ISSN 1436-6207, Volume 49, Number 7

Eur J Nutr (2010) 49:429–434
DOI 10.1007/s00394-010-0101-3

ORIGINAL CONTRIBUTION

Association of dietary AGEs with circulating AGEs, glycated LDL, IL-1α and MCP-1 levels in type 2 diabetic patients

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Received: 19 October 2009 / Accepted: 2 March 2010 / Published online: 13 March 2010

Abstract
Purpose The association of dietary advanced glycation endproducts (AGEs) intake with the oxidative and inflammatory status in type 2 diabetic patients was examined.
Methods Seventy-four healthy controls, 50 low AGEs intake and 68 high AGEs intake type 2 diabetic patients were requested to complete a 7-day dietary record. Blood levels of several oxidative and inflammatory biomarkers were determined.
Results Diabetic patients with high AGEs intake had significantly elevated plasma levels of AGEs, HbA1c, low-density lipoprotein (LDL), LDL-cholesterol and glycated LDL than low AGEs intake patients and controls ($P < 0.05$). These high AGEs intake patients also had significantly increased plasma levels of 8-isoprostane, interleukin (IL)-1α, tumor necrosis factor-α, monocyte chemoattractant protein (MCP)-1 and lower superoxide dismutase (SOD) activity than low AGEs intake patients ($P < 0.05$). Correlation coefficients of dietary AGEs versus plasma AGEs, HbA1c, 8-isoprostane, IL-1α and MCP-1 were >0.6; but the correlation coefficient of dietary AGEs versus plasma SOD activity was <−0.6.
Conclusion Increasing dietary AGEs intake might enrich circulating AGE level and contribute to oxidative and inflammatory progression under diabetic condition. The circulating 8-isoprostane, IL-1α and MCP-1 levels and SOD activity might be appropriate biomarkers used to evaluate dietary AGEs-associated oxidative and inflammatory stress.

Keywords Dietary AGEs · Glycated LDL · IL-1α · MCP-1

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Introduction

The role of advanced glycation endproducts (AGEs) upon diabetic progression has been paid attention because AGEs exacerbated systemic glycative injury and favored the development of micro- and macro-vascular complications [1–3]. Negrean et al. [4] observed a significant increase in plasma levels of vascular cell adhesion molecule 1 and thiobarbituric acid reactive substances in type 2 diabetic patients after consuming a high AGE meal. The studies of Uribarri et al. [5] and Stirban et al. [6] revealed that a single oral AGE challenge could induce acute endothelial and adipocyte dysfunctions in type 2 diabetic patients. In these previous studies [4–6], the acute impairment caused by dietary AGEs was examined by only a single high AGE challenge. Thus, the impact of chronic or habitual dietary AGEs intake on oxidative and inflammatory stress in

diabetic patients remains unknown. It may not be safe or practical to conduct an intervention study to evaluate the influence of long-term high AGEs consumption on pathological development for diabetic patients. However, the association between the amount of habitually consumed AGEs and the variation of circulating oxidative or inflammatory biomarkers in diabetic patients is worthy to be investigated.

The common AGEs in foods and human plasma include pentosidine, carboxymethyllysine (CML) and furosine [7, 8], in which CML has been considered as the predominant AGE in human plasma. Our previous study found that soybean sauce, barbecue sauce and sour–sweet sauce contained AGEs at 10–692 μg/100 ml sample; and the interaction of sauce, frying oil and heating treatment effectively promoted the formation of AGEs in sauce-treated foods [9]. Therefore, it is highly possible that the consumption of these sauces or sauced-treated foods in high frequency favors diabetic deterioration in diabetic patients via increasing exogenous AGEs source.

The purpose of this study was to examine the association of habitual dietary AGEs intake with oxidative and inflammatory status in type 2 diabetic patients. Dietary information including used sauces and cooking methods were collected, and the circulating levels of several biomarkers such as 8-isoprostane, glutathione, interleukin (IL)-1α, tumor necrosis factor (TNF)-α, monocyte chemoattractant protein (MCP)-1 and superoxide dismutase (SOD) activity in these diabetic patients were measured.

Materials and methods

Patients and healthy subjects

This study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving human subjects and patients recruitment were approved by the Ethical Committee of the Medicine Faculty at Chung Shan Medical University Hospital (CSMUH No: CS07083). Written informed consent was obtained from all subjects and patients. From September, 2007 to May, 2008, 118 adult patients with type 2 diabetes were recruited into this study. Patients with mean daily urine albumin higher than 20 mg, or confirmed diabetic nephropathy, cardiomyopathy or retinopathy were excluded. After dietary content of pentosidine, CML and furosine was estimated, the sum of consumed furosine, pentosidine and CML was defined as dietary AGEs for each subject. Then, diabetic patients were arbitrally divided into two groups: high AGE group (H-AGE) with daily AGEs intake >300 μg; low AGE group (L-AGE) with daily AGEs intake $\leqq$ 300 μg. The patient number in L-AGE and H-AGE groups was 50 and 68, respectively. On the other hand, 74 healthy subjects were also recruited in Chung Shan Medical University Hospital between January and May, 2008 as control group for comparison. These subjects, confirmed by blood and ultrasound examination, did not suffer from diabetes or other liver diseases. The baseline characteristics of diabetic patients and healthy controls are presented in Table 1.

Dietary record and nutrients analyses

All subjects were interviewed by a dietician and requested to complete a 7-day dietary record including consumption frequency and portion size of food items. The information regarding cooking methods and used sauces such as soybean sauce or sour–sweet sauce were also collected. Dietary AGEs including furosine, CML and pentosidine were calculated according to the data provided by Goldberg et al. [8] and Chao et al. [9]. Other nutrient composition in diets was calculated based on Taiwan Nutrient Databases [10].

Blood biochemical measurements

A peripheral blood sample, 15 ml, from each subject was drawn after an overnight fasting. Serum levels of triglyceride, glucose, insulin, HbA1c, blood urea nitrogen (BUN) and creatinine were determined by an autoanalyzer (Dr. Lange LP 420, Berlin, German). The total cholesterol and high-density lipoprotein (HDL) cholesterol levels were measured using an analyzer (Beckman Coulter Inc, Fullerton, CA, USA) with intra- and inter-assay CVs at 1.2 and 2.0%, respectively. HDL cholesterol concentration was measured after precipitating plasma apoB-containing lipoproteins by phosphotungstic acid. Low-density lipoprotein (LDL) cholesterol concentration was calculated using the Friedewald formula [11]. Glutathione (GSH) and oxidized glutathione (GSSG) concentrations in plasma were determined by commercial colorimetric GSH and GSSG assay kits (OxisResearch, Portland, OR, USA). Plasma activity of catalase, SOD and glutathione peroxidase (GPX) was measured by catalase, SOD and GPX assay kits, respectively (Calbiochem, EMD Biosciences, Inc. San Diego, CA, USA). Lipid oxidation in plasma was analyzed by measuring the formation of malondialdehyde (MDA) via an HPLC method [12], and the production of 8-isoprostane via a method described in Konishi et al. [13]. Plasma levels of c-reactive protein (CRP), IL-1α, IL-6, IL-10, TNF-α and MCP-1 were measured by using cytoscreen immunoassay kits (BioSource International, Camarillo, CA, USA).

Table 1 Baseline characteristics in controls and type 2 diabetic patients with low AGEs (L-AGE) or high AGEs (H-AGE) intake

Parameters	Controls $n = 74$	L-AGE $n = 50$	H-AGE $n = 68$
Male/female	40/34	22/28	35/33
Mean age, age range	52.3 ± 11.7, 29-71	57.6 ± 10.2, 32-74	54.9 ± 9.3, 34-69
Current smoker	5	2	4
Blood pressure (mmHg)			
Systolic	135.2 ± 19.5	138.7 ± 16.8	131.4 ± 20.7
Diastolic	83.8 ± 10.7	80.1 ± 14.4	86.2 ± 16.3
Duration (year)	NA	7.2 ± 4.3	6.8 ± 5.0
Body mass index (kg/m^2)	27.1 ± 3.6	25.9 ± 4.8	26.7 ± 4.1
Glucose (mg/dl)	92 ± 27	147 ± 56*	162 ± 68*
HbA1c (%)	2.5 ± 0.7	6.9 ± 1.8*	10.5 ± 2.1*,**
Triglyceride (mg/dl)	105 ± 31	164 ± 47*	155 ± 62*
Cholesterol (mg/dl)	129 ± 32	181 ± 46*	223 ± 61*,**
HDL-cholesterol (mg/dl)	45 ± 8	49 ± 12	52 ± 11
LDL-cholesterol (mg/dl)	67 ± 18	114 ± 20*	157 ± 34*,**
Glycated LDL (%)	1.8 ± 0.2	4.5 ± 0.7*	9.6 ± 1.3*,**
BUN (mg/dl)	11 ± 5	12 ± 8	16 ± 9
Creatinine (mg/dl)	0.58 ± 0.17	0.71 ± 0.22	0.95 ± 0.24
Other diseases			
COPD	1	0	1
Gout	2	1	2
Hypertension	2	1	4

Values are means ± SD

NA Means not available

* $P < 0.05$ versus healthy control group

** $P < 0.05$ versus patients at L-AGE

Determination of furosine, CML and pentosidine in plasma

Plasma CML was immunochemically determined by ELISA technique using the CML-specific monoclonal antibody 4G9, and calibration with 6-(N-carboxymethyl-amino) caproic acid (Roche Diagnostics, Penzberg, Germany). Pentosidine was analyzed via an HPLC method described by Miyata et al. [14], in which a Supelco reverse phase C18 column was equipped. Furosine was measured according to the method described by Wu et al. [15].

Measurement of glycated LDL in plasma

LDL fraction with density 1.006–1.063 was isolated from plasma by sequential ultracentrifugation [16]. The method of Duell et al. [17] was used to quantify the degree of LDL glycation.

Statistical analysis

Data were assessed for normality using the Shapiro–Wilk test. Skewed data were logarithmically transformed before statistical analysis. Data were subjected to analysis of variance (ANOVA), and difference with $P < 0.05$ was considered to be significant. Correlation between dietary AGEs level and each haematological measurement was calculated by regression analysis (Minitab Inc., State College, PA, USA).

Results

Baseline characteristics in controls and diabetic patients are presented in Table 1. Diabetic patients had significantly higher plasma levels of glucose, HbA1c, triglyceride, total cholesterol, LDL-cholesterol and glycated LDL than controls ($P < 0.05$). Among diabetic patients, H-AGE patients had significantly higher plasma HbA1c, total cholesterol, LDL-cholesterol and glycated LDL levels than L-AGE patients ($P < 0.05$). As shown in Table 2, H-AGE patients had significantly higher frequency in consuming soybean sauce and frying oil, as well as using deep frying process for food preparation than L-AGE patients and controls ($P < 0.05$). Besides dietary AGEs level, there was no significant difference in the consumed nutrients concerned

Table 2 Dietary frequency (time/week) of consumed frying oil and sauce (soybean sauce, sour–sweet sauce, barbecue sauce, tomato sauce), and cooking method (baked, stir fried, deep fried, boiled) in controls and type 2 diabetic patients with low AGEs (L-AGE) or high AGEs (H-AGE) intake

	Controls	L-AGE	H-AGE
Soybean sauce	8 ± 3	6 ± 2	15 ± 5*
Sour–sweet sauce	2 ± 2	1 ± 1	3 ± 2
Barbecue sauce	4 ± 2	2 ± 1	3 ± 1
Tomato sauce	3 ± 1	1 ± 1	2 ± 1
Frying oil	15 ± 4	11 ± 3	23 ± 5*
Baked	4 ± 2	3 ± 3	9 ± 4
Stir fried	10 ± 4	9 ± 3	11 ± 5
Deep fried	5 ± 3	3 ± 2	14 ± 4*
Boiled	11 ± 4	13 ± 3	13 ± 5

Values are means ± SD

*$P < 0.05$ versus healthy control group

in this study between controls and diabetic patients ($P > 0.05$, data not shown).

Dietary and plasma levels of total AGEs, CML, furosine and pentosidine are presented in Fig. 1. H-AGE patients had significantly greater plasma levels of total AGEs, CML and furosine than L-AGE patients and controls ($P < 0.05$). The daily consumed total AGEs of controls were greater than that of L-AGE patients ($P < 0.05$); however, the plasma total AGEs level of controls was significantly lower than that of L-AGE patients ($P < 0.05$). As shown in Table 3, diabetic patients had significantly higher plasma levels of MDA, 8-isoprostane, GSH, GSSG, CRP, IL-1α, IL-6, IL-10, TNF-α and MCP-1; and lower activity of GPX, SOD and CAT when compared with controls ($P < 0.05$). Among diabetic patients, H-AGE patients had significantly higher plasma levels of 8-isoprostane, IL-1α, TNF-α and MCP-1; and lower plasma activity of SOD than L-AGE patients ($P < 0.05$). The difference in plasma levels of CRP, IL-6, IL-10, MDA, GSH, GSSG and activity of GPX or catalase between H- and L-AGE patients was not significant ($P > 0.05$). As shown in Table 4, the correlation coefficients of dietary AGEs level versus plasma level of AGEs, HbA1c, 8-isoprostane, IL-1α and MCP-1 were >0.6; the correlation coefficient of dietary AGEs level versus plasma SOD activity was <−0.6.

Discussion

It is well known that AGEs possess both prooxidant and proinflammatory activities and are able to facilitate the development of diabetes complications [18, 19]. Thus, dietary AGEs restriction has been considered as a promising therapeutic intervention [19]. Our present study found that high dietary AGEs intake was strongly correlated with several glycative, oxidative and inflammatory factors in circulation of type 2 diabetic patients. These findings reflected that dietary AGEs might be able to promote diabetic progression via enhancing the production of deteriorative factors in circulation.

In our present study, markedly increased plasma AGEs and 8-isoprostane levels and decreased plasma SOD activity were presented in diabetic patients with high dietary AGEs intake. These findings reflected that dietary AGEs might contribute to increase circulating AGEs level, which subsequently enhance oxidative stress and diminish anti-oxidative defense in these diabetic patients. Since both plasma SOD activity and 8-isoprostane level were highly correlated with dietary AGEs as we observed in these type 2 diabetic patients, these two factors, plasma SOD activity and 8-isoprostane level, might be appropriate biomarkers for evaluating dietary AGEs-associated oxidative stress. IL-1α, IL-6 and TNF-α, inflammatory cytokines, could facilitate the progression of endothelial dysfunctions and coagulation disorder and were involved in the development of diabetic complications such as nephropathy [20] and retinopathy [21]. MCP-1, a chemotactic factor for activating monocytes and macrophages, could recruit monocytes to the sites of injury [22]. The results of our present study revealed that diabetic patients with high dietary AGEs intake also had elevated plasma IL-1α, TNF-α and MCP-1 levels. These findings once again reflected that dietary AGEs could increase circulating AGEs content and subsequently favor systemic inflammation progression in diabetic individuals. Since plasma IL-1α and MCP-1 levels

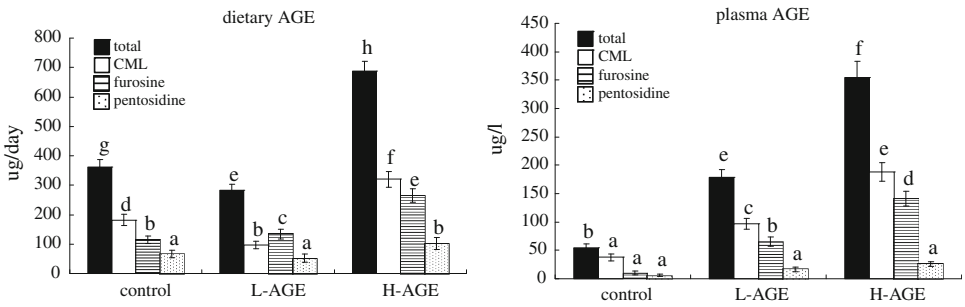

Fig. 1 Levels of total AGEs, CML, furosine and pentosidine in diet (*upper part*) and plasma (*lower part*) from controls and type 2 diabetic patients with low AGEs (L-AGE) or high AGEs (H-AGE) intake. Data are mean ± SD. [a–h]Means among bars without a common letter differ, $P < 0.05$

Table 3 Plasma level of malondialdehyde (MDA), 8-isoprostane, glutathione (GSH), oxidized glutathione (GSSG), activity of glutathione peroxidase (GPX), superoxide dismutase (SOD), catalase (CAT), C-reactive protein (CRP), interleukin (IL)-1α, IL-6, IL-10, TNF-α and monocyte chemoattractant protein (MCP)-1 in controls and type 2 diabetic patients with low AGEs (L-AGE) or high AGEs (H-AGE) intake

Parameters	Controls	L-AGE	H-AGE
MDA (pg/ml)	8.3 ± 1.2	13.9 ± 2.3*	15.0 ± 1.9*
8-isoprostane (pg/ml)	10.5 ± 1.4	18.1 ± 2.5*	27.8 ± 3.7*·**
GSH (μmol/l)	13.8 ± 0.9	11.2 ± 1.4*	10.9 ± 1.2*
GSSG (μmol/l)	0.27 ± 0.10	0.66 ± 0.16*	0.70 ± 0.18*
GPX (U/l)	263 ± 22	213 ± 19*	205 ± 17*
SOD (U/ml)	19.4 ± 0.25	16.8 ± 0.31*	13.6 ± 0.27*·**
CAT (U/ml)	13.1 ± 0.38	11.0 ± 0.60*	11.3 ± 0.53*
CRP (mg/dl)	1.16 ± 0.19	1.58 ± 0.27*	1.64 ± 0.24*
IL-1α (pg/ml)	168 ± 15	308 ± 26*	433 ± 30*·**
IL-6 (pg/ml)	58 ± 18	261 ± 21*	282 ± 25*
IL-10 (pg/ml)	18 ± 6	25 ± 9*	27 ± 10*
TNF-α (pg/ml)	46 ± 10	165 ± 21*	247 ± 32*·**
MCP-1 (μg/ml)	1.87 ± 0.17	2.65 ± 0.20*	3.41 ± 0.23*·**

Values are means ± SD

* $P < 0.05$ versus healthy control group

** $P < 0.05$ versus patients at L-AGE

Table 4 Correlation coefficient between dietary AGEs level and plasma measurements in type 2 diabetic patients

	Dietary AGEs level		Dietary AGEs level
Plasma AGEs	0.817	Catalase activity	−0.104
Glycated LDL	0.572	GPX activity	−0.168
HbA1c	0.661	SOD activity	−0.659
BUN	0.293	CRP	0.238
Creatinine	0.304	IL-1α	0.637
Cholesterol	0.478	IL-6	0.304
LDL-cholesterol	0.535	IL-10	0.146
GSH	−0.237	TNF-α	0.581
MDA	0.351	MCP-1	0.675
8-isoprostane	0.719		

were highly correlated with dietary AGEs level in type 2 diabetic patients, these cytokines might be appropriate biomarkers used for evaluating dietary AGEs-associated inflammatory stress.

In addition, our present study found that diabetic patients with high AGEs intake consumed more soybean sauce, frying oil and deep-fried foods. It is highly possible that these sauces or sauce-treated foods were the partial exogenous source of circulating AGEs for these patients. Soybean sauce and frying oil are commonly used in oriental food preparation. In Taiwan and Japan, soybean sauce could be directly used as table sauce for foods such as tofu and sashimi (raw fish). Although diabetic patients in Taiwan are educated to avoid consuming foods rich in glucose, fructose and carbohydrate, the warning regarding the adverse effects of sauces, frying oil and inappropriate cooking methods is obviously insufficient. On the other hand, we notified that plasma levels of total AGEs, CML and furosine were substantially low in healthy controls although their dietary AGEs intake was marked. This finding might suggest that there is a protective mechanism to decrease the dietary AGEs absorption and/or increase AGEs excretion in people without diabetes, but the pathological development of diabetes disturbs this defensive action.

Hypercholesterolemia occurred in diabetic patients is usually considered as the outcome of poor glycemic control and/or lipid metabolism disorder [23]. Our present study found that plasma total cholesterol and LDL-cholesterol levels were markedly increased in patients with high AGEs intake. Thus, it is possible that dietary AGEs enriched plasma AGEs pool first then impaired lipoprotein metabolism and led to more production of LDL-cholesterol in these patients. These findings also reflected that habitual or long-term high AGEs intake might exacerbate hypercholesterolemia and promote LDL-associated pathological development such as atherosclerotic lesions in diabetic patients. In addition, we notified that both HbA1c and glycated LDL levels were substantially elevated in type 2 diabetic patients with high AGEs intake. These results seemingly implied that exogenous AGEs might enhance glycation reactions of Hb and LDL under diabetic condition. It has been documented that glycosylation of hemoglobin alters nitric oxide binding to Hb thiols and impairs vasodilatation [24, 25]. Thus, glycosylated Hb could be considered as a marker for cardiovascular risk. Furthermore, glycated LDL is an atherogenic marker because glycation increases the LDL proportion taken up by inflammatory cells and facilitates the formation of atheromatous plaques as well as stimulates MCP-1-mediated vascular inflammation [26, 27]. Therefore, the increased HbA1c and glycated LDL levels in diabetic patients with increasing AGEs intake suggested that these patients were at high risk of diabetic-associated cardio-vascular diseases.

In conclusion, our present study found that lower SOD activity, higher 8-isoprostane, IL-1α and MCP-1 levels in circulation were highly associated with dietary AGEs intake in type 2 diabetic patients. These findings reflected that increasing dietary AGEs intake might enrich circulating AGEs level and contribute to oxidative and inflammatory progression under diabetic condition. Furthermore, the circulating 8-isoprostane, IL-1α and MCP-1 levels and

SOD activity might be appropriate biomarkers used to evaluate dietary AGEs-associated oxidative and inflammatory stress.

Acknowledgments All authors would like to thank all subjects participated in this study.

Conflict of interest None of the authors reports a conflict of interest.

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