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The association of plasma adiponectin level with carotid arterial stiffness

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Abstract

Adiponectin plays important roles in protecting against both insulin resistance and the development of atherosclerosis. The aim of the present study was to investigate the clinical impact of plasma adiponectin on arterial stiffness, a functional property of atherosclerosis, in type 2 diabetic and nondiabetic subjects. We evaluated plasma adiponectin levels and stiffness index β for the common carotid artery assessed by ultrasound using a phase-locked echo-tracking system for 98 type 2 diabetic subjects and 116 nondiabetic subjects as controls. Plasma adiponectin levels were significantly lower in the diabetic than in the nondiabetic group. The stiffness index β was significantly higher in the diabetic than in the nondiabetic group. Plasma adiponectin level was significantly correlated with stiffness index β in the group of all subjects ($r = -0.189$, $P = .006$) and the nondiabetic group ($r = -0.187$, $P = .045$), but not in the diabetic group ($r = 0.045$, $P = .665$). On multiple regression analysis, plasma adiponectin level was found to be a significant independent contributor to stiffness index β in the group of all subjects ($\beta = -0.232$, $P = .020$) and the nondiabetic group ($\beta = -0.337$, $P = .016$), but not in the diabetic group. In conclusion, adiponectin is significantly but weakly associated with carotid arterial stiffness independently of known atherogenic factors in the nondiabetic group and that of all subjects, although no significant association between these variables was found in the group of diabetic subjects.

1. Introduction

Adiponectin, an adipocyte-specific plasma protein, exhibits its protective effects against atherosclerosis as well as an insulin-sensitizing effect [1,2]. Several in vivo and in vitro studies have reported that adiponectin inhibits monocyte adhesion to endothelial cells, lipid accumulation [3], and the proliferation of vascular smooth muscle cells [4], and exerts anti-inflammatory effects via suppression of tumor necrosis factor α production [5]. Recent clinical studies have found that hypoadiponectinemia is associated with endothelial dysfunction [6], cardiovascular disease [7], and diabetes mellitus [8]. Furthermore, patients with hypoadiponectinemia are at increased risk of myocardial infarction or cardiovascular death [9,10].

Arterial stiffness is a functional change of atherosclerosis, in contrast to arterial wall thickening, which is a morphological change, at various sites in the vascular tree [11]. Over the last decade, noninvasive ultrasound with echo-tracking systems has been developed to accurately measure arterial stiffness [12]. The stiffness index β is determined by measuring vessel diameter and blood pressure during the cardiac cycle and represents the elastic properties of the local arterial wall of the common carotid artery (CCA) or femoral artery [13,14]. Previous studies revealed that this index was worsened in patients of increased age [13], those with coronary artery disease [14], and those with diabetes mellitus [15]. Furthermore, we previously reported that stiffness index β was associated with insulin resistance, as well as peripheral artery disease in diabetes [16-18].

Taken together, these findings suggest that adiponectin may exert protective effects against arterial stiffness, and might thus improve the outcome of atherosclerotic disease. However, no studies have determined the relationship between plasma adiponectin level and stiffness of the carotid artery. In the present study, we investigated the effect of plasma adiponectin level on stiffness of the CCA using ultrasound examination in type 2 diabetic and nondiabetic subjects.

2. Method and design

2.1. Subjects

Ninety-eight type 2 diabetic subjects, consisting of 50 men and 48 women, were selected among patients attending

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Table 1
Clinical characteristics of type 2 diabetic and nondiabetic subjects

	All subjects	Diabetic	Nondiabetic	*P*
n	214	98	116	
Age (y)	59 ± 10	60 ± 11	58 ± 8	.122
Sex (male/female)	102/112	50/48	52/64	.366
Smoking	55	30	25	.131
BMI (kg/m^2)	24.8 ± 3.6	25.3 ± 4.3	24.4 ± 2.8	.069
Duration of diabetes	–	8 ± 8	–	–
MBP (mm Hg)	95 ± 13	96 ± 13	94 ± 12	.394
FPG (mg/dL)	118 ± 32	141 ± 35	99 ± 8	<.001
HbA_{1c} (%)	6.3 ± 1.8	7.7 ± 1.6	5.0 ± 0.4	<.001
IRI (mU/L)	7.2 ± 5.2	8.9 ± 6.1	5.8 ± 4.0	<.001
HOMA-IR	2.3 ± 2.4	3.2 ± 3.1	1.4 ± 1.0	<.001
TC (mg/dL)	217 ± 43	206 ± 43	227 ± 40	<.001
LDL-C (mg/dL)	134 ± 37	127 ± 32	140 ± 40	.014
TG (mg/dL)	139 ± 125	143 ± 121	134 ± 129	.558
HDL-C (mg/dL)	55 ± 18	49 ± 16	60 ± 18	<.001
GFR (mL/min)	99 ± 35	102 ± 42	96 ± 22	.270
Statin treatment	19	12	7	.112
ARB or ACEI treatment	15	10	5	.093
Hs-CRP (ng/mL)	1232 ± 2250	1808 ± 3114	746 ± 824	<.001
Adiponectin (μg/mL)	7.2 ± 3.4	5.8 ± 3.1	8.3 ± 3.3	<.001
Stiffness index β	13.0 ± 5.0	14.7 ± 5.3	11.4 ± 4.0	<.001

Values are means ± SD or the number of subjects. *P* values were compared between diabetic subjects and nondiabetic subjects.

our diabetes center at the Osaka City University Hospital, and 116 nondiabetic subjects as controls were selected among participants in the health check program of the Osaka Municipal Health Promotion Center [19]. The nondiabetic control group included 9 subjects with impaired fasting glucose, 31 with hypertension, and 78 with hyperlipidemia. The diagnosis of diabetes was based on criteria of the American Diabetes Association [20]. Sixty-six subjects in this group were treated with dietary therapy alone, 23 with sulfonylureas, 2 with α-glucosidase inhibitors, and 7 with a combination of sulfonylureas and α-glucosidase inhibitors. Those who received insulin treatment, thiazolidinediones, and glimepiride, and had a serum creatinine level of more than 1.5 mg/dL were excluded from the study because of the possibility of effects of these factors on plasma adiponectin level. Twelve type 2 diabetic subjects and 7 control subjects were treated with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins), and 10 type 2 diabetic subjects and 5 control subjects were treated with angiotensin II receptor blockers (ARB) or angiotensin-converting enzyme inhibitors (ACEIs).

2.2. Ultrasound

Ultrasonic examinations of the stiffness index β of the common carotid arteries (CCAs) were performed in the supine position with slight hyperextension of the neck using an ultrasonic phase-locked echo-tracking system equipped with a high-resolution, real-time 13-MHz linear scanner (ProSound II SSD-6500, Aloka, Tokyo, Japan). The carotid arteries were scanned bilaterally at the level of the bifurcation and the CCA, and the scanning included ~4 cm in length of the CCA, the carotid bulb, and 1 cm in length of each of the internal and external carotid arteries. The stiffness index β, an index of the elastic properties of the arterial wall, was calculated using the blood pressure and the diameter of the artery as follows: stiffness index $\beta = [\ln(Ps/Pd)] \times Dd/(Ds - Dd)$. Here, Ps and Pd are the systolic and diastolic blood pressures, and Ds and Dd are the systolic and diastolic inner diameters of the artery, respectively. The stiffness index β is a unitless quantity that is adjusted for blood pressure. Blood pressure was measured using a mercury sphygmomanometer placed on the right arm after resting for 15 minutes in the supine position before ultrasonic examination was performed. We used the higher stiffness index β value of the right or left CCA as the stiffness index β for each subject.

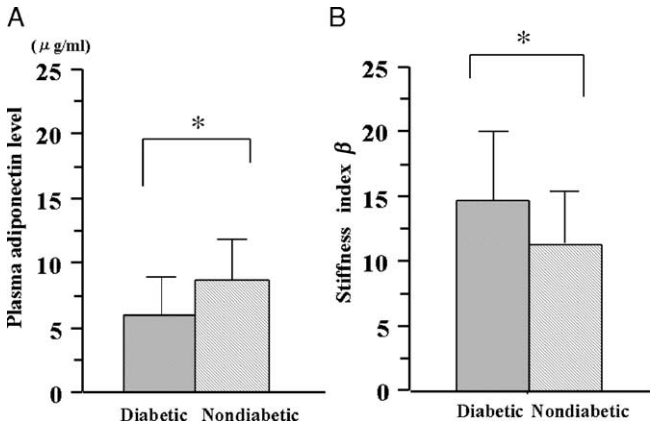

Fig. 1. Comparison of plasma adiponectin levels and stiffness index β of the carotid artery between the diabetic and nondiabetic groups. (A) Plasma adiponectin levels were significantly lower in the diabetic than in the nondiabetic group. (B) The stiffness index β was significantly higher in the diabetic than in the nondiabetic group. *$P < .0001$.

2.3. Assay of plasma adiponectin and biochemical analysis

Plasma adiponectin levels were measured using an enzyme-linked immunosorbent assay kit (Otsuka Pharmaceuticals, Tokyo, Japan) while each patient was in a fasting state. Plasma glucose levels were measured by the glucose oxidase method, HbA_{1c} by high-pressure liquid chromatography (reference range, 4.0%-5.8%), and plasma insulin levels by immunoradiometric assay (Insulin Riabead II kit; Dainabot, Tokyo, Japan), which was confirmed to exhibit no significant cross-reactivity with proinsulin. Serum total cholesterol (TC), triglyceride (TG), and high-density lipoprotein cholesterol (HDL-C) levels were measured using enzymatic methods adapted to an autoanalyzer (Hitachi 7450; Hitachi, Tokyo, Japan). Plasma high-sensitivity C-reactive protein (hs-CRP) levels were measured by nephelometric assay (Behring Nephelometer Analyzer II; Behring, Marburg, Germany). The insulin resistance index by homeostasis model assessment (HOMA-IR) was calculated from fasting plasma glucose (FPG) and insulin (IRI) levels according to a report by Matthews et al [21] with the formula HOMA-IR = IRI in mU/L × FPG in mg/dL/405. Glomerular filtration rate (GFR) was estimated with the formula of Cockcroft-Gault.

2.4. Statistical analysis

All values are the mean ± SD unless otherwise indicated. Statistical analyses were performed with StatView 5.0 software (SAS Institute, Cary, NC). The unpaired Student t test and χ^2 tests were applied where appropriate. Simple linear regression analyses and multiple regression analyses were performed to evaluate the relationships among the stiffness index β and various clinical factors including plasma adiponectin levels. For the analyses, plasma levels of adiponectin and hs-CRP were log transformed to approximate a normal distribution. P values less than .05 were considered to indicate significance.

3. Results

The clinical characteristics of type 2 diabetic and nondiabetic subjects are shown in Table 1. There were no significant differences in age, sex ratio, body mass index (BMI), smoking habits, or mean blood pressure (MBP) between the diabetic and nondiabetic groups. The TC, low-density lipoprotein cholesterol (LDL-C), and HDL-C levels were significantly lower in the diabetic than in the nondiabetic group, although there were no significant differences in triglyceride levels between the 2 groups. High-sensitivity CRP levels were significantly higher in the diabetic than in the nondiabetic group ($P < .001$). There were also no significant differences in either estimated GFR or number of subjects treated with statins or ARB/ACEI.

Plasma adiponectin level was significantly lower in the diabetic than in the nondiabetic group (5.8 ± 3.1 vs 8.3 ± 3.3 μg/mL, $P < .0001$) (Fig. 1A). The stiffness index β was significantly higher in the diabetic than in the nondiabetic group (14.7 ± 5.3 vs 11.4 ± 4.0, $P < .0001$) (Fig. 1B). Plasma adiponectin level was significantly and inversely correlated with the stiffness index β in the group of all subjects ($r = -0.189$, $P = .006$) (Fig. 2A). Table 2 shows the correlation coefficients determined by simple linear regression analyses of clinical variables possibly affecting the stiffness index β. For the group of all subjects, the stiffness index β was significantly and positively correlated

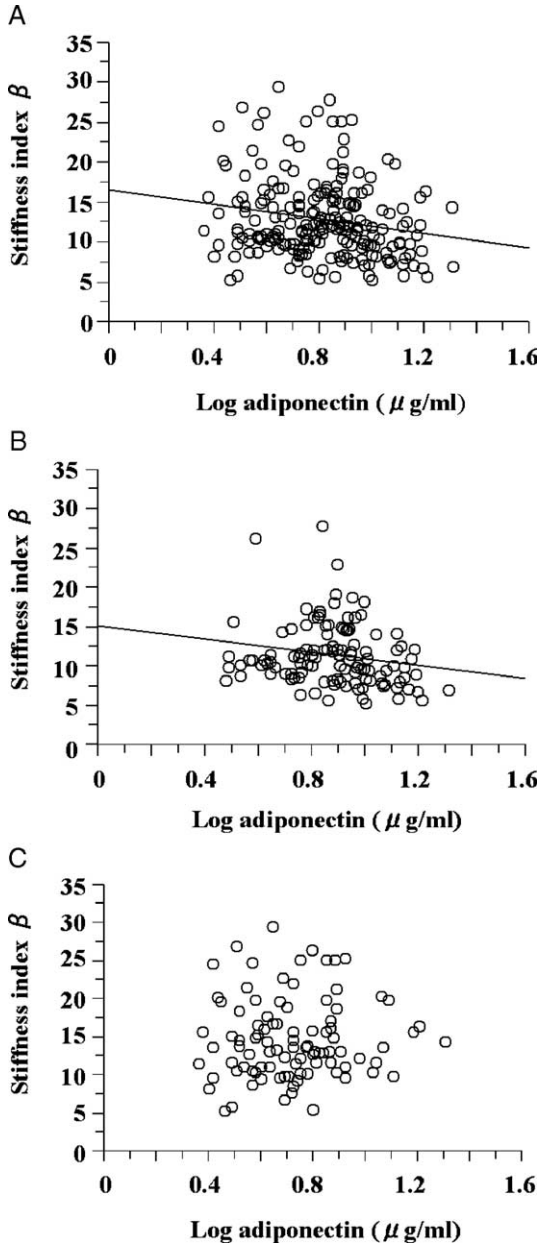

Fig. 2. Association of log-transformed plasma adiponectin levels with stiffness index β of the carotid artery in (A) the group of all subjects, (B) the nondiabetic group, and (C) the diabetic group. Plasma adiponectin level was found to be significantly and inversely correlated with stiffness index β in the group of all subjects ($r = -0.189$, $P = .006$) and in the nondiabetic group ($r = -0.187$, $P = .045$), but not in the diabetic group ($r = 0.045$, $P = .665$).

Table 2
Simple linear regression analysis of associations between stiffness index β and various clinical factors

	All subjects		Diabetic		Nondiabetic	
	r	P	r	P	r	P
Age	0.384	<.001	0.482	<.001	0.223	.016
BMI	0.111	.106	−0.065	.529	0.298	.001
Duration of diabetes	–	–	0.127	.263	–	–
MBP	0.294	<.001	0.373	<.001	0.204	.028
FPG	0.206	.003	−0.029	.775	0.006	.947
HbA_{1c}	0.366	<.001	0.162	.112	0.287	.002
IRI	0.210	.002	0.033	.753	0.261	.005
HOMA-IR	0.157	.023	−0.029	.778	0.246	.008
TC	−0.030	.665	−0.028	.787	0.168	.071
LDL-C	0.028	.688	−0.058	.576	0.233	.012
TG	0.074	.285	0.112	.279	0.015	.872
HDL	−0.233	<.001	−0.126	.221	−0.163	.080
GFR	−0.115	.105	−0.269	.013	0.019	.837
Log hs-CRP	0.166	.016	0.053	.611	0.172	.065
Log adiponectin	−0.189	.006	0.045	.665	−0.187	.045

with age, MBP, FPG, HbA_{1c}, IRI, HOMA-IR, and hs-CRP (log), and inversely correlated with HDL-C level.

To assess the contribution of adiponectin to the stiffness index β, we performed multiple regression analysis (Table 3). Stiffness index β was adopted as dependent variable and age, sex, presence of smoking habit, BMI, MBP, FPG, HOMA-IR, LDL-C, triglyceride, HDL-C, GFR, hs-CRP, and adiponectin as independent variables. For the group of all subjects, adiponectin level ($\beta = -0.232$, $P = .020$) as well as age, MBP, and LDL-C were significant independent contributors to stiffness index β ($R^2 = 0.298$, $P < .001$).

We also examined the relationship between adiponectin and carotid arterial stiffness for the diabetic and nondiabetic groups separately. In the nondiabetic group, plasma adiponectin level was significantly and inversely correlated with the stiffness index β ($r = -0.187$, $P = .045$) (Fig. 2B), although no correlation was found between these in the diabetic group ($r = 0.045$, $P = .665$) (Fig. 2C). On multiple regression analysis, plasma adiponectin level as well as age and LDL-C were significant independent contributors to stiffness index β for the nondiabetic group ($\beta = -0.337$, $P = .016$), but not for the diabetic group ($\beta = 0.015$, $P = .926$) (Table 3).

4. Discussion

The present study found that plasma adiponectin level was independently but weakly associated with stiffness of the carotid artery as well as classic risk factors for atherosclerosis in the nondiabetic group as well as that of all subjects. The intimal-medial thickness of the arterial wall has in many previous studies been used as an early surrogate marker of atherosclerosis. Compared with intimal-medial thickness, few reports are available on arterial stiffness, although arterial stiffness also worsens in accordance with the severity of pathologic atherosclerosis [22]. We therefore first investigated the clinical impact of plasma adiponectin level on arterial stiffness.

From recent in vivo and in vitro studies, evidence has emerged that adiponectin plays a role in protecting against

Table 3
Multiple regression analysis of clinical factors affecting stiffness index β

	All subjects		Diabetic		Nondiabetic	
	β	P	β	P	β	P
Age	0.463	<.001	0.544	.007	0.388	.004
Sex	−0.070	.360	0.001	.995	−0.088	.418
Smoking	0.044	.525	−0.013	.912	0.136	.160
BMI	0.122	.153	0.004	.981	0.130	.273
MBP	0.179	.010	0.263	.024	0.140	.161
FPG	0.149	.071	0.060	.653	−0.119	.231
HOMA-IR	−0.015	.864	−0.016	.904	0.154	.210
LDL-C	0.155	.024	0.052	.656	0250	.011
TG	0.052	.483	0.070	.590	−0.025	.819
HDL	−0.003	.972	−0.168	.329	0.128	.294
GFR	0.065	.579	0.131	.585	0.109	0417
Log hs-CRP	−0.115	.157	−0.059	.681	−0.140	.187
Log adiponectin	−0.232	.020	0.015	.926	−0.337	.016
R^2	0.298	<.001	0.331	.007	0.287	<.001

Independent variables including sex and smoking were entered as follows: sex— male as 1, female as 0; smoking—current or ex-smoker as 1, nonsmoker as 0.

the development of atherosclerosis [3-5]. However, clinical evidence supporting this finding is limited. Hypoadiponectinemia can be used as a predictor of the incidence of coronary artery disease in subjects who have not been diagnosed with cardiovascular disease [10] or with stenotic lesions observed on coronary artery angiography [7]. Plasma adiponectin level was previously found to be associated with endothelium-independent vasodilatation in 68 healthy subjects [23] and forearm blood flow in 76 Japanese subjects without a history of cardiovascular disease or diabetes [6].

The stiffness index β assessed by ultrasound represents the elastic properties of the arterial wall, which is associated with an increase in collagen content and a decrease in elastin content resulting from pathologic structural changes [13,22,24]. It is worsened by aging [13], impaired glucose tolerance, diabetes [15], and coronary artery disease [14]. We previously reported for type 2 diabetic patients that the stiffness index β is associated with various pathologic characteristics of diabetes, such as decreased glomerular filtration rate [25], peripheral vascular disease [17,18], and angiotensin-converting enzyme polymorphism [26]. Furthermore, the stiffness index β was for the carotid and femoral arteries found to be closely correlated with insulin resistance in a euglycemic hyperinsulinemic clamp study [16], and aerobic exercise, at least in part, ameliorates the stiffness index β in accordance with improvements in insulin resistance [27].

In the present study, plasma adiponectin level was significantly but weakly correlated with the stiffness index β in the nondiabetic group and that of all subjects. However, on multiple regression analyses, plasma adiponectin level was a significant independent determinant factor of carotid stiffness index β in the nondiabetic group and that of all subjects. These results suggest that plasma adiponectin level probably contributes to arterial stiffness. This can be explained by 2 possible mechanisms linking hypoadiponectinemia and increased arterial stiffness. According to one, adiponectin is probably associated with arterial stiffness via insulin resistance. Plasma adiponectin was found to be closely correlated with whole-body insulin resistance in a human euglycemic hyperinsulinemic clamp study [28]. In vivo, administration of adiponectin ameliorates insulin resistance by decreasing hepatic glucose production [2]. The stiffness of the carotid and femoral arteries is determined at least in part by insulin resistance as well as by classic risk factors for atherosclerosis [16]. These findings together with our own suggest that adiponectin probably contributes to arterial stiffness via insulin resistance.

According to the other possible mechanism, adiponectin directly regulates the various steps of atherosclerotic alteration of the arterial wall, and the hypothesis is supported by previous experimental studies. Adiponectin inhibits tumor necrosis factor α–induced expression of endothelial adhesion molecules in endothelial cells, reduces the atherogenic transformation of macrophages into foam cells by suppressing scavenger receptor expression [3,5], and inhibits vascular smooth muscle proliferation [4]. To the best of our knowledge, no studies have examined the effects of adiponectin on fibrotic or collagen matrix changes in the arterial wall, which to a large extent regulate arterial stiffness. However, one study found that in the liver adiponectin inhibits fibrosis by suppressing transforming growth factor β (TGF-β) and connective tissue growth factor gene expression [29]. Transforming growth factor β, a potent regulator of the extracellular matrix [30], is expressed during vascular remodeling induced by hypertension [31] and in a balloon catheter denudation model, and regulates collage matrix deposition on the arterial wall [32]. Because the characteristics of hepatic satellite cells, which play a role in regulation of liver fibrosis, are similar to those of vascular smooth cells, it is likely that mechanisms similar to those regulating the matrix metabolism induced by adiponectin are also operative in the arterial wall. Our findings on multiple regression analysis indicated that plasma adiponectin level was a significant independent contributor to the stiffness index β even after adjustment for insulin resistance index, HOMA-IR. This finding suggests a direct effect of adiponectin on arterial stiffness independent of insulin resistance.

In the diabetic group of our study, no independent contribution of adiponectin to the stiffness index β was observed on either simple or multiple regression analyses. This suggests that other factors or mechanisms related to diabetes may contribute more strongly to arterial stiffness than adiponectin. One possibility is effects of advanced glycation endproducts, which are induced by hyperglycemia and promote various atherogenic changes in vascular cells [33]. Advanced glycation endproduct increases TGF-β expression [34] and regulates changes in aortic collagen biochemical characteristics and aortic wall matrix stiffness in vivo [35]. In a recent clinical study, a positive association between adiponectin and endothelium-independent vasodilation was found only for healthy subjects, but not for diabetic subjects [23]. Our present findings for diabetic patients are compatible with this finding. Taken together, these findings suggest that diabetes may conceal the effect of adiponectin on arterial stiffness, at least at clinically measurable levels.

There are a few limitations to our study. First, our nondiabetic group included subjects with IFG, hypertension, and hyperlipidemia, which are known to be associated with hypoadiponectinemia and/or increased arterial stiffness. A study with a large number of healthy subjects may be needed. Second, waist circumference or other indexes of central adiposity, which is known to be associated with plasma adiponectin level, were not measured.

In conclusion, adiponectin is weakly associated with carotid arterial stiffness independently of known atherogenic factors in the nondiabetic group and that of all subjects, which suggests that adiponectin probably contributes to arterial stiffness. However, for the group of

diabetic patients, we failed to find any significant association of adiponectin with arterial stiffness, suggesting that other factors specific to diabetes may influence arterial stiffness more strongly than adiponectin. Further studies are needed to clarify the clinical effects of the various modulator of adiponectin on arterial stiffness, especially in diabetic patients.

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