Single Oral Challenge by Advanced Glycation End Products Acutely Impairs Endothelial Function in Diabetic and Nondiabetic Subjects

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OBJECTIVE — The current study was designed to test the acute effects of dietary advanced glycation end products (AGEs) on endothelial function of diabetic and nondiabetic subjects.

RESEARCH DESIGN AND METHODS — Flow-mediated dilation (FMD) of the brachial artery and serum levels of AGEs, plasminogen activator inhibitor 1 (PAI-1), vascular cell adhesion molecule 1 (VCAM-1), and glucose were assessed before and after a single oral AGE challenge ($\sim 1.8 \times 10^6$ AGE units) in 44 diabetic and 10 nondiabetic subjects.

RESULTS — The diabetic patients had higher baseline levels of serum AGEs ($P = 0.020$), PAI-1 (NS), and VCAM-1 ($P = 0.033$) and lower baseline values of FMD compared with nondiabetic subjects ($P = 0.032$). Ninety minutes after a single oral AGE challenge, serum AGEs and PAI-1 levels increased and FMD decreased significantly in both healthy subjects (AGEs: 7.2 ± 0.5 to 9.3 ± 1 units/ml, $P = 0.014$; PAI-1: 5.4 ± 0.4 to 6.8 ± 0.4 ng/ml, $P = 0.007$; and FMD: 9.9 ± 0.7 to 7.4 ± 0.9%, $P = 0.019$) and diabetic subjects (AGEs: 10.5 ± 0.7 to 14.2 ± 1 units/ml, $P = 0.020$; PAI-1: 6.5 ± 1 to 10 ± 2 ng/ml, $P = 0.030$; and FMD: 5.4 ± 0.4 to 4.0 ± 0.3%, $P = 0.032$). Serum glucose and VCAM-1 levels remained unchanged.

CONCLUSIONS — Significant increases in serum AGEs can occur together with altered clinical measures of endothelial function in diabetic and nondiabetic subjects after a single modest AGE-rich beverage. Thus, repeated or chronic exposure to high AGE diets could over time lead to and/or accelerate vascular disease.

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Cardiovascular disease (CVD) is the leading cause of morbidity and mortality among patients with diabetes (1,2). Elevated levels of oxidants such as advanced glycation end products (AGEs) are known promoters of high oxidative stress, playing a significant role in the pathogenesis of diabetic CVD (3–5). Whereas AGEs are better known as products of hyperglycemia, they are also abundant in the standard Westernized diet (6–9). AGEs are especially elevated in dietary mixtures of proteins, lipids, and sugars processed under elevated temperatures, as in broiling, roasting, or grilling (6,7). Specific immunoassays provide practical and reliable means for the detection of representative types of AGEs that are present in human serum, urine, and tissues, as well as in dietary products (8,10,11). Among the more frequently used assays are immunoreactive probes for N^{ε}-(carboxymethyl)lysine (CML) or methyl-glyoxal derivatives, serving as examples of dietary oxidants, shown to share the proinflammatory and prooxidant properties of the endogenous AGEs, based on in vitro studies (8) and animal models of CVD (12–14). The reduction of certain dietary AGEs has been associated with the prevention of CVD in mice (12–14), whereas in diabetic patients, their restriction has produced significant decreases in serum AGE levels, in parallel with a reduction in circulating vascular cell adhesion molecule 1 (VCAM-1), tumor necrosis factor-α, and C-reactive protein, despite sustained hyperglycemia (15), strengthening the link between chronic exposure to exogenous AGEs, elevated oxidative stress, and diabetic vascular disease.

Recently, we showed that the administration of a single full meal rich in AGEs to human subjects led to acute impairment of arterial vasodilation in response to ischemia (flow-mediated dilation [FMD]), a result interpreted as an early indication of endothelial dysfunction (16). A similar vasodilatory defect has been described after an oral load of glucose or fatty acids (17–19). Because the AGE-rich meal used in the above-mentioned study (16) also contained carbohydrates and fatty acids, it was difficult to distinguish a purely AGE-related effect on FMD. The current study was designed to further assess the hypothesis that dietary AGEs can acutely alter endothelial function in human subjects with or without preexisting diabetes. An AGE-rich beverage free of carbohydrates or lipids or other known vasoactive substances was administered to diabetic as well as healthy subjects, and its acute effects on arterial endothelial function were assessed, based on FMD in response to ischemia and circulating levels of VCAM-1 and plasmino-

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Abbreviations: AGE, advanced glycation end product; CML, N^{ε}-(carboxymethyl)lysine; CVD, cardiovascular disease; FMD, flow-mediated dilation; PAI-1, plasminogen activator inhibitor 1; sAGE, serum AGE; VCAM-1, vascular cell adhesion molecule 1.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Characteristics of the study population*

	Diabetic subjects	Healthy subjects
n	44	10
M:F ratio	36:8	5:5
Age (years)	50.5 ± 2	43 ± 4*
BMI	25.7 ± 0.5	25 ± 2
A1C	8.6 ± 0.3	NA
Fasting blood glucose (mg/dl)	157 ± 16	100 ± 7*
Serum creatinine (mg/dl)	0.8 ± 0.02	0.9 ± 0.02
Serum AGE (units/ml)	10.5 ± 0.7	7.1 ± 0.5*
PAI-1 (ng/ml)	6.5 ± 0.8	5.4 ± 0.4
VCAM-1 (ng/ml)	1,407 ± 115	846 ± 158*
FMD (%)	5.4 ± 0.4	9.9 ± 0.7*

Data are means ± SE. *Statistically significant difference between diabetic and nondiabetic subjects ($P < 0.05$).

gen activator inhibitor 1 (PAI-1). The findings were consistent with abnormal endothelial response to an oral AGE test in normal individuals and a worsening of preexisting vascular dysfunction in diabetic subjects.

RESEARCH DESIGN AND METHODS

— A group of 44 stable diabetic subjects and 10 healthy subjects underwent noninvasive measurement of brachial artery FMD with simultaneous measurement of circulating levels of AGEs, PAI-1, VCAM-1, and glucose, before and after the ingestion of 300 ml of an AGE-rich test beverage. We chose to repeat measurements at 90 min based on preliminary pilot data. The diabetic patients had an average duration of diabetes of 15 ± 1.5 years (Table 1). There were 23 type 1 and 21 type 2 diabetic patients. Most of the patients had no clinical evidence of diabetic complications. Ten patients had diabetic retinopathy, three had peripheral artery disease, and one had coronary artery disease. None of the patients had evidence of nephropathy, as determined by a lack of microalbuminuria or proteinuria and normal serum creatinine. Any patient with symptoms suggestive of diabetic gastroparesis was excluded. Medications, except for basal insulin in type 1 diabetic subjects, were not administered for 12 h before the study to avoid potential interferences with the measured parameters. Medications included insulin (patient, $n = 36$), aspirin ($n = 10$), ACE inhibitors ($n = 6$), statins ($n = 4$), β-blockers ($n = 3$), and fibrates ($n = 1$). Healthy subjects had normal renal function and no clinical evidence of diabetes or CVD (Table 1).

Levels of AGEs in serum and in the test beverage were measured by enzyme-linked immunosorbent assay using a monoclonal antibody against CML-KLH (keyhole limpet hemocyanin) (4G9 mAb; Alteon, Northvale, NJ) (8,10,11). Plasma samples were tested for PAI-1 and serum samples for VCAM-1 using commercially available enzyme-linked immunosorbent assay kits (15,20).

The oral AGE challenge beverage (300 ml) contained 1.8×10^6 AGE units, but neither carbohydrates nor lipids. This beverage was prepared from glucose and caffeine-free Coca-Cola light, which was concentrated 10 times by rotary evaporation at room temperature. Twelve subjects who had a drop of FMD >20% with the test beverage accepted to be retested on a subsequent day, after replacing the AGE beverage with 300 ml drinking water to exclude the potential influences of gastrointestinal distention and incretin release on FMD.

Flow-mediated arterial vasodilation

FMD was assessed by measuring the response of brachial artery diameter to reactive hyperemia, as previously described (21). Endothelium-dependent dilation was defined as the percent change in arterial diameter after reactive hyperemia, relative to the baseline diameter. Repeated measurements of recorded images showed a coefficient of variation of 0.22 ± 0.16%. The day-to-day variability of FMD investigated in 13 subjects was −0.05 ± 1.6% (range −3.1 to 2.44%).

Subjects presented to the testing unit in the morning after an overnight fast, and measurements were performed immediately before and 90 and 150 min after the ingestion of the AGE-rich beverage.

Statistical analysis

All data are given as means ± SE, unless otherwise stated. Differences of means between groups were analyzed by the paired or unpaired Student's *t* test. All reported *P* values are based on two-sided tests. Statistically significant difference was defined as a *P* value <0.05. All data analysis was performed using the SPSS statistical program (SPSS 14.0 for Windows; SPSS, Chicago, IL).

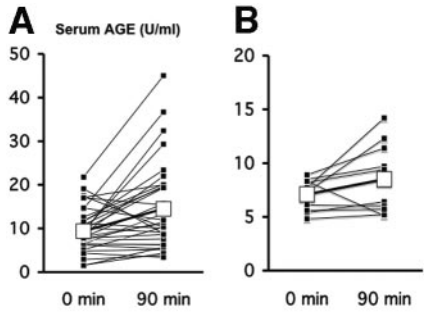

**Figure 1—*Effect of an oral AGE challenge test on sAGEs in diabetic* (A) *and healthy control* (B) *subjects. Values were obtained at baseline and at 90 min after the ingestion of an AGE challenge (300 ml) by 44 diabetic and 10 healthy subjects. Mean differences between baseline and 90 min are statistically significant* ($P < 0.05$).

RESULTS — Diabetic subjects had higher fasting serum AGE (sAGE) levels, based on CML (10.5 ± 0.7 vs. 7.1 ± 0.5 units/ml, $P = 0.020$), higher VCAM-1 (1,407 ± 115 vs. 846 ± 158 ng/ml, $P = 0.033$) and PAI-1 (6.5 ± 0.8 vs. 5.4 ± 0.4 ng/ml, NS), and lower FMD (5.4 ± 0.4 vs. 9.9 ± 0.7%, $P = 0.032$) compared with healthy control subjects (Table 1). The administration of the oral AGE challenge to diabetic subjects was followed at 90 min by a significant increase in serum AGE above the baseline ($P = 0.001$; Fig. 1*A*) and PAI-1 levels ($P = 0.028$; Fig. 2*A*). At 90 min, there was also a significant decrease in maximal arterial dilation after ischemia below the baseline (FMD) ($P = 0.000$; Fig. 3*A*). There were no significant changes in serum levels of glucose during this period (157 ± 16 vs. 153 ± 15 mg/dl, NS). Also, there were no significant changes in plasma levels of VCAM-1 (1,407 ± 115 vs. 1,252 ± 104 ng/ml, NS).

Similar significant changes in sAGE, PAI-1, and FMD were observed in the nondiabetic subjects 90 min after exposure to the same oral AGE challenge (Figs. 1*B*, 2*B*, and 3*B*). By 150 min, FMD values were at baseline (diabetic subjects: 5.5 ± 0.5%; healthy subjects: 9.6 ± 0.7%), although serum AGE levels (diabetic: 17 ± 2 units/ml; healthy: 13 ± 2 units/ml) and PAI-1 (diabetic: 11.7 ± 1 ng/ml; healthy: 7.3 ± 0.5 ng/ml) were still elevated.

There were no significant differences in the percent change of sAGE, PAI-1, or FMD between diabetic and healthy subjects. There were no significant associations between baseline levels of sAGE and either PAI-1 or FMD in diabetic or healthy subjects.

In 12 diabetic subjects, who under-

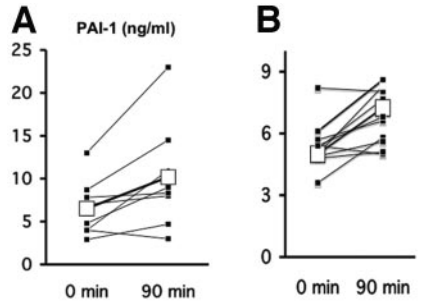

Figure 2—*Effect of an oral AGE challenge test on circulating PAI-1 levels in diabetic* (A) *and healthy control* (B) *subjects. Values were obtained at baseline and at 90 min after the ingestion of an AGE challenge (300 ml) by 44 diabetic and 10 healthy subjects. Mean differences between baseline and 90 min are statistically significant* ($P < 0.05$).

went repeated FMD testing with water, no significant arterial changes were noted between the baseline and the 90-min points (0 min: 5.2 ± 0.7%; 90 min: 5.6 ± 0.7%), although they manifested a significant change in FMD when tested with the oral AGE challenge (0 min: 5.2 ± 0.6%; 90 min: 3.08 ± 0.38%; $P = 0.000$).

CONCLUSIONS — The evidence presented indicates that a single oral load of an AGE-rich beverage free of glucose or lipids to diabetic as well as to healthy subjects is associated with a significant rise of serum AGE levels in parallel with an acute impairment of endothelial function, as reflected both by a decrease in arterial vasodilation in response to ischemia and by an increase in circulating PAI-1 levels.

The significant decrease in brachial artery vasodilation after ingestion of an AGE-rich beverage was similar to the impaired vasodilation observed after an oral load of glucose or fatty acids (17–19). The AGE-rich beverage used in the present study did not contain glucose, lipids, or other substances known to impede vascular dilatory capacity or to affect endothelial cell properties. These effects were therefore attributable to the AGE load ingested, which in addition to the prototype CML tested here, could also include other AGE intermediates, known to mediate endothelial injury, i.e., glyoxal or methylglyoxal derivatives (22). The contribution of additional non-AGE chemical substances is also possible, although none has been known thus far. We have recently reported that the ingestion of a single solid AGE-rich meal is followed by a significant impairment of FMD, which can persist for 6 h (16). The shorter duration of the vasodilatory impairment observed in the current study could reflect the absence of glucose and lipids, the involvement of different AGE compounds and their effects on vascular cells, or variable rates of absorption and elimination, relative to those ingested with a mixed meal (16). Alternatively, this could be due to the induction of a counterregulatory hemodynamic response to the oral load, i.e., release of prostaglandins (a less likely explanation).

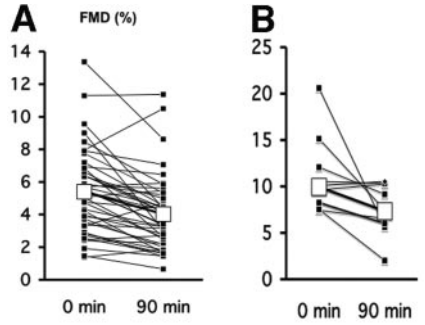

Figure 3—*Effect of an oral AGE challenge test on FMD in diabetic* (A) *and healthy control* (B) *subjects. Values were obtained at baseline and at 90 min after the ingestion of an AGE challenge (300 ml) by 44 diabetic and 10 healthy subjects. Mean differences between baseline and 90 min are statistically significant* ($P < 0.05$).

AGEs, whether endogenous or exogenously derived, have significant and direct effects on endothelial cells, including increased expression and release of VCAM-1 (23,24) and decreased endothelial nitric oxide synthase (25,26). Particularly noteworthy were the findings from the healthy subjects, the vascular endothelium of which seemed on the whole equally vulnerable to an acute AGE load as that of the diabetic subjects. Indeed, the percent change of FMD values as well as PAI-1 and AGE levels were not significantly different in healthy subjects compared with diabetic subjects. In the present study, we did not investigate endothelium-independent vasodilation in response to nitroglycerin because the marked and often persistent vasodilation produced by this agent would have interfered with the second measurement of FMD 90 min after the baseline test. However, this was addressed in our previous report in which endothelium-independent vasodilation was not altered significantly after a single high-AGE meal (16). This could be due to the time-limited impact on tissue AGE levels by a single load. Rather, acutely elevated circulating AGEs could alter endothelium-dependent response by decreasing nitric oxide (NO) production by endothelial cells (25,26) or by inactivating NO (27), causing a decrease in NO bioavailability.

Based on the estimated daily AGE consumption by human subjects of 16×10^6 AGE Eq/day) (6), the amount of AGEs administered during the oral AGE test was similar to that of a regular meal. While a larger challenge might have provoked greater vascular dysfunction, the study was designed so as to provide a more physiological window through which specific events and their significance could be observed. Because the consumption of similar amounts of AGEs is quite common in the general population, similar endothelial insults may occur repeatedly and often. Because endothelial dysfunction represents an early step in the development of atherosclerosis (21), repeated endothelial disturbances of the endothelial integrity may over time lead to CVD in healthy individuals or exacerbate preexisting vascular disease in those with diabetes.

The diabetic patients in this study had high CML levels and established endothelial dysfunction independently of the presence of diabetic complications and despite apparently good glycemic control. Thus, impaired baseline FMD in diabetic subjects, even when under fair glycemic control, may in part be due to the higher steady-state serum AGE levels, relative to that of healthy subjects, possibly involving both endothelium-dependent and -nondependent mechanisms. Higher AGE deposits in the subendothelial matrix of the diabetic subjects could quench NO released by the endothelium and could account for the abnormal baseline values in this group (27). It has indeed been suggested that AGEs are more potent inhibitors of endothelial NO activity than high glucose (26).

The current data are consistent with previous findings demonstrating a rapid increase of serum AGE levels after a single oral AGE challenge in both diabetic and healthy subjects (28). Also, a direct association has been recently found in healthy human subjects between chronically ingested CML and circulating CML, other AGEs (i.e., methyl-glyoxal derivatives) and C-reactive protein (29). Moreover, circulating CML levels were associated with markers of oxidative stress, i.e., 8-isoprostane and insulin resistance (29). Of note, diet-derived AGEs were found to be the best predictors of high sAGEs (29). These studies indicate that, regardless of

hyperglycemia, high sAGEs, whether native or dietary in origin, could signal and/or contribute to alterations in oxidative stress and the vascular cell inflammatory state, which could in turn subvert vascular wall function (29).

AGE-rich beverages, e.g., cocoa with or without sugar, which contains about 0.6 AGE Eq in a serving of 250 ml (6), are often ingested with regular meals and together or independently can contribute to vascular injury. By comparison, low dietary AGE intake can reduce levels of sAGEs and inflammatory markers in diabetic (15) or renal failure patients (20,30). These findings strongly support the view that exogenous AGEs are not only important contributors to the body's AGE pool, but are also a significant risk to the vascular integrity of both diabetic and healthy individuals.

It has been determined that the content of AGEs in foods relates strongly to the amount of exposure to heat (6,7) and that their toxic consequences may depend on a chronic pattern of consumption (29). The current report demonstrates that even a single, modest in size oral AGE challenge can provoke a significant vascular insult in both healthy individuals and in diabetic subjects. It is therefore reasonable to conclude that, during recurrent ingestion of high AGE foods, multiple insults to the vasculature can result in persistent endothelial dysfunction and, over time, in overt vascular disease. Further studies are needed to dissect the mechanistic links between oral AGEs and diabetic or nondiabetic vascular disease and to establish methods for avoiding high dietary AGE intake as an effective nonpharmacological intervention for the diabetic as well as the diabetes-prone population of today.

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