Fasting Serum Level of Fatty-Acid-Binding Protein 4 Positively Correlates With Metabolic Syndrome in Patients With Coronary Artery Disease

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Background: The serum level of fatty-acid-binding protein 4 (FABP4) increases in patients with metabolic syndrome (MetS), so the relationship between FABP4 and MetS among patients with coronary artery disease (CAD) was investigated in the present study.

Methods and Results: Fasting blood samples were obtained from 98 CAD patients. MetS and its components were defined using the diagnostic criteria of the International Diabetes Federation; 50 CAD patients (51.0%) had MetS. The fasting level of FABP4 positively correlated with MetS ($P=0.037$) and serum levels of FABP4 correlated with a number of MetS criteria ($P=0.035$). Univariate linear regression analysis showed that body fat mass ($R=0.234$; $P=0.020$) and the levels of triglycerides ($R=0.348$; $P<0.001$), and low-density lipoprotein-cholesterol ($R=0.217$; $P=0.032$) positively correlated with the serum level of FABP4, whereas the level of high-density lipoprotein-cholesterol ($R=-0.243$; $P=0.016$) negatively correlated with it. Multivariate forward stepwise linear regression analysis of the significant variables showed that the level of triglycerides ($\beta=0.348$, $R^2=0.121$, $P<0.001$) was the independent predictor of fasting serum level of FABP4.

Conclusions: Among CAD patients in the present study, the fasting level of FABP4 positively correlated with MetS and serum levels of FABP4 correlated with a number of MetS criteria. (*Circ J* 2010; **74**: 327–331)

Key Words: Coronary artery disease; Fatty-acid-binding protein 4; Metabolic syndrome

The fatty-acid-binding protein 4 (FABP4; also designated aP2 or adipocyte-fatty-acid-binding protein) is expressed in adipocytes and macrophages, and integrates inflammatory and metabolic responses.^{1,2} Studies in FABP4-deficient mice have shown that this lipid chaperone plays a significant role in several aspects of metabolic syndrome (MetS).^{1,3} FABP4 affects insulin sensitivity, lipid metabolism and lipolysis, and plays an important role in atherosclerosis.³ MetS is a significant risk factor for cardiovascular disease and mortality in the general population,^{4,5} and is also independently associated with coronary artery disease (CAD).⁶ CAD patients with MetS show an increased risk of cardiovascular morbidity after follow-up.⁷ Recent studies have shown that the serum level of FABP4 can predict the development of MetS and is independently associated with carotid intima-media thickness.^{8,9} Studies of the association between the serum level of FABP4 and MetS or the number of MetS criteria in CAD patients are rare, so the aim of this study was to investigate the relationship between the fasting serum level of FABP4 and MetS among CAD patients.

Methods

Patients

Between June 2008 and December 2008, we enrolled 98 CAD patients (CAD defined as >50% stenosis in any segment on coronary angiography) in a medical center in Hualien, eastern Taiwan (73 men, 25 women, age range 32–90 years). The Protection of Human Subjects Institutional Review Board of Tzu-Chi University and Hospital approved the study. Patients were excluded if they had any acute infections, acute myocardial infarction, pulmonary edema, heart failure at the time of blood sampling or if they refused to give informed consent for the study.

Anthropometric Analysis

Body weight was measured in light clothing and without shoes to the nearest 500 g. Height was measured to the nearest 0.5 cm. Waist circumference was measured to the nearest 0.5 cm at the shortest point below the lower rib margin and the iliac crest. Body mass index (BMI) was calculated as

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Table 1. Clinical and Analytical Characteristics of 98 Patients With CAD

Parameter	Result
Anthropometric findings	
Height (cm)	62.42±7.48
Weight (kg)	67.81±11.36
BMI (kg/m ²)	25.65±3.60
M/F	73/25
WC (cm)	90.32±9.83
Body fat mass (%)	27.65±6.80
Age (years)	68.04±10.89
Biochemical findings	
Albumin (g/dl)	4.42±0.34
TG (mg/dl)	143.67±73.89
Fasting glucose (mg/dl)	119.32±41.04
hs-CRP (mg/dl)	0.41±1.18
TC (mg/dl)	168.90±36.23
HDL-C (mg/dl)	47.32±13.49
Creatinine (mg/dl)	1.80±6.91
FABP 4 (ng/ml)	35.26±22.57
Complications	
Diabetes	36 (36.7)
Hyperlipidemia	59 (60.2)
Hypertension	77 (78.6)
Drugs	
ARBs	34 (34.7)
CCBs	18 (18.4)
Thiazides	22 (22.4)
PPAR-γ agonists	11 (11.2)
Clopidogrel	31 (31.6)
ACEIs	26 (26.5)
β-blockers	59 (60.2)
Statins	56 (57.1)
Aspirin	65 (66.3)

Data are mean ± SD or proportion.

CAD, coronary artery disease; BMI, body mass index; WC, waist circumference; TG, triglycerides; hs-CRP, high-sensitivity C-reactive protein; TC, total cholesterol; HDL, high-density lipoprotein-cholesterol; FABP 4, fatty-acid-binding protein 4; ARB, angiotensin-receptor blocker; CCB, calcium-channel blocker; PPAR, peroxisome proliferator-activated receptor; ACEI, angiotensin-converting enzyme inhibitor.

weight (kilograms) divided by height squared (meters). Bioimpedance measurements of fat mass were performed at the bedside according to the standard, tetrapolar, whole body (hand-foot) technique, using a single-frequency (50-kHz) analyzer (Biodynamic-450, Biodynamics Corporation, Seattle, WA, USA). Measurements were carried out by the same operator; fat mass data were collected and analyzed by the specific formulas supplied by the manufacturer.¹⁰

Biochemical Investigations

Fasting blood samples taken from each subject were immediately centrifuged at 3,000×g for 10 min for biochemical study. The serum was stored at 4°C for examination within 1 h of collection. Serum levels of creatinine (Cre), fasting glucose, total cholesterol, triglycerides (TG), high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C), albumin, globulin, and high-sensitivity C-reactive protein (hs-CRP) were measured using an autoanalyzer (COBAS Integra 800, Roche Diagnostics, Basel, Switzerland).

Table 2. Clinical Characteristics and Fasting Serum Levels of FABP4 in the 98 Patients With CAD

	n (%)	FABP 4 (ng/ml)	P value
Sex			
Male	73 (74.5)	35.44±24.62	0.191
Female	25 (25.5)	34.75±15.45	
Age			
<65 years	36 (36.7)	38.95±23.71	0.355
≥65 years	60 (63.3)	33.12±21.78	
Diabetes			
No	62 (63.3)	35.67±24.35	0.918
Yes	36 (36.7)	34.57±19.42	
Hypertension			
No	21 (21.4)	33.86±23.46	0.622
Yes	77 (78.6)	35.65±22.46	
Hyperlipidemia			
No	39 (39.8)	35.36±17.24	0.268
Yes	59 (60.2)	35.20±21.63	
Metabolic syndrome			
No	48 (49.0)	29.56±13.36	0.037*
Yes	50 (51.0)	40.76±27.82	
ARB			
No	64 (65.3)	33.95±21.76	0.224
Yes	34 (34.7)	37.73±24.15	
ACEI			
No	72 (73.5)	35.36±23.48	0.787
Yes	26 (26.5)	34.99±20.25	
CCB			
No	80 (71.6)	35.86±24.00	0.901
Yes	18 (18.4)	32.60±14.81	
β-blocker			
No	39 (39.8)	36.20±24.08	0.928
Yes	59 (60.2)	34.65±21.70	
Thiazide			
No	76 (77.6)	34.19±20.30	0.512
Yes	22 (22.4)	38.98±29.35	
Statin			
No	42 (42.8)	34.12±13.18	0.125
Yes	56 (57.2)	36.12±27.69	
PPAR-γ agonist			
No	87 (88.8)	35.83±23.24	0.719
Yes	11 (11.2)	30.75±16.43	
Aspirin			
No	33 (33.7)	39.23±25.27	0.054
Yes	65 (66.3)	33.25±20.98	
Clopidogrel			
No	67 (68.4)	33.42±15.58	0.167
Yes	31 (31.6)	35.90±25.60	

*P<0.05 considered statistically significant after performing the Mann-Whitney U test.

Abbreviations see in Table 1.

Serum FABP4 (SPI-BIO, Montigny le Bretonneux, France) levels were measured using a commercially available enzyme immunoassay.^{10,11}

MetS and its Components

The prevalence of MetS was defined using the International

Diabetes Federation definition.¹² Subjects were classified as having MetS if they had central (abdominal) obesity with a waist circumference ≥ 90 cm (men) or ≥ 80 cm (women) (Chinese criteria), and 2 or more of the following criteria: fasting serum glucose ≥ 110 mg/dl, TG ≥ 150 mg/dl, HDL-C < 40 mg/dl in men or < 50 mg/dl in women, or blood pressure $\geq 130/85$ mmHg. The use of antihypertensive medication was considered as high blood pressure in this analysis. Type 2 diabetes was determined according to World Health Organization criteria.¹³ A person was regarded as diabetic if the fasting plasma glucose was ≥ 126 mg/dl or the 2-h glucose during an oral glucose tolerance test was ≥ 200 mg/dl or diabetes medication (oral or insulin) was being taken.

Statistical Analysis

Data are expressed as mean $\pm$ standard deviation and tested for normal distribution by Kolmogorov-Smirnov statistics. Categorical variables were analyzed by the chi-square test. Comparisons between patients were performed using Student's independent t-test (2-tailed) for normally distributed data or the Mann-Whitney U test for parameters that presented with non-normal distribution (fasting glucose, hs-CRP, Cre, and FABP4). Clinical variables that correlated with serum FABP4 levels in the CAD patients were evaluated by univariate linear regression analyses. The significance of differences in the FABP4 level between groups (number of vessels occluded because of CAD and number of MetS criteria) was analyzed by the Kruskal-Wallis analysis of variance test. Variables that were significantly associated with FABP4 in CAD patients were tested for independency in a multivariate forward stepwise regression analysis. Data were analyzed using SPSS for Windows (version 13.0; SPSS Inc, Chicago, IL, USA). A P-value < 0.05 was considered statistically significant.

Results

The clinical and laboratory characteristics of the CAD patients are presented in Table 1. Medical histories included diabetes (n=36; 36.7%), hypertension (n=77; 78.6%), and hyperlipidemia (n=59; 60.2%). Drugs being used included angiotensin-receptor blockers (ARBs; n=34; 34.7%), angiotensin-convert-

Table 3. Correlation of Fasting Levels of Serum FABP4 and Clinical Variables by Univariate Linear Analyses of 98 Patients With CAD

S	β	P value
Age (years)	-0.145	0.153
Height (cm)	0.017	0.865
Weight (kg)	0.154	0.131
WC (cm)	0.118	0.249
BMI (kg/m ²)	0.168	0.098
Body fat mass (%)	0.234	0.020*
Albumin (g/dl)	0.073	0.476
Globulin (g/dl)	-0.114	0.265
TC (mg/dl)	0.189	0.062
TG (mg/dl)	0.348	$< 0.001^*$
HDL-C (mg/dl)	-0.243	0.016*
LDL-C (mg/dl)	0.217	0.032*
Fasting glucose (mg/dl)	0.135	0.186
Creatinine (mg/dl)	-0.040	0.696
Uric acid (mg/dl)	-0.098	0.335
hs-CRP (mg/dl)	-0.062	0.543

*P < 0.05 considered statistically significant after univariate linear analyses.

LDL-C, low-density lipoprotein-cholesterol. Other abbreviations see in Table 1.

ing enzyme inhibitors (ACEIs; n=26; 26.5%), calcium-channel blockers (CCBs; n=18; 18.4%), β -blockers (n=59; 60.2%), thiazide (n=22; 22.4%) and statins (n=56; 57.1%).

The clinical characteristics and fasting serum levels of FABP4 of the 98 CAD patients are presented in Table 2: 50 patients (51.0%) had MetS and 48 (49.0%) did not. CAD patients who had MetS had higher serum fasting levels of FABP4 than those without MetS (P=0.037). FABP4 levels did not differ statistically by sex, age, diabetes, hypertension, hyperlipidemia, ARBs, ACEIs, CCBs, β -blockers, thiazide or statins.

Fasting serum levels of FABP4 according to the number of stenotic coronary arteries and MetS diagnostic criteria are presented in Figures 1 and 2. There was a tendency for increased fasting levels of FABP4 as the number of stenotic

coronary arteries or diagnostic criteria for MetS increased. The highest fasting level of FABP4 occurred with 3-vessel CAD or a combination of 5 MetS diagnostic criteria and the lowest value occurred with 1-vessel CAD vessel or no MetS diagnostic criteria. There was no statistically significant difference between the number of stenotic coronary arteries and the serum level of FABP4 ($P=0.124$). However, a statistically significant difference with the number of MetS criteria ($P=0.035$) was established.

Univariate linear analysis of the fasting serum levels of FABP4 in the CAD patients is presented in **Table 3**. Body fat mass ($R=0.234$; $P=0.020$) and the levels of TG ($R=0.348$; $P<0.001$) and LDL-C ($R=0.217$; $P=0.032$) positively correlated with fasting serum levels of FABP4, whereas the level of HDL-C ($R=-0.243$; $P=0.016$) showed a negative correlation.

Multivariate forward stepwise linear regression analysis of the variables that were significantly associated with the fasting serum levels of FABP4 among the CAD patients (body fat mass, TG, HDL-C, LDL-C) showed that the level of TG ($\beta=0.348$, $R^2=0.121$, $P<0.001$) was the independent predictor.

Discussion

The results of our study show that the fasting level of FABP4 positively associated with MetS in CAD patients, among whom the serum levels of FABP4 correlated with a number of MetS criteria and TG was an independent predictor.

MetS is a constellation of physical and laboratory abnormalities, including hypertension, hyperglycemia, hyperlipidemia, and abdominal obesity.¹² Visceral fat accumulation may contribute to the development of CAD through progression of insulin resistance and an increase in apo-B-containing lipoproteins and small-sized LDL-C.¹⁴ However, another study noted that lower levels of HDL-C may be most useful for predicting CAD independent of other metabolic markers such as adiponectin, visceral fat or present medication.¹⁵ MetS constitutes a major health problem in the West and is estimated to affect at least 20% of the adult population.¹⁶ Recent studies have also demonstrated that MetS is a significant risk factor for cardiovascular disease and mortality in the general population;^{4,5} it is also predicted that MetS will increase the all-cause and cardiac mortality, especially after 10 years, in non-diabetic patients undergoing coronary artery bypass grafting.¹⁷ The overall prevalence of MetS in CAD patients is between 45.1% and 65.5%.^{7,18,19} In our study it was 50.1%, which is almost the same as reported by other studies of CAD patients.^{7,18} FABP4 is a major cytoplasmic protein that is involved in the regulation of lipid metabolism and is expressed abundantly in mature adipocytes and activated macrophages.^{2,20} It binds fatty acid ligands with high affinity and functions in intracellular fatty acid trafficking, regulation of lipid metabolism, and modulation of gene expression.^{1,21} The serum level of FABP4 increases in patients with MetS,^{22,23} and predicts the development of MetS.⁸ Our study also found that CAD patients with MetS had higher fasting serum levels of FABP4. A recent study noted that FABP4 levels increase significantly as the number of stenotic coronary vessels increases from 0 to 3.¹⁸ We also noted a tendency for increasing fasting levels of FABP4 as the number of stenotic coronary vessels increased in the CAD patients; however, there was no statistically significant difference between the number of stenotic vessels and serum levels of FABP4. Moreover, our study also noted a tendency for increasing fasting levels of FABP4 as the number of

diagnostic criteria for MetS increased. The highest fasting level of FABP4 occurred with a combination of 5 MetS diagnostic criteria and the lowest value was noted in patients with none.

Individuals with a fatty acid-binding protein aP2 variant have lower levels of TG and a reduced risk of coronary heart disease and obesity-induced type 2 diabetes.²⁴ Serum levels of FABP4 positively correlate with TG and negatively correlate with HDL-C;^{21,22} the fasting level of TG has been identified as a significant risk factor for CAD in middle-aged Japanese men.²⁵ In patients with diabetes, FABP4 positively correlates with plasma levels of TG, apolipoprotein C-III, and all the components of TG-rich lipoproteins, including very low-density lipoprotein (VLDL) TG, VLDL-C, and VLDL apoB.²⁶ Cabré et al also noted that plasma levels of FABP4 are increased in familial combined hyperlipidemia,²⁷ which manifests as increased production of TG-rich lipoproteins, mainly liver-derived VLDL, with the ensuing hyperlipidemia characterized by increased plasma levels of both TG and cholesterol.²⁸ Our study of CAD patients also noted that serum levels of TG and LDL-C positively correlated with the fasting serum level of FABP4, and that HDL-C had a negative correlation. Some studies have noted that serum levels of FABP4 positively correlate with central adiposity and fasting glucose,^{21,22} but we did not find such an association. FABP4 is expressed in adipocytes,^{1,2} but our study also showed that body fat mass positively correlates with the fasting serum level of FABP4. Multivariate forward stepwise linear regression analysis of the significant variables showed that in our study the TG level was the independent predictor of the fasting serum level of FABP4.

Pharmacological interventions have been shown to influence serum levels of FABP4 in humans; 3 months' treatment with atorvastatin in hyperlipidemic non-diabetic subjects substantially decreased the serum FABP4 value.²⁹ Another study of subjects with type 2 diabetes found no difference in the levels of FABP4 in statin-treated subjects, but reported increased levels in a thiazolidinedione-treated subgroup.³⁰ The FABP4 level was lower in subjects taking aspirin, and higher in subjects taking statins and anti-hypertensive drugs.¹⁸ Our results did not show a relationship between statins, peroxisome proliferator-activated receptor γ agonists or other drugs (ARBs, ACEIs, CCBs or thiazide diuretics) and the serum level of FABP4. Further studies are required to elucidate the relationship between medications and the level of FABP4 in CAD patients.

Study Limitations

Firstly, this study was cross-sectional, so our findings should be investigated in long-term prospective studies before a causal relationship between the serum level of FABP4 and MetS in CAD patients can be established. Secondly, we did not have data for serum levels of insulin or the incidence of insulin resistance. Some studies have noted that the level of FABP4 positively correlates with insulin resistance or the fasting serum level of insulin.^{21,22} Another limitation is that we did not assess the relationship between FABP4 and MetS among patients without CAD and did not compare them with the CAD group. Further studies are needed to show the association of MetS and serum FABP4 level in patients with and without CAD.

Conclusion

We found a positive association between the circulating

fasting level of FABP4 and MetS among CAD patients. Serum FABP4 levels correlated with the number of MetS criteria and TG was an independent predictor in this cohort.

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