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ORIGINAL ARTICLE

Highly purified eicosapentaenoic acid reduces cardio-ankle vascular index in association with decreased serum amyloid A-LDL in metabolic syndrome

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A recent clinical trial revealed that highly purified eicosapentaenoic acid (EPA), an *n-3* polyunsaturated fatty acid, reduces the incidence of cardiovascular diseases. However, the detailed mechanism underlying the anti-atherogenic effect of EPA is still poorly understood. In this study, we examined the effect of EPA on cardio-ankle vascular index (CAVI), a new index of arterial stiffness that is less influenced by blood pressure (BP), as well as on serum amyloid A-low-density lipoprotein (SAA–LDL), an oxidized LDL (oxLDL), in the metabolic syndrome. Ninety-two obese Japanese subjects with metabolic syndromes were randomly divided into two groups (n=46): the EPA-treated group (1.8 g administered daily for 3 months) and the control group. Measurements were taken to assess the changes in glucose-lipid metabolism, SAA–LDL, C-reactive protein (CRP), leptin, adiponectin and pulse wave velocity (PWV), and CAVI. EPA treatment significantly reduced the levels of immunoreactive insulin, triglycerides, SAA–LDL, CRP, PWV and CAVI and increased the levels of adiponectin relative to the control group for 3 months ($P<0.05$). Stepwise multivariate linear regression analysis revealed that the only significant determinant for a decrease in CAVI by EPA is a reduction in SAA–LDL ($P<0.05$). Moreover, the EPA-induced reduction of SAA–LDL was only significantly correlated with a decrease in total cholesterol and an increase in adiponectin ($P<0.05$). This study is the first demonstration that EPA improves arterial stiffness and is less influenced by BP, possibly through the suppression of SAA–LDL, thereby leading to a reduction in the frequency of cardiovascular disease development in metabolic syndrome.
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INTRODUCTION

Atherosclerosis is a complex pathological process that involves multiple cardiovascular and metabolic irregularities, including high blood pressure (BP), lipid abnormalities, hyperglycemia, insulin resistance, dysregulation of adipocytokines, hypercoagulability, oxidative stress and inflammation, which are often accompanied by metabolic syndrome.[1] Metabolic syndrome increases the risk of all-cause mortality and cardiovascular morbidity and mortality.[2,3] Therefore, mechanistic exploration for the prevention and treatment of cardiovascular disease in metabolic syndrome is of considerable importance.

Fish oil rich in *n-3* polyunsaturated fatty acids or *n-3* polyunsaturated fatty acids has been shown to reduce the incidence of coronary heart disease in epidemiological and clinical trials.[4,5] Recently, the Japan EPA Lipid Intervention Study (JELIS) reported that the addition of highly purified eicosapentaenoic acid (EPA) to low-dose statin therapy significantly reduced the incidence of major coronary events without altering the reduction in low-density lipoprotein (LDL) cholesterol levels, suggesting a pleiotropic effect in addition to its well-known lipid-lowering effect.[6] *n-3* polyunsaturated fatty acids or EPA exert various beneficial effects in a multistep treatment of atherosclerosis, such as antiplatelet action (because of the antagonizing effects of arachidonic acid) and plaque stabilization.[7,8] We have recently shown that treatment with EPA decreased small, dense LDL, remnants, high-sensitive C-reactive protein (CRP) and soluble endothelial adhesion molecules and increases adiponectin, an anti-atherogenic adipocytokine.[9–11] All of the abovementioned factors may

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contribute to the anti-atherogenic effect of EPA. However, details underlying the anti-atherogenic effect of EPA in patients with metabolic syndrome remain to be elucidated.

In diabetic patients, there is only a single report on the effect of *n-3* polyunsaturated fatty acids on arterial stiffness; treatment with EPA for 2 years improves intima-media thickness and pulse wave velocity (PWV).[12] However, as PWV tends to be affected by the change in BP,[13] it is not currently known whether EPA can directly improve arterial stiffness. Recently, the cardio-ankle vascular index (CAVI), an index for estimating arterial stiffness, has been developed. This new index is less influenced by the change in BP.[14,15] Importantly, CAVI has more significant correlations with left ventricular diastolic function, the number of stenotic coronary vessels and the severity of coronary atherosclerosis than with arterial intima-media thickness and plaque score.[16,17]

There is evidence that oxidative modification of LDL (or oxidized LDL (oxLDL)) is relevant to atherosclerotic lesions, in which the LDL is easily taken up by damaged endothelial cells and macrophages, along with remnants and small, dense LDL.[18–20] Indeed, recent studies suggest that the serum amyloid A–LDL (SAA–LDL) complex, a novel oxLDL unique in its formation under inflammation conditions, is intravascularly detected and may serve as a surrogate marker of arterial plaque activity in patients with stable coronary artery disease.[21,22]

In this study, we investigated the effect of highly purified EPA on CAVI and SAA–LDL, precursors of cardiovascular disease, to elucidate the detail underlying the cardioprotective effect of EPA in metabolic syndrome. To accurately evaluate the vascular dysfunction associated with metabolic syndrome, we used CAVI.[14,15]

METHODS

Subjects

This study enrolled 92 obese Japanese patients with dyslipidemia (39 men and 53 women, mean age 51.7 ± 1.5 years, mean body mass index (BMI) 30.0 ± 0.5 kg m^{-2}, mean hemoglobin A1c (HbA1c) 6.3 ± 0.1%) at our clinics between April 2006 and June 2007 (Table 1). Patients were diagnosed with metabolic syndrome according to the modified National Cholesterol Education Program-Adult Treatment Panel III definition,[1] which requires that three or more of the following criteria be met: a triglyceride (TG) level $\geqslant$1.69 mmol l^{-1}, high-density lipoprotein-cholesterol (HDL-C) $<$1.04 mmol l^{-1} for men and $<$1.29 mmol l^{-1} for women, BP $\geqslant$130/85 mm Hg or diagnosed earlier with hypertension, fasting plasma glucose (FPG) level $\geqslant$100 mg per 100 ml or diagnosed earlier with diabetes mellitus, and a waist circumference (WC) of $\geqslant$85 cm for men and $\geqslant$90 cm for women. The cutoff of WC used to determine abdominal obesity followed the guidelines established in 2005 by the National Metabolic Syndrome Criteria Study Group of Japan.[23] The study protocol was approved by the Ethics Committee for Human Research at Kyoto Medical Center and Tokyo Medical and Dental University. Written informed consent was obtained from all participants.

Study protocol

In this single-blind, run-in period study, patients were randomly assigned to one of two treatment groups: 3-month treatment with either diet alone (the control group, composed of 19 men and 27 women; mean age, 52.2 ± 2.1 years) or diet+EPA (the EPA group, administered 1.8 g EPA daily, composed of 20 men and 26 women; mean age, 51.3 ± 2.1 years). Subjects in the EPA group received an EPA capsule containing highly purified (>98%) EPA ethyl ester.[9,10] No patients in this study had taken part in any of our earlier studies. Patient diet was based on that prescribed in the Japan Atherosclerosis Society Guidelines for Diagnosis and Treatment of Atherosclerotic Cardiovascular Diseases. The diet consisted of 25 kcal kg^{-1} of ideal body weight per day (60% of total energy as carbohydrates, 15–20% as protein and 20–25% as fat, with the ratio of polyunsaturated, monounsaturated and saturated fatty acids being 3:4:3). Lipid-lowering medications such as statins and fibrates were excluded. Patients taking angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists or insulin-sensitizing agents such as thiazolidinediones were also excluded from the study. Several patients in both groups were taking oral antidiabetic agents (sulfonylurease or α-glucosidase inhibitors) and antihypertensive agents (calcium channel blockers), but underwent no changes in medication during this study. Placebo control studies with clinically approved drugs such as EPA are currently not approved in Japan. No participants dropped out of this study.

Data collection and laboratory methods

Measurements of patient height and weight were taken, and BMI was calculated as weight in kilograms divided by the square of the height in meters and used as an index of obesity. WC measurements were taken at the umbilicus with the subject in the standing position. Systolic and diastolic BP (SBP and DBP) were measured twice using an automatic electronic sphygmomanometer (BP-103i II; Nippon Colin, Komaki, Japan). Blood was taken from the antecubital vein in the morning after fasting for 12 h to determine the FPG, HbA1c, plasma immunoreactive insulin, total cholesterol (TC), LDL-C, HDL-C, TG, SAA–LDL, leptin, adiponectin and CRP levels. Blood was centrifuged at 3000 r.p.m. for 10 min at 4 °C within 1 h of collection. Blood levels of FPG, HbA1c, plasma immunoreactive insulin, TC, LDL-C, HDL-C and TG were determined according to the standard procedures.[9] Plasma concentrations of leptin, adiponectin and CRP were determined as described earlier.[9,10]

A sandwich enzyme-linked immunosorbent assay was used to determine the serum SAA–LDL level.[21,22] Intra-assay variations in low and high concentrations were 2.6 and 4.7%, respectively, whereas inter-assay variations in low and high concentrations were 5.0 and 6.7%, respectively.[21]

Measurement of PWV and CAVI

A Vasera VS 1000 (Fukuda Denshi, Tokyo, Japan) was used to measure ECG, phonocardiograph, pressures and waveforms of brachial and ankle arteries, as well as PWV.[14] CAVI values were automatically calculated by substituting the stiffness parameter β in the following equation for detecting vascular elasticity and cardio-ankle PWV:

$$\text{Stiffness parameter } \beta = 2\rho \times 1/(\text{Ps} - \text{Pd}) \times \ln(\text{Ps}/\text{Pd}) \times \text{PWV}^2,$$

where ρ is blood density, Ps and Pd are SBP and DBP in mm Hg, respectively, and PWV is measured between the aortic valve and the ankle. CAVI, which represents the stiffness of the aorta, is therefore unaffected by BP. The principles underlying CAVI have been described in detail by Shirai *et al.*[14] The average coefficient of variation of CAVI is less than 5%, which is small enough for clinical use and confirms that CAVI has good reproducibility.[14]

Statistical analysis

Data are presented as means ± s.e. and $P<0.05$ was considered statistically significant. Repeated analysis of variance measurements (control and EPA groups×pre- and post-treatment) were used to assess the comparative effects of EPA treatment on the variables measured. A two-tailed, paired *t*-test was applied to evaluate variable changes from baseline to 3 months. The χ^2-test was used for baseline comparison between categorical variables, whereas Student's two-tailed *t*-test was used for comparison of continuous variables. Pearson's correlation coefficients were used to investigate the correlations of SAA–LDL and CAVI with metabolic parameters at the baseline, as well as the correlations of these changes between measurements pre- and post-EPA treatment. Changes from baseline conditions to those at 3 months were abbreviated as Δ. Stepwise multivariate regression analysis clarified those factors related to the SAA–LDL and CAVI values at baseline in all subjects, as well as changes between pre- and post-EPA treatment. The independent variables in the multivariate regression analysis were all metabolic variables measured in this study. All analyses were performed using Stat View version 5.0 for Windows (SAS Institute, Cary, NC, USA).

Table 1 Clinical characteristics and metabolic parameters baseline and after treatment with EPA

	Control		*EPA*	
	Baseline	*After 3 months*	*Baseline*	*After 3 months*
Male/female	19/27		20/26	
Age (years)	52.2 ± 2.1		51.3 ± 2.1	
BMI (kg m^{-2})	30.0 ± 0.6	29.2 ± 0.6	30.0 ± 0.7	29.7 ± 0.6
Waist circumference (cm)	96.7 ± 1.7	94.1 ± 1.5	98.0 ± 1.5	97.5 ± 1.5
Systolic blood pressure (mm Hg)	141 ± 1.9	137 ± 2.1	140 ± 2.4	137 ± 2.6
Diastolic blood pressure (mm Hg)	84.1 ± 1.4	82.7 ± 1.4	84.8 ± 1.5	84.4 ± 1.7
Fasting plasma glucose (mmol l^{-1})	6.19 ± 0.2	6.15 ± 0.2	6.13 ± 0.2	6.02 ± 0.2
HbA1c (%)	6.34 ± 0.2	6.13 ± 0.1	6.21 ± 0.2	6.01 ± 0.2
IRI (pmol l^{-1})	110 ± 8.3	103 ± 9.9	113 ± 13	98.9 ± 14
Total cholesterol (mmol l^{-1})	5.65 ± 0.1	5.39 ± 0.1	5.70 ± 0.1	5.31 ± 0.1
LDL-C (mmol l^{-1})	3.39 ± 0.1	3.28 ± 0.1	3.47 ± 0.2	3.30 ± 0.2
HDL-C (mmol l^{-1})	1.43 ± 0.1	1.42 ± 0.1	1.46 ± 0.1	1.47 ± 0.1
Triglyceride (mmol l^{-1})	2.56 ± 0.2	2.24 ± 0.2	2.68 ± 0.2	2.00 ± 0.1**
SAA–LDL (μg ml^{-1})	47.5 ± 4.7	51.2 ± 5.3	48.6 ± 5.6	40.4 ± 5.0**
Leptin (ng ml^{-1})	15.2 ± 1.9	14.0 ± 1.6	16.1 ± 1.8	13.8 ± 1.6
Adiponectin (μg ml^{-1})	7.02 ± 0.5	7.00 ± 0.4	6.99 ± 0.5	7.53 ± 0.5**
CRP (μg ml^{-1})	1.46 ± 0.2	1.63 ± 0.3	1.57 ± 0.2	1.16 ± 0.2**
PWV (cm s^{-1})	1388 ± 40	1399 ± 41	1400 ± 39	1321 ± 32**
CAVI	7.76 ± 0.2	7.80 ± 0.2	7.87 ± 0.2	7.59 ± 0.2**
Proportion of				
Hypertension (%)	82.6		78.2	
Diabetes (%)	45.7		47.8	
Dyslipidemia (%)	100.0		100.0	
Taking antihypertensive agents (*n*)	18		16	
Taking antidiabetic agents (*n*)	17		18	

Abbreviations: BMI, body mass index; CAVI, cardio-ankle vascular index; CRP, high-sensitive C-reactive protein; EPA, eicosapentaenoic acid; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; IRI, immunoreactive insulin; LDL-C, low-density lipoprotein cholesterol; PWV, pulse wave velocity; SAA–LDL, serum amyloid A–LDL.
Data are mean ± s.e. $^{**}P<0.01$ *vs.* baseline measurement as determined by a two-way repeated measures analysis of variance (control and EPA groups×before and after treatment).

RESULTS

Subject baseline characteristics

No significant differences were observed in any variables between the control and EPA groups at baseline (Table 1). The proportions of hypertension, diabetes, dyslipidemia and prescriptions of antihypertensive agents and antidiabetic agents were not significantly different in both groups.

Effects of EPA treatment on the metabolic variables

With regard to the control group, BMI, WC, SBP, DBP, FPG, HbA1c, plasma immunoreactive insulin, TC, LDL-C, HDL-C, TG, SAA–LDL, leptin, adiponectin, CRP, PWV and CAVI remained unchanged throughout the study (Table 1). After 3 months of treatment with EPA, analysis of variance showed that TG decreased significantly (TG, $P<0.05$), whereas BMI, WC, SBP, DBP, FPG, HbA1c, plasma immunoreactive insulin, TC, LDL-C, HDL-C and leptin all remained unchanged. EPA treatment significantly increased the plasma adiponectin concentrations and decreased the CRP concentrations (adiponectin: $6.99 \pm 0.5 \rightarrow 7.53 \pm 0.5$ μg ml^{-1}, $P<0.01$; CRP: $1.57 \pm 0.2 \rightarrow 1.16 \pm 0.2$ μg ml^{-1}, $P<0.01$) (Table 1), which is consistent with our earlier reports.[9,10] In this study, EPA treatment also resulted in a significant reduction in SAA–LDL, PWV and CAVI (SAA–LDL, $48.6 \pm 5.6 \rightarrow 40.4 \pm 5.0$ μg ml^{-1}, $P<0.01$; PWV: $1400 \pm 39 \rightarrow 1321 \pm 32$ cm s^{-1}, $P<0.01$; CAVI, $7.87 \pm 0.2 \rightarrow 7.59 \pm 0.2$, $P<0.01$) (Table 1).

Baseline correlation among the metabolic variables, SAA–LDL and CAVI

Table 2 lists the simple correlations of the metabolic variables with SAA–LDL and CAVI among all study subjects at baseline. Analysis of Pearson's correlation revealed that SAA–LDL has a significantly positive correlation with CRP, PWV and CAVI ($P<0.05$) (Table 2). CAVI also had a significant positive correlation with age, SBP, FPG and SAA–LDL, and a negative correlation with BMI and adiponectin (Table 2). Notably, stepwise multivariate linear regression analysis revealed that CRP was only independently and significantly correlated with SAA–LDL ($\beta=0.270$, $P<0.05$) (Table 2). Furthermore, multivariate regression analysis for CAVI showed that the independent variables contributing to high levels of CAVI were advanced age, high level of FPG and TC, and low levels of adiponectin (age, $\beta=0.630$, $P<0.01$; FPG, $\beta=0.155$, $P<0.05$; TC, $\beta=0.285$, $P<0.01$; adiponectin, $\beta=-0.243$, $P<0.01$) (Table 2).

Correlation between the changes in metabolic variables, SAA–LDL and CAVI following EPA treatment

Table 3 lists the data for all subjects regarding the simple correlations observed during EPA treatment between the metabolic variables, SAA–LDL, PWV and CAVI. In all study subjects, analysis of Pearson's correlation revealed that changes in SAA–LDL correlated positively with the changes in TC, CRP, PWV and CAVI and negatively with changes in adiponectin ($P<0.05$). Furthermore, the decrease in CAVI

Table 2 Regression analysis for SAA–LDL and CAVI values at baseline

	SAA–LDL		*CAVI*	
	Univariate	*Multivariate*	*Univariate*	*Multivariate*
Age (years)	0.065	—	0.578**	0.630**
BMI (kg m^{-2})	0.023	—	−0.401**	—
Waist circumference	0.019	—	−0.179	—
Systolic blood pressure	−0.066	—	0.208*	—
Diastolic blood pressure	−0.034	—	0.119	—
Fasting plasma glucose	0.188	—	0.220*	0.155*
HbA1c	0.184	—	0.106	—
IRI	0.072	—	0.024	—
Total cholesterol	0.150	—	0.190	0.285**
LDL-C	0.083	—	0.169	—
HDL-C	−0.098	—	−0.038	—
Triglyceride	0.182	—	0.134	—
SAA–LDL			0.225*	—
Leptin	0.175	—	−0.088	—
Adiponectin	−0.150	—	−0.291**	−0.243**
CRP	0.270*	0.270*	0.044	—
PWV	0.222*	—		
CAVI	0.225*	—		

Abbreviations: BMI, body mass index; CAVI, cardio-ankle vascular index; CRP, high-sensitive C-reactive protein; EPA, eicosapentaenoic acid; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; IRI, immunoreactive insulin; LDL-C, low-density lipoprotein cholesterol; PWV, pulse wave velocity; SAA–LDL, serum amyloid A–LDL.
Multivariate regression analysis was performed with adjustments for all metabolic parameters as independent variables.
*$P<0.05$, **$P<0.01$.

Table 3 Regression analysis for changes in SAA–LDL and CAVI during treatment with EPA

	ΔSAA–LDL		*ΔCAVI*	
	Univariate	*Multivariate*	*Univariate*	*Multivariate*
ΔBW	0.191	—	−0.083	—
ΔBMI (kg m^{-2})	0.255	—	−0.025	—
ΔWaist circumference	0.090	—	0.004	—
ΔSystolic blood pressure	−0.137	—	0.218	—
ΔDiastolic blood pressure	−0.110	—	0.066	—
ΔFasting plasma glucose	0.147	—	0.101	—
ΔHbA1c	−0.066	—	−0.068	—
ΔIRI	−0.044	—	−0.037	—
ΔTotal cholesterol	0.360*	0.293*	0.278	—
ΔLDL-C	−0.005	—	−0.075	—
ΔHDL-C	0.081	—	−0.141	—
ΔTriglyceride	0.287	—	0.160	—
ΔSAA–LDL			0.381*	0.381*
ΔLeptin	0.003	—	0.211	—
ΔAdiponectin	−0.331*	−0.305*	−0.213	—
ΔCRP	0.365*	—	0.158	—
ΔPWV	0.366*	—		
ΔCAVI	0.381*	0.325*		

Abbreviations: BMI, body mass index; CAVI, cardio-ankle vascular index; CRP, high-sensitive C-reactive protein; EPA, eicosapentaenoic acid; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; IRI, immunoreactive insulin; LDL-C, low-density lipoprotein cholesterol; PWV, pulse wave velocity; SAA–LDL, serum amyloid A–LDL.
Multivariate regression analysis was performed with adjustments for all metabolic parameters as independent variables.
*$P<0.05$.

correlated significantly only with the decrease in SAA–LDL ($P<0.05$). In this study, multivariate regression analysis for change in SAA–LDL revealed that the independent variables that contribute to decreased SAA–LDL following EPA treatment are the decrease in TC and CAVI, as well as the increase in adiponectin (TC, β=0.293; CAVI, β=0.325; adiponectin, β=−0.305, $P<0.05$) (Table 3). Of all the variables, only decreased SAA–LDL was an independent determinant for decreased CAVI following EPA treatment (β=0.381, $P<0.05$).

DISCUSSION

In a large-scale, prospective, randomized clinical trial, highly purified EPA earlier reduced the risk of major coronary events through cholesterol-independent mechanisms.[6] In this study, we focus on the beneficial effect of highly purified EPA on two new indexes, CAVI and SAA–LDL, in patients with metabolic syndrome.

Eicosapentaenoic acid treatment for 3 months significantly reduced the value of CAVI in patients with metabolic syndrome. In this study, we also confirmed the significant reduction of PWV by EPA treatment, which is consistent with an earlier report on the effect of EPA on carotid intima-media thickness and PWV in diabetic patients.[12] In the multicentered Japan Obesity and Metabolic Syndrome Study, we recently reported that CAVI is less influenced by BP and more closely correlated than PWV with the severity of metabolic syndrome and hypoadiponectinemia in obese subjects. We suggested that CAVI is useful to evaluate atherogenic risks in metabolic syndrome.[15] Given that BP elevation is included as a diagnostic criterion of metabolic syndrome[2] and that almost 80% of the subjects with metabolic syndrome who enrolled in this study had hypertension, CAVI may be a more suitable index than PWV for evaluating atherosclerotic changes in metabolic syndrome. Although hypertension is an established risk for atherosclerosis, our data also suggest that EPA improves arterial stiffness in metabolic syndrome through a mechanism independent of BP.

This study shows that EPA markedly reduces SAA–LDL, an oxLDL, in patients with metabolic syndrome. Furthermore, of all the cardiovascular disease risk factors tested, only the decrease in SAA–LDL is significantly correlated with the reduction of CAVI by EPA. SAA–LDL is a complex molecule generated through the oxidative interaction of SAA with lipoproteins, in the context of intravascular inflammation.[21,22] Accumulated oxLDL, which is easily taken up by macrophages through damaged endothelial cells, has a key role in the initiation and progression of inflammation and atherosclerosis.[18,19,24] Indeed, elevated oxLDL blood levels reflect the pathologic condition of the vessel wall, endothelial dysfunction and coronary plaque instability.[25] Furthermore, oxLDL increases endothelial stiffness, force generation and network formation.[20] There is also a report that SAA–LDL serves as a direct marker of arterial plaque activity in patients with stable coronary artery disease.[21] The oxidation of LDL tends to be accompanied by overall metabolic syndrome, as well as abdominal obesity, hyperglycemia and hypertriglyceridemia.[26,27] Multivariate regression analysis also revealed that a decrease in SAA–LDL following treatment with EPA is the only independent determinant contributing to the reduction of CAVI. Collectively, we postulate that the attenuation of SAA–LDL is an important step for the anti-atherogenic effect of EPA in metabolic syndrome, which is independent of BP. On the other hand, we observed that a 3-month treatment with EPA also mildly reduced SAA–LDL and CAVI in 15 obese dyslipidemic subjects without metabolic syndrome (unpublished data). It is, therefore, conceivable that there may also be beneficial effects of EPA on SAA–LDL and CAVI in subjects without metabolic syndrome. Further

studies are needed to evaluate the accurate effects of EPA in subjects without metabolic syndrome.

Although high TC and low adiponectin increase the risk of atherosclerosis,[2,3,28] we found that both decreased TC and increased adiponectin have no significant correlations with the reduction in CAVI. In this study, multivariate regression analysis for the change in SAA–LDL also revealed that only the decrease in TC and increase in adiponectin are independent variables that contribute to the EPA-induced decrease in SAA–LDL. This is consistent with an earlier report that low adiponectin is associated with high circulating oxLDL in patients with type II diabetes and coronary artery disease.[29] Therefore, it is conceivable that decreased SAA–LDL is more closely related to the anti-atherogenic effect of EPA than decreased TC and increased adiponectin. Furthermore, in this study, EPA significantly reduced plasma CRP, a representative marker of inflammation, as described by us earlier.[9] Moreover, baseline values and the change in CRP levels were closely correlated with those of SAA–LDL during EPA treatment. The findings discussed above also support the notion that the oxidative interaction of SAA with lipoproteins under inflammation represents one of the common pathways where the anti-atherogenic mechanisms of EPA may converge.

In conclusion, this is the first study to show that EPA improves arterial stiffness independent of BP in patients with metabolic syndrome in parallel with decreases in SAA–LDL. These data also suggest that the reduction of oxidative LDL modification is a part of the mechanism behind the anti-atherogenic effect of EPA. Given that EPA has been proven to reduce the risk of major coronary events,[7] this study provides important insights into its therapeutic implications in obesity-related metabolic syndrome.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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