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High serum pentosidine concentrations are associated with increased arterial stiffness and thickness in patients with type 2 diabetes

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Abstract

Accumulation of advanced glycation end products in vessel walls may increase arterial stiffness and/or thickness, contributing to a high incidence of cardiovascular disease (CVD) in patients with diabetes.

We investigated whether serum concentrations of pentosidine, a well-defined advanced glycation end product, are associated with arterial stiffness or thickness in patients with type 2 diabetes. Pentosidine was measured in sera from 98 patients with type 2 diabetes and 61 age-matched control subjects by a competitive enzyme-linked immunosorbent assay. Arterial stiffness was evaluated by heart-brachial and brachial-ankle pulse wave velocities (PWVs) measured using an automatic device. Arterial thickness was determined ultrasonographically as carotid intima-media wall thickness (IMT). Serum concentrations of pentosidine were significantly higher in patients with diabetes than in control subjects (64.4 ± 21.0 vs 22.8 ± 7.0 μg/L; $P < .0001$). In patients with diabetes, serum pentosidine correlated positively with heart-brachial PWV ($r = 0.304$; $P < .01$) but not with brachial-ankle PWV. Serum pentosidine also correlated positively with carotid IMT in patients with diabetes ($r = 0.300$; $P < .01$). Serum pentosidine concentrations were significantly higher in patients with diabetes with CVD than in those without (72.3 ± 23.7 vs 62.3 ± 19.8 μg/L; $P = .0453$). By multivariate analysis, only age (partial coefficient = 0.308; $P < .05$) and serum creatinine (partial coefficient = 0.328; $P < .01$) retained significant influence on serum pentosidine. After adjustment for renal function, carotid IMT still correlated positively with serum pentosidine (partial coefficient = 0.2736; $P = .021$). In conclusion, serum pentosidine was positively associated with both arterial stiffness and thickness and CVD in patients with type 2 diabetes.

1. Introduction

Advanced glycation end products (AGEs) are generated by nonenzymatic glycation and oxidation of protein and reducing sugars [1]. Because AGEs accumulate in the kidneys and in coronary artery atherosclerotic plaques [2,3], AGEs are considered to be pivotal in the development of micro- and macroangiopathy in patients with diabetes. Among the few AGEs characterized to date, pentosidine is chemically well defined [4]. Free pentosidine, with a relative molecular weight of 379 d, can be synthesized through nonenzymatic reactions of pentoses such as ribose, xylose, arabinose, and lyxose with L-lysine, L-arginine, or collagen [5]. Because the formation of pentosidine requires oxidation as well as glycation [6], serum pentosidine concentrations may be a useful marker of glycoxidation. Previous studies have reported that serum pentosidine was significantly higher in patients with diabetes than in subjects without diabetes and was associated with an increased incidence of cardiovascular disease (CVD) [7,8]. Both pentosidine levels in sera and skin of patients with type 1 diabetes correlate with the severity of diabetic complications [9].

Recently, clinical interest has been growing in noninvasive methods for detecting early atherosclerosis. Carotid intima-media wall thickness (IMT), an ultrasonographic marker of early atherosclerosis [10], not only shows a strong relationship with CVD risk factors but also predicts cardiovascular events such as myocardial infarction [11,12]. Carotid IMT has been reported to be greater in patients with type 2 diabetes than in age-matched control subjects [13,14]. A different parameter, pulse wave velocity (PWV), can noninvasively measure aortic and peripheral arterial stiffness [15] because it is increased in more rigid arteries. Several reports have demonstrated that patients with type 2 diabetes have higher PWVs as compared with

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individuals without diabetes [16,17]. Furthermore, high aortic PWV has been associated with the development of CVD [16,18]. Accumulation of AGEs in vessel walls could induce arterial stiffness, contributing to the development of CVD.

Considering these points, we suspected that increased AGEs contributed to high PWV and increased carotid IMT observed in patients with type 2 diabetes. As few reports have examined relationships between serum AGEs and PWV or carotid IMT in type 2 diabetes, we investigated whether serum pentosidine in patients with type 2 diabetes was associated with early markers of atherosclerosis such as carotid IMT and brachial-ankle PWV (baPWV). We also compared serum pentosidine concentrations between those with and without CVD.

2. Subjects and methods

We studied 98 patients with type 2 diabetes (44 women and 54 men). The patients with diabetes had been referred to the diabetes outpatient clinic of the Dokkyo University Hospital because of inadequate glycemic control. Patients with any liver disease or peripheral vascular disease (PVD) were also excluded. Peripheral vascular disease, defined as symptoms of intermittent claudication or a history of peripheral artery reconstruction or amputation of a foot, was chosen as an exclusion criteria because baPWV could be decreased in a leg affected by PVD. Before measurements, all patients received optimal diet therapy (105 kJ/kg standardized body weight, 50% carbohydrate, 20% protein, and 30% fat) for at least 3 months.

Forty-four of the patients with diabetes had hypertension, defined as systolic blood pressure exceeding 140 mm Hg and/or diastolic blood pressure exceeding 90 mm Hg or alternatively as treatment with one or more antihypertensive agents. The latter included angiotensin-converting enzyme inhibitors (n = 12), calcium blockers (n = 22), and angiotensin receptor blockers (n = 9).

Cardiovascular disease was defined as coronary artery disease (CAD) or stroke. Coronary artery disease was defined as a history of myocardial infarction, coronary artery bypass grafting, or an abnormal coronary angiogram. Stroke was defined as a history of ischemic stroke confirmed by cerebral computed tomography or magnetic resonance imaging. Twenty-two of the patients with diabetes had CVD (12 with CAD, 10 with stroke).

As a control group, 61 subjects without diabetes were selected to match the overall age and sex distribution of the diabetic group. Their age was 60.1 ± 9.8 years, and their body mass index (BMI) was 23.8 ± 3.9 (mean ± SD). All subjects gave informed consent. The study was approved by the Dokkyo University Institutional Review Board.

Venous blood was obtained between 6:00 and 7:00 AM after an overnight fast. Serum pentosidine concentrations were measured using a commercially available competitive enzyme-linked immunosorbent assay (ELISA; FSK pentosidine ELISA kit, Fushimi Pharmaceutical, Kagawa, Japan). This method involves pretreating sera with a proteolytic enzyme (pronase) and then measuring concentrations of pentosidine in the sample by ELISA [19]. Intra- and interassay coefficients of variation were 5.1% to 14.0% and 9.5% to 13.0%, respectively. Hemoglobin A1c (HbA1c) was measured by high-performance liquid chromatography. Serum C-peptide was determined by radioimmunoassay.

Urinary albumin excretion concentrations after a 24-hour collection were measured with an immunoturbidimetric assay. Creatinine clearance was calculated using the same urine collection.

3. Carotid intima-media wall thickness measurements

Carotid IMT was determined in the common carotid artery using duplex ultrasonography with a high-resolution 7.5-MHz transducer (SSA-380A; Toshiba, Tokyo, Japan). Carotid IMT was defined as the distance from the leading edge of the first echogenic line to the leading edge of the second echogenic line in the sonographic image. Twenty measurements were obtained automatically from each image on both left and right sides. Carotid IMT was defined as the mean for right and left common carotid artery IMTs. All scans were performed by a physician trained in ultrasonography (KK).

4. Pulse wave velocity measurements

Pulse wave velocity was measured after 20 minutes in a supine position by an automatic device (form PWV/ABI, Colin Medical Technology, Komaki, Japan). This device simultaneously recorded pressure waveforms at the base of the aorta and in brachial and tibial arteries [20]. The distance traveled by the pulse wave was measured over the body surface as the distance between the 2 recording sites. Pulse wave velocity was calculated as the ratio of distance to

Table 1
Characteristics of control subjects and patients with type 2 diabetes

	Control subjects	Patients with diabetes
n (M/F)	61 (31:30)	98 (54:44)
Age (y)	60.1 ± 9.8	58.9 ± 12.3
BMI (kg/m^2)	23.4 ± 3.8	23.7 ± 3.9
Duration of diabetes (y)	–	11.4 ± 7.8
FPG (mg/dL)	103 ± 12.6	165 ± 84.0*
HbA1c (%)	5.0 ± 0.3	9.57 ± 1.79*
Serum creatinine (mg/dL)	0.74 ± 0.24	0.78 ± 0.34
Serum pentosidine (μg/L)	22.8 ± 7.0	64.4 ± 21.0*
Carotid IMT (mm)	0.59 ± 0.11	0.75 ± 0.24*
hbPWV (cm/s)	520 ± 63	602 ± 94*
baPWV (cm/s)	1293 ± 153	1760 ± 406*
Treatment (D/OHA/Ins)	–	31:49:18

Data are mean ± SD or median and interquartile. FPG indicates fasting plasma glucose; D, diet alone; OHA, oral hypoglycemic agents; Ins, insulin.
* $P < .0001$ vs control.

Table 2
Linear regression analysis of relationships between serum pentosidine concentrations and characteristics of patients with type 2 diabetes

Variables	Pentosidine	
	r	*P*
Age (y)	0.3484	.0004
BMI	−0.1961	.0529
Duration of diabetes (y)	0.2702	.0119
SBP (mm Hg)	−0.080	.4477
DBP (mm Hg)	−0.0245	.8173
FPG (mg/dL)	0.0028	.9780
HbA1c (%)	−0.097	.3457
Total cholesterol (mg/dL)	−0.2182	.0309
Triglyceride (mg/dL)	−0.1531	.1343
HDL-C (mg/dL)	0.2382	.0188
Serum C-peptide (ng/mL)	−0.2908	.0045
Serum creatinine (mg/dL)	0.2727	.0089
UAE ($\log_{10}$ mg/24 h)	−0.1601	.1231

SBP indicates systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; UAE, urinary albumin excretion.

transit time. Heart-brachial PWV (hbPWV) and baPWV were used for analysis.

5. Statistical analysis

Data are expressed as the mean ± SD. Differences between groups were analyzed by an unpaired *t* test. Correlation was determined by linear regression analysis. Significance of difference in prevalence between groups was analyzed by χ^2 tests. A logarithmic transformation of urinary albumin values was used to render the distribution normal for parametric tests. Multivariate analysis was performed to determine the relationship of serum pentosidine concentration to age, diabetes duration, glycemic control, urinary albumin, and renal function. A *P* value below .05 was accepted as statistically significant.

6. Results

Characteristics of all subjects including their serum concentrations of pentosidine are shown in Table 1. No significant differences were evident in age or BMI between control subjects and patients with diabetes. Serum concentrations of pentosidine were significantly higher in patients with diabetes than in age-matched control subjects (64.4 ± 21.0 vs 22.8 ± 7.0 μg/L; $P < .0001$). Carotid IMT was significantly greater in patients with diabetes than in control subjects (0.75 ± 0.24 vs 0.59 ± 0.11 mm; $P < .0001$). The hbPWV was significantly higher in patients with diabetes than in control subjects (602 ± 94 vs 520 ± 63 cm/s; $P < .0001$). The baPWV also was significantly higher in patients with diabetes than in control subjects (1760 ± 406 vs 1293 ± 153 cm/s; $P < .0001$).

By linear regression analysis in the 98 patients with type 2 diabetes, serum pentosidine concentrations correlated positively with age, high-density lipoprotein cholesterol (HDL-C), and serum creatinine, whereas serum pentosidine correlated negatively with total cholesterol and serum C-peptide (Table 2). Furthermore, serum concentrations of pentosidine correlated positively with carotid IMT in patients with diabetes ($r = 0.300$; $P < .01$; Fig. 1). Serum pentosidine

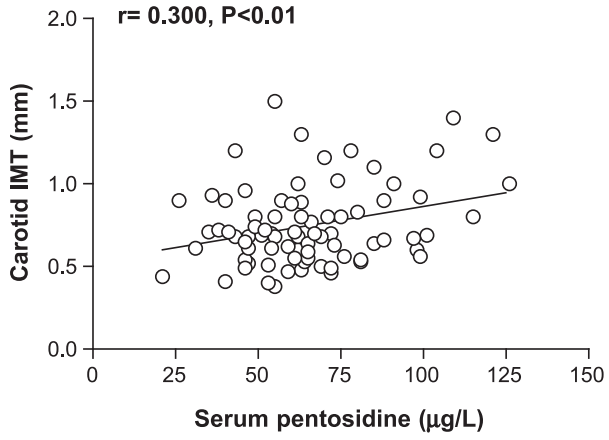

Fig. 1. Correlation between carotid IMT and serum pentosidine concentrations in patients with type 2 diabetes.

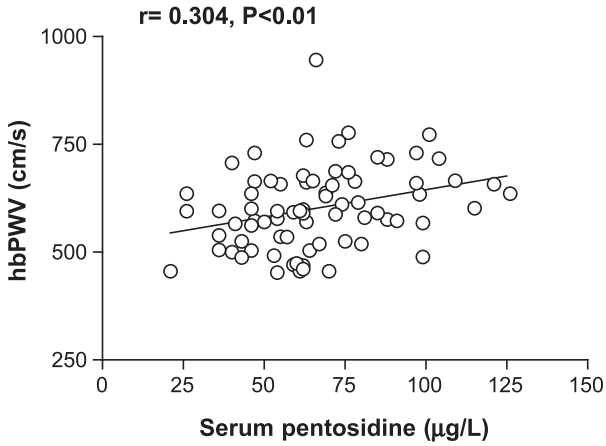

Fig. 2. Correlation between serum pentosidine concentrations and hbPWV in patients with type 2 diabetes.

Table 3
Multivariate analysis of relationships between serum pentosidine concentrations and selected variables in patients with type 2 diabetes

Variable	Partial coefficient	*P*
Age (y)	0.308	.020
Duration of diabetes (y)	0.102	.450
BMI	−0.047	.728
SBP (mm Hg)	−0.140	.298
DBP (mm Hg)	0.106	.432
FPG (mg/dL)	0.043	.751
HbA1c (%)	−0.063	.644
Total cholesterol (mg/dL)	−0.015	.889
Triglyceride (mg/dL)	0.030	.772
HDL-C (mg/dL)	0.005	.968
Serum C-peptide (ng/mL)	−0.174	.125
Serum creatinine (mg/dL)	0.328	.003
UAE ($\log_{10}$ mg/24 h)	−0.205	.125

$R^2 = 0.399$.

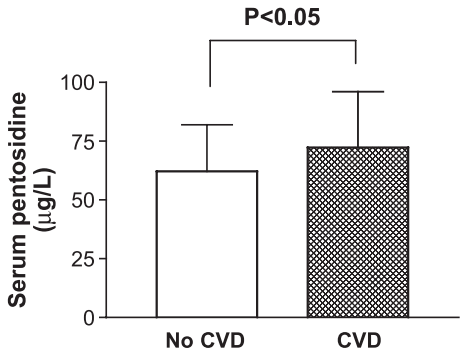

Fig. 3. Serum concentration of pentosidine in patients with type 2 diabetes with and without CVD.

correlated positively with hbPWV ($r = 0.304$;$P < .01$; Fig. 2) but not with baPWV($r = 0.181$; not significant).

To determine independent factors for serum pentosidine concentrations, we performed multivariate analysis controlling for age, BMI, diabetes duration, blood pressure, blood lipids, glycemic control, and renal function. In a model that explained 63.2% of variation of serum pentosidine, only age and serum creatinine were independent determinants of serum pentosidine in patients with diabetes (Table 3).

To investigate whether serum pentosidine is an independent risk factor for arterial stiffness or thickness, we performed multivariate analysis controlling creatinine clearance because renal function is a major determinant of serum pentosidine concentration. After adjustment for creatinine clearance carotid IMT (partial coefficient = 0.2736; $P = .021$), but not hbPWV (partial coefficient = 0.2140; $P = .120$), still correlated positively with serum pentosidine in patients with type 2 diabetes.

Next, we divided the patients with diabetes into 2 groups according to the presence of CVD. We found no difference in age, BMI, or duration of diabetes between these groups (data not shown). Hemoglobin A1c was significantly lower in patients with CVD than in those without CVD (8.8% ± 1.5% vs 9.8% ± 2.0%; $P < .05$). No difference was found in total cholesterol or HDL-C between patients with and without CVD (data not shown). Triglyceride was significantly higher in patients with CVD than in those without CVD (225 ± 221 vs 136 ± 68 mg/dL; $P < .01$), as was serum creatinine (0.98 ± 0.47 vs 0.72 ± 0.27 mg/dL; $P < .01$). Hypertension was more prevalent in patients with CVD (68% vs 25%; $P < .05$). Finally, serum pentosidine concentrations were significantly higher in patients with than in those without CVD (72.3 ± 23.7 vs 62.3 ± 19.8 μg/L; $P < .05$; Fig. 3).

7. Discussion

The present study confirmed that serum pentosidine concentrations were significantly higher in patients with diabetes than in age-matched control subjects, in agreement with previous studies [8,21]. One possible explanation for high serum pentosidine in patients with diabetes is that pentosidine production is accelerated in a hyperglycemic state. A previous study reported that plasma pentosidine was significantly higher in patients with diabetes and was influenced mainly by renal function and glycemic status [8]. However, we found no significant correlation between serum pentosidine and HbA1c concentrations in patients with diabetes. Several previous studies similarly failed to confirm a significant correlation between serum AGEs and glycemia as measured by HbA1c or fasting plasma glucose in patients with diabetes [22,23]. We speculate that factors other than hyperglycemia such as genetic differences [24] may contribute to the formation of pentosidine in diabetes. Increased oxidative stress also may be responsible for increased serum pentosidine in diabetes because pentosidine is a glycoxidation product [6].

We also found a positive correlation between serum pentosidine and serum creatinine concentrations in patients with diabetes. Multivariate analysis also showed serum creatinine to be an independent factor influencing serum pentosidine. Because the kidney is the main elimination site for pentosidine [25], several studies have examined serum pentosidine concentrations in patients with diabetes with overt nephropathy or those with chronic renal disease, reporting elevations [8,26,27]. Especially, a dramatic increase in plasma pentosidine was reportedly found in patients with end-stage renal disease [28]. Renal insufficiency thus may lead to accumulation of pentosidine in the blood because renal insufficiency is a major determinant of serum pentosidine [29].

The present study demonstrated that by multivariate analysis, age was an independent factor increasing serum pentosidine, even in patients with diabetes. This may reflect declining glomerular filtration rates in association with aging because renal insufficiency may be a major determinant of serum pentosidine. Advancing age is similarly a major risk factor for atherosclerotic vascular disease, irrespective of the presence or absence of diabetes. A growing body of evidence has linked age-associated vascular changes, including increased large-artery thickening and stiffness as well as endothelial dysfunction, with higher risks of developing clinically manifest atherosclerosis [27]. Several studies [30,31] confirmed that both carotid IMT and aortic PWV increase with age in adults, suggesting that aging is associated with a number of changes in cardiovascular structure and function. Because serum pentosidine also increases with aging, this AGE may play a role in age-associated increases in CVD incidence.

In the present study, serum pentosidine concentrations showed a significant positive correlation with carotid IMT in patients with diabetes. Even after adjustment for renal function, carotid IMT still correlated positively with serum pentosidine. Carotid IMT, a marker of early atherosclerosis, not only shows a strong relationship with CVD risk factors but also predicts cardiovascular events such as myocardial infarction [11,12]. Several reports have demonstrated that

carotid IMT was greater in patients with type 2 diabetes than in age-matched control subjects [13,14]. A previous study demonstrated greater amounts of pentosidine in the intima and media of autopsy specimen from the descending aorta in 9 patients with type 1 diabetes than in 18 control subjects; furthermore, a significant correlation was evident between stiffness and pentosidine content in the aorta [32]. The increase in IMT may reflect the hypertrophy of vascular smooth muscle, which has been shown to cause thickening of intimal and medial layers [33]. Accumulation of pentosidine in vascular walls or, possibly, stimulation of smooth muscle cell proliferation by pentosidine may contribute to increased carotid IMT in patients with type 2 diabetes. Thus, elevated serum pentosidine may prove to be a useful marker for carotid arterial thickness in patients with diabetes.

The present study also demonstrated that serum pentosidine concentrations correlated positively with hbPWV, a measure of peripheral arterial stiffness, in patients with type 2 diabetes. Previous studies reported that aortic PWV was significantly higher in patients with type 2 diabetes than in subjects without diabetes [16,17], suggesting stiffer arteries in patients with diabetes. One possible explanation is nonenzymatic glycosylation of matrix proteins caused by chronic hyperglycemia. A previous study in rats demonstrated that administration of aminoguanidine, an inhibitor of AGE formation, reduces aortic PWV in aged rats by decreasing the degree of AGE-induced cross-linking of the extracellular matrix scleroprotein [34]. Another explanation might be the simple accumulation of AGEs in arterial walls because AGE deposits can be found in atherosclerotic plaques in vessels from patients with diabetes [3]. Thus, accumulation of AGEs in arteries or glycation of their extracellular matrix constituents may contribute to arterial stiffness, making CVD more likely in patients with diabetes. Taken together, the results suggest that high serum pentosidine may contribute importantly to arterial stiffness in patients with type 2 diabetes.

We found no significant correlation between serum pentosidine and baPWV, another measure of peripheral arterial stiffness, in patients with diabetes. Several reports showed decreased baPWV in the affected leg in patients with PVD [35,36]. Because PWV is influenced significantly by blood pressure, arterial stenosis in the affected leg may reduce ankle blood pressure, resulting in lowered PWV. Although we excluded patients with clinical PVD from analysis, we might have included some patients with diabetes who have subclinical PVD; this might have obscured a correlation between serum pentosidine and baPWV in patients with diabetes. In any case, baPWV appears to be a less reliable marker for arterial stiffness in patients with diabetes, especially those with PVD.

We found serum concentrations of pentosidine to be significantly higher in patients with diabetes with than in those without CVD, in agreement with previous studies [8,23,37]. Sugiyama et al [8] similarly reported that plasma pentosidine was significantly higher in patients with diabetes with than those without ischemic heart disease. Our groups as well as others have reported that serum concentrations of AGEs including pentosidine are associated with the development of CAD in patients with type 2 diabetes [23,37]. Because synthesis of pentosidine involves both glycation and oxidation, high serum pentosidine concentrations may reflect oxidative stress in patients with diabetes. Indeed, oxidative stress has been implicated in vascular damage associated with atherosclerosis. We believe that the association of high serum pentosidine with arterial thickness and stiffness is likely to lead to CVD in patients with diabetes.

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