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Bezafibrate Ameliorates Arterial Stiffness Assessed by Cardio-Ankle Vascular Index in Hypertriglyceridemic Patients with Type 2 Diabetes Mellitus

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Aim: Cardio-ankle vascular index (CAVI) reflects arterial stiffness and has been established as a useful surrogate marker of atherosclerosis. Contrary to the abundant data indicating slower progression of atherosclerosis with statins, studies on fibrates remain scarce. The aim of this study was thus to clarify the effect of bezafibrate on CAVI as well as on oxidative stress.

Methods: A randomized, open-label, controlled study was performed. 66 hypertriglyceridemic patients with type 2 diabetes were assigned to two groups: bezafibrate (400 mg/day) group and eicosapentaenoic acid (EPA 1.8 g/day) group. Patients were administered the respective treatment for 12 weeks. CAVI, glycolipid metabolic parameters, and diacron-reactive oxygen metabolites (d-ROMs) were evaluated before and after the study period.

Results: Serum triglycerides (TG), remnant-like particle cholesterol (RLP-C), fasting plasma glucose, HbA1c and d-ROMs decreased, while HDL-cholesterol increased significantly in the bezafibrate group but did not change in the EPA group. The decreases in TG, RLP-C, HbA1c and d-ROMs were significantly greater in the bezafibrate group than in the EPA group. CAVI decreased significantly only in the bezafibrate group and the decrease was significantly greater in bezafibrate group than in EPA group. Simple regression analysis showed no significant relationship between the change in CAVI and changes in other variables. Multivariate logistic regression analysis identified high baseline CAVI, low HDL-cholesterol level, and bezafibrate administration as significant independent predictors of CAVI decrease.

Conclusion: Bezafibrate treatment ameliorates arterial stiffness accompanied by improvement of glycolipid metabolism and oxidative stress. These effects potentially have important beneficial health consequences in hypertriglyceridemic patients with type 2 diabetes.

Key words: Cardio-ankle vascular index (CAVI), Arterial stiffness, Bezafibrate, Triglyceride

Introduction

Atherosclerosis is a primary disease leading to cardiovascular events[1, 2]. One of the difficulties to establish the factors involved in the progression of arteriosclerosis and the factors to prevent arteriosclerosis is that quantitative measurement of the degree of arteriosclerosis is difficult in routine clinical practice. Measuring arterial stiffness is a candidate to estimate the progression of arteriosclerosis quantitatively[3].

The cardio-ankle vascular index (CAVI) was developed recently[4]. CAVI reflects arterial stiffness of the arterial tree from the origin of the aorta to the ankle. The major feature of this method is that the result is

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independent of the blood pressure at the time of measurement. Recent studies have shown that CAVI predicts both all-cause and cardiovascular mortality in patients with risk factors of cardiovascular disease[5]. Moreover, CAVI appropriately monitors the change in arterial stiffness after various therapeutic interventions[6-9]. Nagayama *et al*. Previously demonstrated that CAVI reflects vascular damage caused by oxidative stress, which is considered central to the pathophysiology of atherosclerosis in patients with metabolic syndrome[10]. We also reported that CAVI reflects lipid-induced early vascular damage in healthy subjects[11]. Therefore, CAVI assessment is potentially useful both to identify individuals at high risk of cardiovascular disease and to indicate if intervention has been beneficial.

Type 2 diabetes mellitus is one of the most important contributors to cardiovascular disease and increases the risk of coronary heart disease at least two- to threefold[12, 13]. A primary cause for the increased risk of atherosclerosis in diabetes is an increase of atherogenic lipoproteins such as triglyceride-rich lipoproteins (TGRLs), which are closely associated with insulin resistance and oxidative stress[14, 15]. Recent studies have demonstrated that serum triglycerides (TG) level and low density lipoprotein-cholesterol (LDL-C) levels are leading predictors of coronary heart diseases in patients with type 2 diabetes[16, 17].

Fibrates act mainly as a ligand for peroxisome proliferator-activated receptors (PPARs), which are nuclear receptors activated by fatty acids and derivatives[18, 19]. PPARα mediates the hypolipidemic action of fibrates and stimulates β-oxidative degradation of fatty acids to control the plasma levels of cholesterol and TG[20, 21]. While bezafibrate has low affinity for PPARα, it is also a ligand for PPARγ, exhibiting the actions of improving insulin sensitivity and promoting the clearance of TGRLs via its enhancing effect on lipoprotein lipase (LPL)[22]. We previously reported that bezafibrate administration decreased serum TG level and TGRLs along with elevation of LPL mass level[23].

Clinical trials have shown that fibrates reduce coronary heart events in subjects with type 2 diabetes and metabolic syndrome[24, 25]. However, these results were not demonstrated as primary end points, but were obtained in subgroup analyses. Moreover, studies with carotid intima-media thickness (IMT) as a surrogate end point have produced inconsistent results. One study found slower progression of carotid atherosclerosis in patients on fenofibrate compared with placebo[26], whereas another study reported no effect of bezafibrate on IMT[24]. Contrary to the abundant data indicating slower progression of atherosclerosis with statins, studies on fibrates are scarce. Therefore, the effect of fibrates on atherosclerosis needs further confirmation.

It is well-known that a low level of eicosapentaenoic acid (EPA), an n-3 polyunsaturated fatty acid, in circulation is associated with atherosclerotic diseases[27]. Supplementation with EPA lowers serum TG level but the degree of decrease is smaller than fibrates[28]. Nevertheless, EPA has been demonstrated to show anti-atherosclerotic effect. The Japan EPA Lipid Intervention Study (JELIS) reported that treatment with highly purified EPA in addition to low-dose statin significantly reduced the incidence of major coronary events compared with statin alone[29]. Satoh *et al*[30] reported that EPA decreased CAVI in patients with metabolic syndrome, supporting the anti-atherosclerotic effect of EPA.

Aim

The aim of this study was to clarify the role of bezafibrate on arterial stiffness of the arterial tree consisting of the aorta, iliac artery, femoral artery, and tibial artery by measuring CAVI in hypertriglyceriemic patients with type 2 diabetes mellitus comparing with EPA as control, and to investigate the underlying mechanism by which bezafibrate and EPA may change CAVI.

Methods

The study protocol was prepared in accordance with the Declaration of Helsinki and was approved by the institutional review board of Toho University Sakura Medical Center (approval number 2010-025). Before participation, the purpose and procedures of the study were explained to each patient, and written consent was obtained for both participation in this study and for release of the study data.

Study Protocol

This randomized, open-label, controlled study enrolled 66 hypertriglyceridemic patients (serum triglycerides >150 mg/dl) with type 2 diabetes. Diabetes was diagnosed according to the Japan Diabetes Society diagnostic standards. We excluded patients with moderate or severe hypertension (systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥100 mmHg), nephrotic syndrome, hypothyroidism, history of angina, peripheral vascular disease, or atrial fibrillation.

We assigned the patients to two groups by simple randomization using sealed envelopes. Three of the 66 patients were excluded from the study because they stopped visiting our hospital. One group was administered bezafibrate (Kissei Co., Ltd., Tokyo, Japan) 400 mg/day (bezafibrate group, $n=33$), and the other group was administered EPA capsule 1.8 g/day (EPA group, $n=31$), containing highly purified (>98%) EPA ethyl ester (Mochida Pharmaceutical Co., Ltd., Tokyo, Japan).

Table 1 shows the clinical characteristics of the patients at baseline. There were no significant differences in any of the variables between the two groups.

The following parameters were measured before and after 12-week treatment: body weight, body mass index, HbA1c, fasting plasma glucose (FPG), serum total cholesterol (TC), TG, high density lipoprotein (HDL)-cholesterol, LDL-cholesterol, apolipoprotein (APO) A-1, A-2, B, C-2, C-3, E, remnant-like particle (RLP)-cholesterol, LPL mass, diacron-reactive oxygen metabolites (d-ROMs), a marker of oxidative stress as well as markers of liver and renal functions. CAVI and systolic/diastolic blood pressure were measured before and after 12 weeks of treatment. Carotid IMT and plaque score were assessed by ultrasound only at the beginning of this study.

All patients maintained the same diet and exercise therapies and did not change medications during this study. A dietician provided nutritional guidance to all patients on a monthly basis, analyzing meals and suggesting changes if necessary. None of the patients received any hormone replacement therapy or antioxidant vitamin supplement during this study. Several patients were taking antidiabetic agents, antihypertensive agents, and/or lipid-lowering agents (statins). The proportions of subjects using these agents did not differ significantly between the two groups.

Data Collection

Body mass index (BMI) was calculated from height and body weight (weight in kilogram divided by square of height in meter). Blood samples were collected in the morning after 12 hours of fasting. Serum was separated within 1 hour and used for measuring FPG, HbA1c, TG, LDL-cholesterol, HDL-cholesterol, and APO A-1, A-2, B, C-2, C-3, E, and LPL mass.

HbA1c and Plasma Lipid Concentrations

To measure HbA1c, blood was collected in tubes containing ethylenediaminetetraacetic acid. The stable and unstable fractions of HbA1c were measured by a high-pressure liquid chromatography method (Hi-Auto A1C analyzer system; Kyoto Daiichi Kagaku, Kyoto, Japan). Data of stable form were used in the present analysis. HbA1c was expressed as the value of the National Glycohemoglobin Standardization Program.

Plasma total cholesterol and triglyceride levels were measured enzymatically using kits from Nippon Shoji Co, Ltd (Osaka, Japan) and a 7150 Analyzer (Hitachi, Ltd, Tokyo, Japan). Serum high-density lipoprotein cholesterol was measured using a selective inhibition assay (Daiichi Pure Chemicals Co, Ltd, Tokyo, Japan). Serum LDL-cholesterol level was calculated using the Friedwald formula.

Preheparin LPL Mass Assay

LPL mass in preheparin serum was measured by a sandwich enzyme-linked immunosorbent assay using a specific monoclonal antibody against bovine milk LPL, as described by Kobayashi *et al*[31]. A commercial kit from Daiichi Pure Chemicals (Tokyo, Japan) was used in this study. For this assay system, linearity was observed from 5 to 400 ng/ml, with within-run coefficient variation (Cv) of 2.8%, and between-day Cv of 4.3%.

d-ROMs Assay

The d-ROMs levels were measured using a kinetic spectrophotometric assay (F.R.E.E System; Diacron, Italy) with intra- and inter-assay Cv of 2.1% and 3.1%, respectively. Briefly, a serum sample (25 μL) is mixed with an acetic acid buffered solution (pH 4.8) in a pipette to stabilize the hydrogen ion concentration, and a chromogenic substrate was added to the mixture. In an acidified medium, bivalent and trivalent iron from the protein component of the blood ionizes and acts as a catalyst to break down hydroperoxide groups in the blood into alkoxyl and peroxy radicals to form free radicals. The mixture was then incubated in the thermostatic block of the system, then transferred to a cuvette containing colorless chromogen. The chromogen is oxidized by free radicals to radical cations with a magenta color, which was measured photometrically (505 nm) after centrifugation for 1 min. The intensity of the magenta color reflects the concentration of hydroperoxides in the blood, which is proportional to the quantity of ROMs. The data were expressed in U. Carr. (1 U. Carr. corresponds to 0.08 mg/dL H_2O_2).

Measurements of CAVI and Blood Pressure

CAVI was measured with a VaSera CAVI instrument (Fukuda Denshi Co Ltd, Tokyo), and the details have been described in previous reports[4]. Briefly, cuffs were applied to the bilateral upper arms and ankles of a subject lying supine with the head held in a midline position. Examinations were performed after resting for 10 minutes. To detect the brachial and ankle pulse waves with cuffs, a low cuff pressure from 30 to 50 mmHg was used to minimize the effect of cuff pressure on hemodynamics. CAVI was calculated using the following formula: $CAVI = a\{(2\rho/\Delta P) \times \ln(Ps/Pd) PWV2\} + b$; where Ps is systolic blood pressure, Pd is diastolic blood pressure, PWV is pulse wave velocity, ΔP is $Ps - Pd$, ρ is blood density, and a and b are constants. Blood pressure was measured using the cuff applied to the upper arm. PWV was obtained by dividing the length of the blood vessel by the time taken for the pulse wave to propagate from the aortic valve

Table 1. Various parameters at baseline and after 12-week treatment of bezafibrate and EPA

	bezafibrate					EPA				
	Baseline		After 12 weeks		*p* value	Baseline		After 12 weeks		*p* value
	mean	s.d.	mean	s.d.		mean	s.d.	mean	s.d.	
Age (y)	58.1 ± 12					58.90 ± 10.20				
Gender (m/f)	20/13					19/12				
Height (cm)	165.9 ± 9.7					163.8 ± 8.6				
mean IMT (mm)	0.84 ± 0.17					0.91 ± 0.18				
plaque score	4.8 ± 4.5					4.9 ± 3.2				
body weight (kg)	70.0 ± 17		69.2 ± 13		n.s.	71.1 ± 16		70.8 ± 16		n.s.
body mass index (kg/m^2)	25.2 ± 4.8		25.1 ± 4.5		n.s.	26.4 ± 4.8		26.2 ± 4.7		n.s.
systolic BP (mmHg)	142 ± 22		140 ± 16		n.s.	146 ± 18		145 ± 17		n.s.
diastolic BP (mmHg)	86 ± 13		83 ± 11		n.s.	87 ± 14		92 ± 16		n.s.
HbA1c (%)	6.8 ± 1.2		6.4 ± 1.1		<0.05	6.8 ± 1.3		7.0 ± 1.5		n.s.
FPG (mg/dL)	156 ± 58		136 ± 49		<0.05	157 ± 57		162 ± 68		n.s.
TC (mg/dL)	224 ± 36		214 ± 47		n.s.	210 ± 44		210 ± 52		n.s.
TG (mg/dL)	289 ± 148		190 ± 117		<0.005	295 ± 225		278 ± 224		n.s.
HDL-C (mg/dL)	47 ± 9.9		50 ± 9.1		<0.05	43 ± 11.0		43 ± 10.1		n.s.
LDL-C (mg/dL)	120 ± 36		126 ± 36		n.s.	109 ± 40		112 ± 44		n.s.
Apo A-1 (mg/dL)	149 ± 18		140 ± 30		n.s.	135 ± 24		136 ± 25		n.s.
Apo A-2 (mg/dL)	32.7 ± 5.2		38.2 ± 7.5		<0.001	29.2 ± 4.3		29.2 ± 6.2		n.s.
Apo B (mg/dL)	113 ± 22		104 ± 29		<0.05	109 ± 27		112 ± 31		n.s.
Apo C-2 (mg/dL)	7.5 ± 2.3		6.9 ± 3.7		n.s.	7.9 ± 3.9		8.6 ± 5.0		n.s.
Apo C-3 (mg/dL)	14.8 ± 4.9		11.3 ± 5.4		<0.001	18.4 ± 9.2		18.1 ± 11.8		n.s.
Apo E (mg/dL)	5.1 ± 1.9		4.1 ± 1.1		<0.005	5.4 ± 2.0		5.4 ± 2.2		n.s.
LPL mass (ng/mL)	53.0 ± 19.8		56.9 ± 23.2		n.s.	57.2 ± 20.0		54.8 ± 16.0		n.s.
RLP-C (mg/dL)	19.5 ± 12.9		13.7 ± 10.7		<0.001	20.4 ± 16.2		20.1 ± 15.9		n.s.
creatinine (mg/dL)	0.80 ± 0.22		0.90 ± 0.24		n.s.	0.85 ± 0.37		1.01 ± 1.10		n.s.
uric acid (mg/dL)	6.0 ± 1.6		6.1 ± 1.4		n.s.	6.0 ± 1.8		5.7 ± 1.9		n.s.
CK (IU/L)	111 ± 67		97 ± 42		n.s.	103 ± 35		151 ± 218		n.s.
d-ROMs (U.CARR)	383 ± 89		341 ± 55		<0.001	359 ± 54		374 ± 88		n.s.
AST (IU/L)	24.2 ± 8.3		27.6 ± 13.2		n.s.	21.9 ± 6.2		22.7 ± 8.6		n.s.
ALT (IU/L)	26.8 ± 13.1		25.0 ± 17.1		n.s.	25.4 ± 8.1		24.7 ± 9.3		n.s.
γGTP (IU/L)	67.9 ± 65.3		40.5 ± 31.7		<0.005	58.2 ± 42.2		58.3 ± 38.1		n.s.

EPA: eicosapentaenoic acid, CAVI: cardio-ankle vascular index, BP: blood pressure, HbA1C: hemoglobin A1C, FPG: fasting plasma glucose, TC: total cholesterol, TG: triglyceride, HDL-C: HDL-cholesterol, LDL-C: LDL cholesterol, Apo: apolipoprotein, LPL: preheparin lipoprotein lipase, RLP-C: RLP-cholesterol, CK: creatine kinase, d-ROMs: diacron-reactive oxygen metabolites, AST: aspartate aminotransferase, ALT: alanine aminotransferase, γGTP: gamma-glutamyl transpeptidase. Data are expressed as mean ± standard deviation (s.d.), except gender (in number of patients). At baseline, there were not significant differences in all variables between two groups.

to the ankle, and was measured using the cuffs attached to the upper arms and ankles. To facilitate comparison with the aortic PWV method established by Hasegawa and coworkers[32], scale conversion constants (a, b) were determined to match CAVI with the aortic PWV method. Using the scale conversion constants, the CAVI data obtained can be compared with the massive previous data of PWV. All the measurement and calculation functions are integrated in the VaSera CAVI instrument that automatically calculates and generates the final data. The average Cv of CAVI is less than 5%, which is small enough for clinical usage and indicates that CAVI has good reproducibility[4].

Statistical Analysis

All data are expressed as mean ± standard deviation. The SPSS 15.0 software (SPSS Inc., Chicago, Ill, USA) was used for statistical processing. Paired *t*-test was performed to analyze intragroup differences between data at baseline and those at 12 weeks. Student's *t*-test was used for comparisons of baseline data between two groups. The relationship between changes in CAVI and

Table 2. Comparison of changes in various parameters between bezafibrate and EPA groups

	Bezafibrate			EPA			*p* value
	mean		s.d.	mean		s.d.	
⊿body weight (kg)	−0.81	±	12.8	0.48	±	2.8	n.s.
⊿systolic BP (mmHg)	−2.2	±	22.7	−0.9	±	13.4	n.s.
⊿diastolic BP (%)	−2.7	±	13.5	4.4	±	10.1	<0.05
⊿HbA1C (mg/dL)	−0.46	±	1.0	0.15	±	1.4	<0.05
⊿FPG (mg/dL)	−20.1	±	56.7	3.8	±	65.8	n.s.
⊿TC (mg/dL)	−10.5	±	32.8	−2.5	±	26.9	n.s.
⊿TG (mg/dL)	−98.9	±	107	−16.4	±	72	<0.001
⊿HDL-C (mg/dL)	2.8	±	6.6	−0.2	±	7.6	n.s.
⊿LDL-C (mg/dL)	6.6	±	28.2	1.0	±	24.9	n.s.
⊿Apo A-1 (mg/dL)	3.3	±	15.7	0.0	±	20.9	n.s.
⊿Apo A-2 (mg/dL)	5.5	±	6.8	0.1	±	6.0	<0.005
⊿Apo B (mg/dL)	−8.9	±	18.9	1.5	±	19.2	<0.05
⊿Apo C-2 (mg/dL)	−0.62	±	2.8	0.57	±	2.6	0.090
⊿Apo C-3 (mg/dL)	−3.46	±	4.8	−0.66	±	6.4	0.056
⊿Apo E (ng/mL)	−1.0	±	1.8	−0.1	±	1.6	<0.05
⊿LPL mass (mg/dL)	3.9	±	14.9	−3.2	±	9.9	<0.05
⊿RLP-C (mg/dL)	−5.8	±	8.6	−0.2	±	7.7	<0.05
⊿creatinine (mg/dL)	0.10	±	0.2	0.17	±	0.9	n.s.
⊿uric acid (IU/L)	0.1	±	1.3	−0.3	±	1.0	n.s.
⊿CK (U.CARR)	−15.4	±	69.0	6.6	±	36.0	n.s.
⊿d-ROMs (IU/L)	−42.7	±	66.0	12.1	±	66.0	<0.005
⊿AST (IU/L)	3.5	±	12.7	0.9	±	6.8	n.s.
⊿ALT (IU/L)	−1.7	±	13.7	−0.8	±	6.7	n.s.
⊿γGTP	−27.4	±	46.0	−1.1	±	23.0	<0.01

EPA: eicosapentaenoic acid, CAVI: cardio-ankle vascular index, BP: blood pressure, HbA1C: hemoglobin A1C, FPG: fasting plasma glucose, TC: total cholesterol, TG: triglyceride, HDL-C: HDL-cholesterol, LDL-C: LDL cholesterol, Apo: apolipoprotein, LPL: preheparin lipoprotein lipase, RLP-C: RLP-cholesterol, CK: creatine kinase, d-ROMs: diacron-reactive oxygen metabolites, AST: aspartate aminotransferase, ALT: alanine aminotransferase, γGTP: gamma-glutamyl transpeptidase. Data are expressed as mean ± standard deviation (s.d.)

other variables were analyzed using simple regression analysis (Pearson's product-moment correlation coefficient: r). Multivariate logistic regression analysis was used to identify the factors associated with CAVI decrease, and results were expressed as odds ratio with 95% confidence interval. In all comparisons, *p* values less than 0.05 were considered statistically significant. The primary end point was change in CAVI, and the secondary end points were changes in TG, HDL-cholesterol, RLP-cholesterol, HbA1c, FPG and d-ROMs during this study.

Results

Changes in Lipid Parameters

All parameters measured, including lipid parameters, did not change significantly after the 12-week treatment in EPA group. On the other hand, TG, APO C-3, APO E and RLP-C decreased, while HDL-C and APO A-2 increased significantly after 12-week treatment in bezafibrate group, compared with no significant changes in the EPA group (Table 1). Although TG apparently decreased slightly in the EPA group, the change was not significant. TC, LDL-C, APO A-1, APO B, APO C-2 and LPL mass showed no significant changes in both groups (Table 1).

In the comparison of changes in levels between two groups, the decreases in TG, APO-B, APO E and RLP-C, the increase in APO A-2 were significantly greater in bezafibrate group than those in EPA group. The decreases in APO C-2 and APO C-3 tended to be greater in bezafibrate group than those in EPA group. The change in LPL mass was significantly different between the bezafibrate group (increase) and the EPA group (decrease) (Table 2).

Changes in FPG, HbA1c and d-ROMs

FPG, HbA1c and d-ROMs decreased significantly

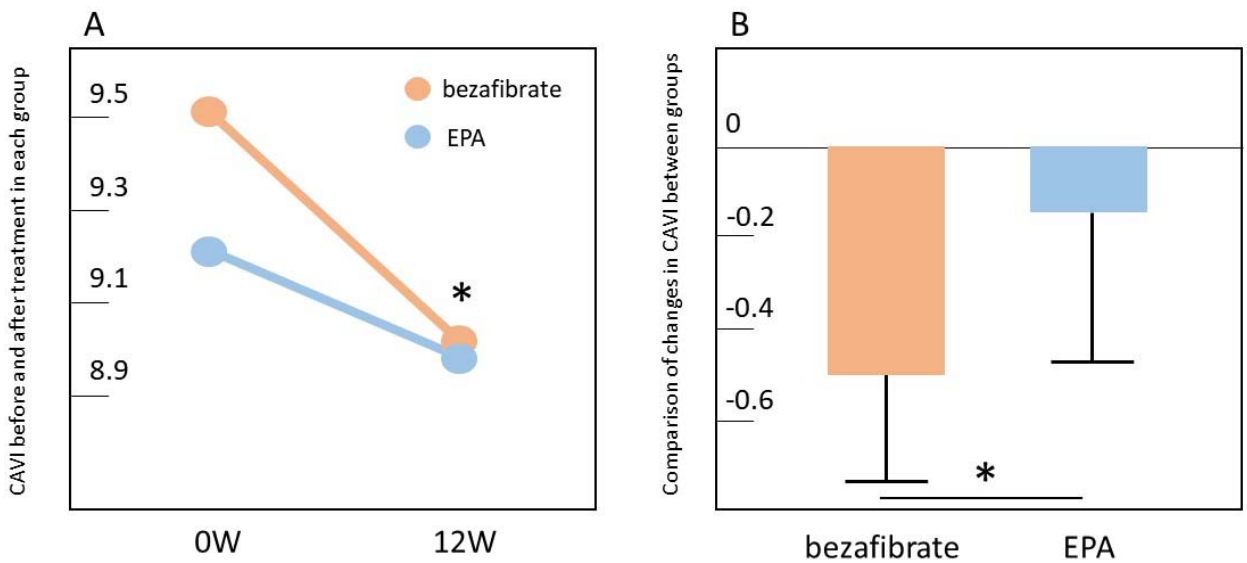

Fig. 1. Changes in CAVI during 12-week treatment by bezafibrate and EPA. (A) Relationship between baseline CAVI and CAVI after 12-week treatment in bezafibrate and EPA groups. (B) Comparison of changes in CAVI after 12-week treatment between bezafibrate and EPA groups. *p value less than 0.05.

in the bezafibrate group, but did not change in the EPA group (**Table 1**). The changes (decreases) in HbA1c and d-ROMs in the bezafibrate group were significantly different than those (increases) in the EPA group (**Table 2**).

Changes in CAVI

CAVI decreased significantly ($p<0.005$) after 12-week treatment in the bezafibrate group but did not change significantly in the EPA group (**Fig. 1A**). The decrease in CAVI was significantly ($p<0.005$) greater in the bezafibrate group than in the EPA group (**Fig. 1B**).

Relationship between Change in CAVI and Other Variables

To identify the factors that contribute to the improvement of CAVI, we first performed a simple regression analysis. Simple regression showed no significant relationship between the change in CAVI and changes in other variables (**Table 3**). We further performed univariate and multivariate logistic regression analyses to investigate the association between decrease in CAVI greater than 0.5 and clinical variables. As shown in **Table 4**, high baseline CAVI, low baseline HDL-cholesterol level, and bezafibrate administration were identified as significant independent predictors of CAVI decrease greater than 0.5.

Discussion

We observed that bezafibrate therapy for 12 weeks in hypertriglyceridemic patients with type 2 diabetes resulted in a greater decrease in CAVI compared to EPA therapy, accompanied by decreases in blood TG, RLP-cholesterol, HbA1c and d-ROMs levels, and increase in HDL-cholesterol level. In comparison, EPA therapy for 12 months resulted in no significant changes in all the parameters measured, and TG level apparently decreased slightly, but not significantly. Furthermore, multivariate logistic regression analysis clearly demonstrated an association between bezafibrate administration and decrease in CAVI.

A previous study reported beneficial effects of fibrate on IMT, which is an atherogenic index and an independent predictor of cardiovascular events[33]. Brachial-ankle PWV (baPWV) has been used as a noninvasive index of arterial stiffness or arterial distensibility[34]. However, there are several limitations to using baPWV to evaluate arterial stiffness. First, baPWV is affected by systolic blood pressure at the time of measurement and thus, overestimates arterial stiffness in hypertensive subjects[35]. Second, baPWV is an index calculated from a formula using only indirect indices[36]. In contrast, the formula for CAVI includes direct indices, a stiffness parameter β, and indirect indices[4]. Our previous studies demonstrated that CAVI is an accurate and blood pressure-independent index of arterial stiffness[4]. CAVI is associated with cardiovascular morbidity and mortality, and predicts cardiovascular events in patients with various risk factors[5]. Moreover, CAVI can be used reliably to follow changes in arterial stiffness after various therapeutic interventions[6-8]. Taken

Table 3. Simple regression analysis for the relationships between change in CAVI and changes in various variables.

	Bezafibrate		EPA	
	r	*p* value	*r*	*p* value
⊿body weight	0.141	n.s.	0.159	n.s.
⊿systolic BP	0.223	n.s.	0.148	n.s.
⊿diastolic BP	0.179	n.s.	−0.190	n.s.
⊿HbA1c	0.163	n.s.	0.345	n.s.
⊿FPG	0.162	n.s.	0.138	n.s.
⊿TC	0.149	n.s.	0.240	n.s.
⊿TG	0.235	n.s.	−0.090	n.s.
⊿HDL-C	−0.299	n.s.	−0.091	n.s.
⊿LDL-C	0.065	n.s.	0.338	n.s.
⊿Apo A-1	−0.241	n.s.	−0.253	n.s.
⊿Apo A-2	0.046	n.s.	−0.253	n.s.
⊿Apo B	0.187	n.s.	0.133	n.s.
⊿Apo C-2	0.215	n.s.	0.183	n.s.
⊿Apo C-3	0.198	n.s.	0.203	n.s.
⊿Apo E	0.248	n.s.	−0.029	n.s.
⊿LPL mass	0.106	n.s.	0.077	n.s.
⊿RLP-C	0.276	n.s.	0.109	n.s.
⊿d-ROMs	−0.263	n.s.	−0.189	n.s.
⊿uric acid	−0.020	n.s.	−0.209	n.s.

EPA: eicosapentaenoic acid, CAVI: cardio-ankle vascular index, BP: blood pressure, HbA1C: hemoglobin A1C, FPG: fasting plasma glucose, TC: total cholesterol, TG: triglyceride, HDL-C: HDL-cholesterol, LDL-C: LDL cholesterol, Apo: apolipoprotein, LPL: preheparin lipoprotein lipase, RLP-C: RLP-cholesterol, d-ROMs: diacron-reactive oxygen metabolites. Data are expressed as mean ± standard deviation (s.d.)

together, the present data that bezafibrate therapy improved arterial stiffness assessed by CAVI may contribute to the prevention of atherosclerosis. To the best of our knowledge, this is the first study to demonstrate the effect of bezafibrate on CAVI in hypertriglyceridemic patients with type 2 diabetes.

Interestingly, the degree of CAVI reduction achieved by bezafibrate treatment was greater than by EPA in this study. Moreover, the degree was equivalent to that of statins in a previous report[37], although a direct comparison is not possible. This favorable effect of bezafibrate may be due to the clinical conditions of the subjects in the present study. In clinical trials, bezafibrate was highly effective at reducing cardiovascular diseases in patients with obesity, type 2 diabetes, higher TG level and lower HDL-cholesterol level[24, 25]. In this study, our subjects had type 2 diabetes with high mean TG and low HDL-cholesterol levels, and more than half (52%) of them were obese (BMI ≥25 kg/m^2). Under these clinical conditions, bezafibrate may demonstrate a powerful arterial stiffness-lowering effect. On the other hand, EPA administration decreased CAVI slightly, but the change was not statistically significant. Previous reports on the effect of EPA administration on arterial stiffness are controversial. One study reported that EPA administration did not change atherogenic markers[38]. Conversely, Satoh *et al*[30] reported that the administration of EPA reduced peripheral arterial stiffness measured by baPWV and CAVI, and their results contradicted our findings. Because the subjects in Satoh's study were dyslipidemic but not diabetic, and a smaller proportion was obese, the conflicting results may be due to the different clinical conditions of the subjects. These findings suggest that subjects for whom EPA can be expected to prevent atherosclerosis may differ from fibrates.

In the present study, we evaluated d-ROMs level as a marker of oxidative stress. Bezafibrate significantly decreased d-ROMs level. The d-ROMs level is known to be proportional to serum hydroperoxide concentration. In this test, the concentrations of peroxidation products of proteins, peptides, amino acids, lipids, and fatty acids are measured by color reaction. The d-ROMs test comprehensively evaluates the status of oxidative stress level *in vivo*[39]. Blood d-ROMs level increases in diseases with enhanced oxidative stress[40], and decreases by treatment that reduces oxidative stress[41]. Regarding the effect of fibrates on oxidative stress, Iglarz *et*

Table 4. Multivariate logistic regression analysis for the association of CAVI decrease greater than 0.5 with clinical variables

Variable	Univariate Analysis			Multivariate Logistic Regression		
	Odds ratio	95% confidence interval	*P* value	Odds ratio	95% confidence interval	*P* value
Gender (Male; 1, Female; 0)	0.72	0.24−2.12	0.301	0.55	0.15−2.05	0.376
Elderly (Age ≥65; 1, <65; 0)	0.82	0.24−2.79	0.056	0.36	0.08−1.53	0.164
Higher CAVI (≥9.0; 1, <9.0; 0)	3.60	0.91−14.36	0.011	8.24	1.51−45.12	0.015
Obesity (BMI ≥25; 1, <25; 0)	0.62	0.21−1.81	0.227	0.75	0.22−2.59	0.645
Hypertension (+; 1, −; 0)	0.89	0.31−2.59	0.167	1.04	0.29−3.74	0.952
Low HDL-C (HDL-C ≤40; 1, >40; 0)	1.75	0.58−5.24	0.014	4.74	1.09−20.63	0.038
Bezafibrate administration (+; 1, −; 0)	3.06	0.98−9.49	0.005	6.12	1.39−26.81	0.016

AIC=47.535, $p<0.05$
CAVI: cardio-ankle vascular index, HDL-C: HDL-cholesterol

al[42] reported that fenofibrate reduced ROS production induced by NF-κB in animal experiments, and Beltowski *et al*[43] reported that fenofibrate reduced lipid peroxide generation in rodent models. Oxidative stress is known to be elevated in diabetic conditions through the generation of advanced glycation end products and activation of NADPH oxidase[44], contributing to the development of atherosclerosis[45]. We previously reported that glucose-lowering treatment using oral hypoglycemic agent decreased oxidative stress[6]. Taken together, the previous and the present finding of oxidative stress reduction by bezafibrate therapy suggests that bezafibrate may contribute to the prevention of atherosclerosis. Since changes in d-ROMs level was a secondary outcome in this study, our finding of improved oxidative stress should be regarded as pilot data for a more focused study on oxidative stress.

Plausible mechanisms underlying improvement of CAVI following bezafibrate treatment include changes of lipoproteins, glucose metabolism, and oxidative stress. To prove this hypothesis, we performed simple regression analyses on factors related to change in CAVI. However, we could not find any parameter associated with the reduction of CAVI, suggesting that multiple factors may be involved in substantial change in CAVI, or bezafibrate may have a direct effect on arterial stiffness. Fibrates act as a ligand for PPARs, which are nuclear receptors activated by fatty acids and derivatives[18]. PPARα mediates the hypolipidemic action of fibrates and stimulates β-oxidative degradation of fatty acids to control plasma levels of cholesterol and triglycerides, which constitute major risk factors for coronary vascular disease[20]. Activation of PPARα directly promotes LPL activity, enhancing LPL mRNA expression and suppression of APO C-3[46]. Bezafibrate has low affinity for PPARα, and also serves as a ligand for PPARγ, causing further enhancement of LPL[22]. Through these mechanisms, bezafibrate promotes the clearance of atherogenic lipoproteins. It is also reported that fibrates elevate HDL-cholesterol level by enhancing APO A expression[47]. In the present study, bezafibrate administration resulted in a slight elevation of LPL mass level together with a reduction of TGRLs and an elevation of HDL-cholesterol level, suggesting that these complex changes may contribute to the improvement of arterial stiffness.

Furthermore, experimental studies have shown that PPARs regulate the expression of key proteins involved in all stages of atherogenesis including vascular inflammation, suggesting that PPARs exert direct antiatherogenic actions at the level of the vascular wall. Kitajima *et al*[48] reported that a PPARα agonist reduced the secretion of IL-6 and IFN-γ through inactivation of NF-κB in human coronary endothelial cells, without affecting cell proliferation or tube formation. Zahradka *et al*[49] reported that a PPARα agonist attenuated smooth muscle cell (SMC) migration probably by reducing matrix metalloproteinase-9 production, which is known to cause aberrant movement of SMCs in atherosclerotic lesions. Our current data showed no relationships between CAVI reduction and other factors, suggesting that the direct vascular effects of fibrates may contribute to the improvement of arterial stiffness.

Several studies have reported that bezafibrate improves glucose metabolism through up-regulation of insulin sensitivity, especially in patients with metabolic syndrome[50, 51]. In the present study, bezafibrate therapy significantly decreased HbA1c level accompanied by reduction of TGRLs and increase of HDL-cholesterol in diabetic subjects with a high rate of obesity, consistent with previous reports. These results support previous evidence that fibrates potently prevent cardiovascular events in patients with diabetes and obe-

sity. Taken together, improvement of glucose metabolism observed in this study may ameliorate arterial stiffness.

Our study has several limitations. Firstly, medication adherence may have affected the results in this study because we conducted neither a measurement of serum EPA levels nor a study of medication adherence. Secondly, the sample size was too small. Thirdly, this was an open-label study with potential selection bias. Finally, baseline HDL-cholesterol and APO A-2 levels were slightly higher (not significant) in the bezafibrate group than in the EPA group. Those differences may have affected the results in this study. Thus, a double-blind study with a large sample size will be necessary to confirm our results.

Conclusion

In conclusion, the effects of bezafibrate treatment in ameliorating arterial stiffness, improving glucose and lipid metabolism, and reducing oxidative stress potentially have important beneficial health consequences for cardiovascular disease prevention in hypertriglyceridemic patients with type 2 diabetes.

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Conflicts of Interest

None.

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