Heart Vessels (2011) 26:408–413
DOI 10.1007/s00380-010-0060-x

ORIGINAL ARTICLE

Olmesartan reduces arterial stiffness and serum adipocyte fatty acid-binding protein in hypertensive patients

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Received: 13 July 2009 / Accepted: 30 April 2010 / Published online: 10 November 2010
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Abstract Adipocyte fatty acid binding protein (A-FABP) has been reported to be involved in insulin resistance, lipid metabolism, and atherosclerosis; however, little is known about the effect of medication on the change in circulating A-FABP in human subjects. We evaluated the effects of angiotensin II type 1 receptor blocker (ARB) on arterial stiffness and its association with serum A-FABP in patients with hypertension. Thirty patients newly diagnosed with essential hypertension were treated with olmesartan (20 mg/day), an ARB, for 6 months. Serum levels of A-FABP and high-sensitivity C-reactive protein (hsCRP) were examined and the cardio-ankle vascular index (CAVI), which is a marker of arterial stiffness, was also determined. Serum A-FABP at baseline was significantly correlated with the body mass index ($r = 0.45$, $P = 0.01$), homeostasis model assessment as a marker of insulin resistance ($r = 0.53$, $P < 0.01$), and systolic blood pressure ($r = 0.37$, $P = 0.047$), and tended to be correlated with low-density lipoprotein cholesterol, triglyceride, and CAVI. Olmesartan treatment resulted in a significant decrease in CAVI, serum A-FABP levels, and hsCRP, besides a significant reduction of blood pressure. Multiple regression analysis revealed that the change in CAVI was independently correlated with the change in serum A-FABP. Olmesartan ameliorated arterial stiffness in patients with hypertension, which may be involved in the reduction of serum A-FABP.

Keywords Adipocyte · Angiotensin II receptor antagonist · Atherosclerosis · Fatty acid · Hypertension · Inflammation

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Introduction

Adipose tissue has been shown to be an endocrine organ that secretes various molecules, called adipokines [1]. Several adipokines, such as adiponectin, leptin, adipocyte-type fatty acid binding protein (A-FABP), and tumor necrosis factor-α, are closely involved in visceral adipose tissue [2]. Those adipokines are now considered key players not only in the role of glucose metabolism but also in vascular inflammation. Among adipokines, A-FABP, also known as aP2 or FABP4, is one of the most abundant proteins in adipocytes and activated macrophages [3]. In animal experiments, it has been shown that A-FABP-deficient mice were protected from the development of insulin resistance [4] and atherosclerosis in models of hypercholesterolemia [5]. In humans, A-FABP levels have been detected in serum [6], although A-FABP was originally a cytoplasmic protein. It has been reported that the serum A-FABP level predicts the development of metabolic syndrome [7], and is associated with carotid intima-media thickness [8] and coronary atherosclerosis [9, 10].

Essential hypertension is associated with insulin resistance [11], although the underlying mechanisms remain

largely unknown. Several studies have shown that inhibition of the renin angiotensin system by antihypertensive agents, such as angiotensin II type 1 receptor blockers (ARB), reduced the incidence of the new onset of diabetes [12–14]. Among the several ARBs available in the clinical setting, olmesartan is thought to have significantly stronger blood pressure-lowering effects than losartan or valsartan at their respective starting dose [15, 16]. Recent studies have demonstrated that olmesartan reduced serum markers of vascular inflammation in patients with hypertension [17, 18]. Those improvements in inflammation could ameliorate atherosclerosis and arterial stiffness.

In this study, we evaluated the effects of olmesartan on arterial stiffness and serum A-FABP in patients with hypertension.

Methods

Patients

We prospectively studied 30 patients with untreated, uncomplicated essential hypertension. Hypertension was diagnosed in accordance with the Guidelines for the management of hypertension JSH 2009 [19]. Patients complicated with cerebrovascular disease, coronary artery disease, renal disease, cardiomyopathy, or arrhythmia were excluded. Patients with hemoglobin A1c (HbA1c) exceeding 6.5% and/or patients treated with antidiabetic medication or insulin were also excluded. Dyslipidemia was defined as one or more of the following criteria: (1) serum triglyceride $\geq$150 mg/dl, (2) high-density lipoprotein (HDL)-cholesterol $<$40 mg/dl in men and $<$50 mg/dl in women, (3) low-density lipoprotein (LDL)-cholesterol $\geq$130 mg/dl, (4) already on lipid-lowering drugs. The test procedure complied with the Helsinki Declaration; informed consent was obtained, and the study was approved by our institutional ethics committee for human research [20].

Patients were enrolled in a 6-month, open-label study and given 20 mg oral olmesartan once daily. All patients were reviewed for general health and compliance with medication, which was assessed by tablet counts, and checking blood pressure and body weight at each visit every month.

Biochemical measurements

Blood pressure was measured by trained physicians using a conventional mercury sphygmomanometer after a 5-min rest. Blood samples were collected from an antecubital vein after a 12-h overnight fast. Routine hematology and biochemistry were measured immediately using an autoanalyzer. Aliquots of serum were stored at -80°C until use. Commercially available kits based on the enzyme-linked immunosorbent assay were used to measure serum levels of A-FABP (BioVendor, Candler, NC, USA) and high-sensitivity C-reactive protein (hsCRP) (R&D Systems, Minneapolis, MN, USA), as previously reported [21, 22]. Insulin resistance was determined using homeostasis model assessment (HOMA-IR), which is calculated as the product of fasting plasma insulin (μU/ml) $\times$ fasting plasma glucose (mg/dl)/405.

Cardio-ankle vascular index

To assess arterial stiffness, the cardio-ankle vascular index (CAVI) was measured automatically using a VaSera VS-1000 (Fukuda Denshi, Tokyo, Japan) from the measurement of blood pressure and pulse wave velocity (PWV), while monitoring the electrocardiogram and heart sounds [23, 24]. Pulse wave velocity was calculated by dividing the distance from the aortic valve to the ankle artery by the sum of the time between the aortic valve closing sound and the notch of the brachial pulse wave, and the time between the rise of the brachial pulse wave and the ankle pulse wave. The CAVI was determined using the following equation: $\mathrm{CAVI} = a[(2\rho/\Delta P) \times \ln(\mathrm{Ps}/\mathrm{Pd}) \times \mathrm{PWV}^2] + b$, where Ps and Pd are systolic and diastolic blood pressures, respectively, PWV is the pulse wave velocity between the heart and ankle, ΔP is Ps $-$ Pd, ρ is blood density, and a and b are constants. The average of right and left CAVI was used for analysis.

Statistical analysis

Data are expressed as the mean $\pm$ SD. Differences between groups were analyzed by Student's paired t-test or the Mann–Whitney test as appropriate. Data that were not normally distributed, as determined using the Kolmogorov–Smirnov test, were logarithmically transformed before analysis. Relationships between variables were tested by Pearson and Spearman correlations. Univariate and multivariate linear regression analyses were performed to evaluate the relationship between the change in CAVI and the change in other parameters. Differences at $P < 0.05$ were considered significant. Data were analyzed using SPSS 11.0 for Windows (SPSS, Chicago, IL, USA).

Results

All enrolled patients completed the trial. Table 1 shows the baseline characteristics of all subjects. No subject had received antihypertensive therapy before enrolling in this study. Table 2 shows the relationship between the serum A-FABP level and other parameters. The serum A-FABP

Table 1 Clinical characteristics of the study population ($n = 30$)

Age (years)	61 ± 12
Gender (Male)	17
Body mass index (kg/m^2)	23.7 ± 2.7
Current smokers (*n*)	5
Dyslipidemia (*n*)	17
Medications	
Statins (*n*)	3
Aspirin (*n*)	1

Table 2 Relationship between serum A-FABP level and other parameters

Dependent variable: log serum A-FABP	*r*	*p*
Age (years)	0.108	0.572
Gender (male)	−0.084	0.659
BMI (kg/m^2)	0.453	0.012
SBP (mmHg)	0.366	0.047
DBP (mmHg)	0.100	0.598
FPG (mg/dl)	0.227	0.236
Insulin (μU/ml)	0.480	0.010
HbA1c (%)	0.375	0.412
HOMA-IR	0.530	0.004
LDL-cholesterol (mg/dl)	0.330	0.075
Triglyceride (mg/dl)	0.348	0.059
HDL-cholesterol (mg/dl)	−0.163	0.300
Uric acid (mg/nl)	0.047	0.804
Creatinine (mg/dl)	0.155	0.414
log hsCRP	−0.040	0.841
CAVI	0.318	0.086

A-FABP adipocyte-type fatty acid binding protein; *BMI* body mass index; *SBP* systolic blood pressure; *DBP* diastolic blood pressure; *FPG* fasting plasma glucose; *HOMA-IR* homeostasis model assessment of insulin resistance; *LDL* low-density lipoprotein; *HDL* high-density lipoprotein; *hsCRP* high-sensitivity C-reactive protein; *CAVI* cardio-ankle vascular index

level was significantly correlated with the body mass index, systolic blood pressure, insulin, and HOMA-IR, and tended to be correlated with LDL-cholesterol, triglyceride, and CAVI. Patients with dyslipidemia had a significantly higher serum A-FABP level (ng/ml) than subjects without dyslipidemia (27.5 ± 17.2 vs. 19.9 ± 10.4, expressed as the median ± interquartile, respectively; $P = 0.03$). The difference in the serum A-FABP level between men and women was not significant (22.7 ± 10.9 vs. 20.7 ± 12.3, respectively; $P = 0.66$).

Table 3 shows parameter changes before and after treatment with olmesartan. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were significantly reduced after 6-month treatment. There was no difference in body mass index between at the baseline and after 6-month

Table 3 Clinical and laboratory characteristics before and after treatment with olmesartan

	Baseline	6 month	*p*
SBP (mmHg)	152 ± 9	136 ± 10	<0.01
DBP (mmHg)	91 ± 9	81 ± 10	<0.01
Body mass index (kg/m^2)	23.7 ± 2.7	23.7 ± 2.6	0.98
FPG (mg/dl)	103 ± 9	104 ± 10	0.33
Insulin (μU/ml)	6.8 ± 3.6	5.8 ± 2.9	0.09
HbA1c (%)	5.36 ± 0.46	5.29 ± 0.42	0.19
Total cholesterol (mg/dl)	207 ± 46	196 ± 32	0.31
HOMA-IR	1.8 ± 0.9	1.5 ± 0.8	0.10
LDL-cholesterol (mg/dl)	118 ± 41	117 ± 27	0.73
Triglyceride (mg/dl)	142 ± 103	134 ± 104	0.58
HDL-cholesterol (mg/dl)	60 ± 16	57 ± 12	0.25
Uric acid (mg/nl)	6.0 ± 1.2	5.9 ± 1.0	0.95
Creatinine (mg/dl)	0.72 ± 0.12	0.75 ± 0.15	0.06
hsCRP (mg/L)	0.94 (0.46–1.67)	0.82 (0.43–1.23)	<0.01
serum A-FABP (ng/ml)	22.7 (18.2–28.2)	20.3 (16.4–27.1)	0.04
CAVI	8.70 ± 0.98	8.37 ± 0.97	<0.01

Values are mean ± SD or median value (25th to 75th percentile range)

treatment. Furthermore, olmesartan resulted in a significant decrease in A-FABP, hsCRP, and CAVI. The markers of insulin resistance, such as HOMA-IR, also tended to be reduced. Lipid profiles were not affected in this study.

To evaluate the potential mechanisms regarding the effects of olmesartan on arterial stiffness and serum A-FABP, univariate and multivariate linear regression analyses were performed. Univariate analysis regarding the change in CAVI showed that the change in CAVI before and after treatment was significantly correlated with the change in the serum A-FABP level and the change in systolic blood pressure, but not the change in HOMA-IR and hsCRP (Fig. 1). As shown in Table 4, multivariate analysis revealed that the reduction of CAVI was independently associated with the decrease in serum A-FABP. Univariate analysis showed that the change in serum A-FABP was significantly correlated with HOMA-IR ($r = 0.404$, $P = 0.027$) in addition to CAVI, and tended to be correlated with insulin ($r = 0.327$, $P = 0.096$) and triglyceride ($r = 0.307$, $P = 0.105$). Multivariate analysis demonstrated that the change in serum A-FABP was independently associated with the change in HOMA-IR and CAVI (Table 5).

Discussion

Treatment with olmesartan, an ARB, for 6 months significantly reduced arterial stiffness and the serum levels of

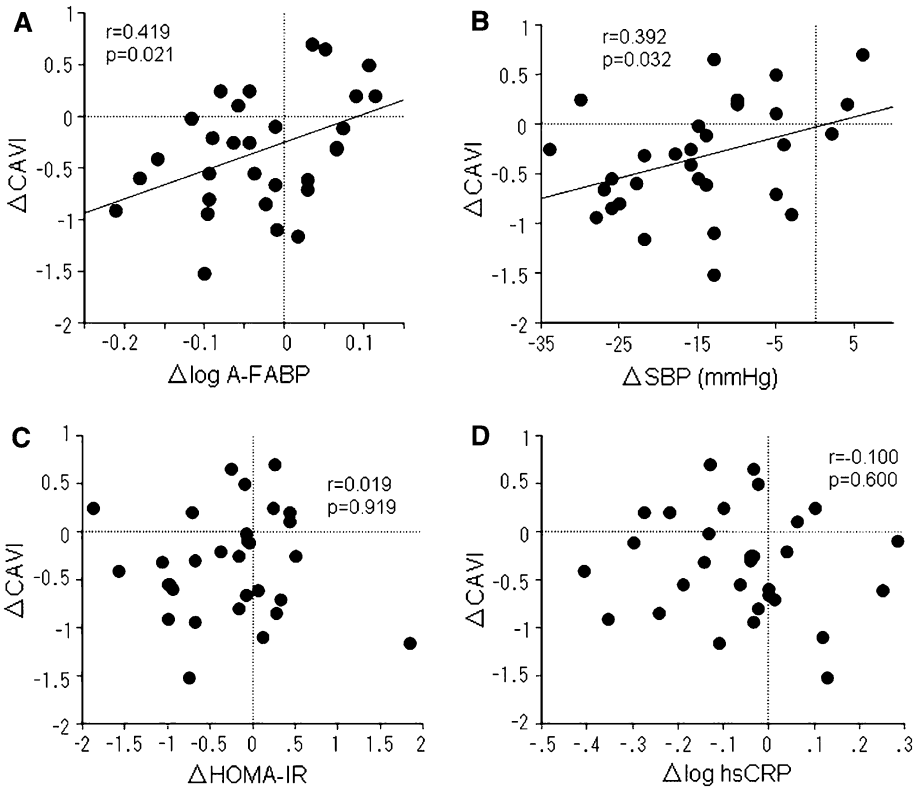

Fig. 1 Associations of the change in cardio-ankle vascular index (ΔCAVI) with changes in adipocyte fatty acid binding protein (ΔA-FABP) (**a**), systolic blood pressure (ΔSBP) (**b**), homeostasis model assessment (HOMA-IR) (**c**), and high-sensitivity C-reactive protein (hsCRP) (**d**)

Table 4 Multivariate linear regression analysis of the relationship between the change in CAVI and the change in other parameters

Dependent variable: ΔCAVI	β	p
ΔSBP (mmHg)	0.401	0.089
ΔDBP (mmHg)	−0.159	0.505
ΔHOMA-IR	−0.179	0.377
ΔCreatinine (mg/dl)	−0.09	0.656
Δlog hsCRP	−0.092	0.607
Δlog A-FABP	0.413	0.044

$R^2 = 0.33$

Table 5 Multivariate linear regression analysis of the relationship between the change in serum A-FABP and the change in other parameters

Dependent variable: Δlog A-FABP (ng/ml)	β	p
ΔSBP (mmHg)	0.106	0.656
ΔDBP (mmHg)	−0.094	0.691
ΔHOMA-IR	0.411	0.031
ΔCreatinine (mg/dl)	−0.004	0.981
Δlog hsCRP (mg/L)	0.049	0.778
ΔCAVI	0.399	0.044

$R^2 = 0.35$

A-FABP and hsCRP in patients with hypertension. The change in serum A-FABP with olmesartan treatment was significantly correlated with the change in CAVI and is a marker of insulin resistance. In addition, multivariate analysis revealed that the reduction of CAVI was independently associated with the reduction of the serum A-FABP.

Pulse wave velocity has been used as a noninvasive clinical index of aortic stiffness, which reflects atherosclerotic change in the arterial wall [25]. The CAVI was developed as an arterial stiffness parameter, characterizing the weaker correlation with systolic blood pressure than pulse wave velocity [23]. Previous reports have shown that CAVI is an age-dependent parameter. Kadota et al. [26] reported that CAVI in healthy subjects (mean age: 62.5 ± 10.8 years) was 8.1 ± 1.3. In this study, the mean age of enrolled subjects was similar, while CAVI at the baseline seemed to be higher than in a previous report. The CAVI might have been affected by the cardiovascular risk factors of our subjects. Our findings demonstrated that CAVI was significantly ameliorated after 6-month olmesartan treatment. In an animal study, a study has also shown the favorable effect of olmesartan on aortic properties [27]. The alteration of serum A-FABP might be a potential mechanism to improve CAVI with ARB treatment; however, the direct interaction is currently unknown. Another possibility is that adiponectin and inflammatory cytokines regulate atherosclerotic alteration of the arterial wall [28], while those levels were not evaluated in this study. Olmesartan has not been reported to act as a partial agonist of peroxisome proliferator-acivated receptor

gamma (PPARγ)-modulating activity [29]. A possible explanation for the effect on A-FABP is that a strong effect on the reduction of inflammatory cytokines may modulate the dysregulation of adipocytes.

In this study, we evaluated the effect of olmesartan on serum levels of A-FABP, which belongs to the fatty acid-binding protein superfamily and is highly expressed in adipose tissue [30]. Serum levels of A-FABP, which is released from adipocytes, have been reported to be associated with obesity and metabolic syndrome [6]. Consistent with previous studies, our results showed that serum A-FABP levels were positively correlated with the body mass index and markers of insulin resistance. In addition, the serum A-FABP level had a tendency to be correlated with CAVI. In this study, we found for the first time that treatment with olmesartan, an ARB, for 6 months significantly reduced the serum A-FABP level in patients with hypertension. A previous study demonstrated that thiazolidinedione, which regulates PPARγ activity, increased serum A-FABP in patients with diabetes [31], while little is known about the effect of medication on A-FABP levels. Olmesartan has been reported to reduce oxidative stress [32, 33], but not to act as a PPARγ ligand, in in vitro experiments [29]; therefore, olmesartan might modulate serum A-FABP by mediating the improvement of adipose tissue function through the suppression of oxidation and inflammation. Further experiments are needed to evaluate the role of angiotensin II in the regulation of A-FABP, especially circulating A-FABP.

The mechanisms for the correlation of serum A-FABP and atherosclerosis can be explained in several ways. Studies have shown that A-FABP deficiency in macrophages reduced foam cell formation in response to oxidized LDL and an increased cholesterol efflux pathway [34]. In an animal model, apolipoprotein E-deficient mice also showed a substantial reduction of vascular atherosclerosis in the absence of differences in serum lipids or insulin sensitivity, and this effect was attributed to the action of A-FABP in macrophages [5]. In this study, we could not find a significant correlation between A-FABP and hsCRP; however, in other studies, associations of the increase in serum A-FABP with elevated hsCRP and decrease in adiponectin were reported, which may be involved in the development of carotid intima-media thickness in diabetic patients and coronary plaque volume in ischemic heart disease [8, 10]. These data suggest that serum A-FABP is associated with vascular inflammation, leading to atherosclerosis. Despite several lines of evidence, the mechanism of A-FABP secretion from cells and the causal relationship between circulating A-FABP and the pathological effects on vasculature remain to be elucidated.

There are several limitations of this study. First, the cohort was rather small, and the observation period was relatively short. A further clinical study with a larger population will be required to draw a more definite conclusion. Second, food intake in terms of total calories and the physical activity of each patient were not carefully monitored. Despite no differences in body mass index before and after treatment, these factors can affect the amount of visceral and subcutaneous fat, which may be associated with adipocyte function.

In conclusion, we showed that treatment with olmesartan for 6 months significantly reduced arterial stiffness as well as serum levels of A-FABP and hsCRP. Multivariate analysis revealed that the change in CAVI was independently associated with the change in serum A-FABP in addition to the change in systolic blood pressure. Thus, current findings warrant future studies that would clarify whether treatment designed specifically to reduce serum A-FABP could substantially contribute to the regression of arterial stiffness.

Acknowledgments This work was supported in part by funding from a grant-in-aid for Scientific Research from the Japan Society for the Promotion of Science (20790531 to T.M.).

Conflict of interest None.

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