traditional nutrition is a higher intake of fruits and vegetables, whereby many of which have greater proportions of fructose (F) than glucose (G). This was also true of our vegetarians, who indicated a significantly higher F consumption, as evaluated by the dietary questionnaires. Since F is more effective in the production of AGEs, a substantially higher intake of F may contribute to the increase in plasma AGE levels [34]. However, the biochemical relevance of the higher fructose intake is questionable. A recent long-term study (20 weeks) in rats fed with various dietary carbohydrates (including fructose) at non-excessive doses showed that the source of carbohydrate intake had only a minimal influence both on markers of glycemic stress and on accumulation of AGEs [35]. Moreover, we did not find a correlation between the time on vegetarian diet and fluorescent AGE or CML levels.

Intake of proteins

In comparison to the omnivores, the vegetarians consumed less protein (absolute intake as well as in relation to body weight). All of the groups met the RDA, but in omnivores, the dietary intake exceeded the recommended protein intake value by a factor of 1.5–1.7 [36–38]. Lower energy intake in vegetarians was reflected by a lower BMI and a lower plasma total protein concentration, without any sign of malnutrition. Theoretically, the moderate protein consumption in vegetarians could also be associated with a lower absolute intake of MRPs. In addition, their lysine intake was significantly lower because of its 31–60 % content in cereals vs. 119–151 % in animal proteins when compared to reference protein [39]. In the mentioned study of Lingelbach [35] only calorie restriction resulted in lower serum and tissue AGE levels. In spite of these findings, plasma AGE levels in vegetarians were higher than those observed in omnivores. Thus, we focused on consumption of heated and technologically processed proteins.

Although a majority of animal proteins ingested as regular food is heat processed, they are unlikely to contribute substantially to elevation of plasma AGE levels in VS and VLO. Moreover, vegans do not consume animal proteins at all. Vegetarians eat more legumes/pulses than omnivores. In spite of the assumption that all are consumed after heat processing, it does not seem very likely that the higher intake of plant proteins is responsible for the observed rise in plasma AGE levels. The total amount of the consumed grain products was comparable among all of the investigated groups, particularly the technologically processed grain products (such as muesli and oat flakes) and the whole grain products (dark bread, baked grains, whole grain pasta) could represent a potential source of MRPs. Consumption of the technologically processed grains by vegetarians exceeded that of omnivores by a factor of 3–6, and that of cooked and baked whole grain products was 2 to 4 times higher. In total, the intake of whole grain products contributing to total grain consumption represented 19.7 % in omnivores, but 36.3 % in VS, 60.8 % in VLO, and even 71.3 % in V group. Since these products contain a relatively high amount of CML, they may potentially account for the observed mild rise in CML levels in the investigated groups of vegetarians. Additionally to the putatively elevated intake of MRPs in the vegetarians the lower BMI in comparison with the omnivores has to be considered as well. Metabolically, the lower the BMI the lower the metabolic (energy) turn over, possibly resulting in a lower metabolic activity of the kidney which is responsible for the excretion of AGEs [12, 23].

Summarizing our study, it was shown that serum CML levels are slightly elevated in vegetarians in comparison to omnivores. The underlying mechanisms may be an enhanced dietary AGE intake, since an impaired renal or liver function as well as an enhanced oxidative stress – as pathogenetic factors – seemed unlikely. To elucidate the complex interplay of exo- and endogenous production of AGEs, long-term, prospective, cross-over studies with defined diets are needed.

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