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Serum adipocyte-specific fatty acid-binding protein is associated with nonalcoholic fatty liver disease in apparently healthy subjects

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Abstract

Adipocyte-specific fatty acid-binding protein (A-FABP) is a cytoplasmic protein that is expressed in adipocytes and is closely associated with insulin resistance, metabolic syndrome, and Type 2 diabetes. We investigated the relationship between A-FABP as a surrogate marker of metabolic syndrome and non-alcoholic fatty liver disease (NAFLD) in apparently healthy subjects. We assessed clinical and biochemical metabolic parameters and measured serum levels of A-FABP, high-sensitivity C-reactive protein and tumor necrosis factor-α (TNF-α) in 494 subjects who were divided into two groups according to the presence of NAFLD by abdominal ultrasonography. All parameters associated with metabolic syndrome were significantly higher in patients with NAFLD ($P<.001$). A-FABP showed positive correlation with TNF-α, homeostasis model assessment index of insulin resistance (HOMA-IR), and metabolic syndrome ($P<.001$) when adjusted for age and sex. The odds ratio for the risk of NAFLD in the highest tertile of A-FABP compared with the lowest tertile was 7.36 (CI 3.80–14.27, $P<.001$) after adjustment for age and sex; 4.52 (CI 2.22–9.20, $P<.001$) after adjustment for age, sex, HOMA-IR and metabolic syndrome and 2.86 (CI 1.11–7.35, $P<.05$) after further adjustment for all metabolic parameters including TNF-α. The serum level of A-FABP was independently associated with NAFLD and showed significant correlation with TNF-α, HOMA-IR, and metabolic syndrome.

Keywords: Non-alcoholic fatty liver disease; Adipocyte-specific fatty acid-binding protein; Metabolic syndrome

1. Introduction

There is evidence that adipokines and cytokines play a major role at various stages of non-alcoholic fatty liver disease (NAFLD) and that imbalance in their proinflammatory and anti-inflammatory effects might directly lead to insulin resistance (IR) [1–3].

Adipocyte-specific fatty acid-binding protein (A-FABP, also designated aP2 or FABP4) is an emerging serum predictive biomarker associated with metabolic disorders such as type-2 diabetes, atherosclerosis, and metabolic syndrome [4–7]. This 14–15-kDa lipid-binding protein is the major cytosolic protein of mature adipocytes and macrophages, accounting for approximately 6% of the total cellular protein, and coordinates inflammatory and lipotoxic effects on insulin signaling and glucose uptake, thus contributing to metabolic deterioration [5,8,9]. However, there are few studies on the relationship between A-FABP as a surrogate marker of metabolic disorders and NAFLD. We hypothesized that the serum level of A-FABP is associated with NAFLD and could predict development of the disease. To investigate the role of A-FABP as a biomarker for NAFLD, we examined the relationship between serum A-FABP levels and NAFLD prevalence in 494 apparently healthy Korean subjects in a cross-sectional manner. We also measured high-sensitivity C-reactive protein (hsCRP), a well-known marker of systemic inflammation, and tumor necrosis factor-α (TNF-α), an important cytokine involved in NAFLD progression especially in insulin-resistant states.

2. Materials and methods

2.1. Study subjects

The study included 494 patients who underwent medical screening in Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Korea. We performed cross-sectional analysis from KBSMC-Adipokine study (Kangbuk Samsung Medical Center-Adipokine study), an observation cohort in which participants underwent medical screening in industrial medical check-up at 2003 and were followed up. Subjects with viral hepatitis B, hepatitis C, other liver disease, acute or chronic inflammation, malignancy, excessive alcohol consumption (>20 g/day) or who

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were receiving treatment with peroxisome proliferator-activated receptor-γ agonists, metformin, and antioxidants (vitamin E or C) were excluded. Alcohol intake, smoking habits, medication and medical history were assessed by chart review and standardized questionnaire. The study protocol was approved by the institutional review board and the ethics committee of the Kangbuk Samsung Hospital and carried out according to the principles of the 1975 Declaration of Helsinki. Written informed consent was provided by all subjects.

2.2. Anthropometric data

Anthropometric data including height, body weight and systolic and diastolic blood pressures (BP) were measured in duplicate and the results were averaged. The body mass index (BMI) was calculated by dividing the weight in kilograms by the square of the height (kg/m^2).

2.3. Biochemical test

Blood samples were obtained after 12 h of overnight fasting and used to determine fasting plasma glucose (FPG); total cholesterol; low-density lipoprotein cholesterol (LDL-C); high-density lipoprotein cholesterol (HDL-C); triglyceride (TG); fasting insulin; creatinine; high sensitivity C-reactive protein (hsCRP) and the following parameters of liver function: aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyltransferase (GGT) and alkaline phosphatase (ALP). Samples for measurement of A-FABP and TNF-α were separated and stored at −80°C prior to measurement of serum levels by an ELISA method (Bio Vendor Laboratory Medicine, Modrice, Czech Republic). Based on the American Heart Association/National Heart, Lung, and Blood Institute criteria with BMI (≥25 kg/m^2) substituted for waist circumference, metabolic syndrome was diagnosed when the subject satisfied more than three of the following criteria: obesity (BMI≥25 kg/m^2), hypertriglyceridemia (≥150 mg/dl), low HDL-C (≤40 mg/dl in men and ≤50 mg/dl in women), hypertension (≥130/85 mmHg) and fasting hyperglycemia (≥100 mg/dl) [10,11].

2.4. Insulin resistance and NAFLD

Insulin resistance was estimated using the Homeostasis Model Assessment Index of Insulin Resistance (HOMA-IR), calculated by the following formula: (fasting plasma glucose (mg/dl)×fasting insulin (μU/ml)/405). Fatty liver disease was assessed by abdominal ultrasonography performed by the same radiology specialists and was defined as diffuse increased echogenicity of the hepatic parenchyma compared with the kidneys, vascular blurring and deep-echo attenuation [12–14]. Thereafter, the NAFLD group was defined as subjects with fatty liver disease and without a history of excessive alcohol consumption (>20 g/day).

2.5. Statistical analysis

Statistical analysis was performed with SPSS version 16.0 (Chicago, IL, USA). The normality test was performed using the Kolmogorov–Smirnov test. The chi-square test was used to compare categorical variables between groups. For continuous variables, parameters that followed normal distribution were analyzed with *t* test or analysis of variance and described as mean±S.D., whereas parameters that did not follow normal distribution were analyzed with Mann–Whitney test or Kruskal–Wallis test and expressed as median±interquartile range.

Multiple comparisons were performed with post hoc tests to compare the mean values between individual groups and corrected with the Bonferroni method. Correlations between A-FABP and metabolic syndrome, HOMA-IR and TNF-α were analyzed using Pearson's correlation method. A-FABP levels were grouped into tertiles and multiple logistic regression analysis was used to calculate odds ratios for the presence of NAFLD in subjects with rising A-FABP tertiles (second and third tertiles) compared with the lowest tertile. Two-sided values of $P<.05$ were considered significant.

3. Results

The subjects included 324 (65.6%) men and 170 (34.4%) women whose mean age was 40.8 years (range 28–75 years). The subjects were divided into two groups according to the presence ($n=109$) or absence ($n=385$) of NAFLD. The mean age of the NAFLD and non-NAFLD groups was not significantly different (41.7 and 40.5 years respectively; $P=.076$); however, the NAFLD group contained a higher proportion of male subjects ($P<.001$) and more smokers ($P=.015$).

All parameters of metabolic syndrome such as BMI, systolic BP, diastolic BP, FPG and TG were significantly higher in the NAFLD group than the non-NAFLD group ($P<.001$), whereas levels of HDL-C were significantly lower ($P<.001$). Moreover, the prevalence of metabolic syndrome and HOMA-IR, a hallmark of metabolic disorder, were also significantly higher in the NAFLD group ($P<.001$) (Table 1).

Table 1
Baseline characteristics of subjects according to the presence of NAFLD

	Non-NAFLD ($n=385$)	NAFLD ($n=109$)	*P*
Age (years)	39 (36–44)	42 (37–45)	.097
Sex (male %)	57.9%	92.7%	<.001
Smokers (%)	14.1%	23.9%	.015
BMI (kg/m^2)	22.9±2.6	26.3±2.5	<.001
Systolic BP (mmHg)	110 (100–120)	120 (110–130)	<.001
Diastolic BP (mmHg)	70 (60–80)	80 (70–80)	<.001
FPG (mg/dl)	92 (87–97)	96 (91–103)	<.001
Total cholesterol (mg/dl)	197.9±36.2	211.6±31.9	<.001
LDL-C (mg/dl)	111.4±28.1	125.4±25.8	<.001
HDL-C (mg/dl)	55.8±11.5	49.3±8.6	<.001
TG (mg/dl)	96.0 (71.0–138.5)	158.0 (120.5–206.0)	<.001
Metabolic syndrome (%)	9.4%	48.6%	<.001
Fasting insulin (μU/ml)	5.6 (4.0–7.5)	8.3 (6.4–11.4)	<.001
HOMA-IR	1.3 (0.9–1.7)	2 (1.5–2.8)	<.001
AST (IU/L)	24 (21–28)	28 (24–33)	<.001
ALT (IU/L)	21 (17–28)	35 (24–46)	<.001
ALP (IU/L)	49.0 (39.0–59.0)	56.0 (44.0–68.5)	<.001
GGT (IU/L)	15.0 (10.0–26.0)	30.0 (20.5–49.5)	<.001
Serum Creatinine (mg/dl)	1.0 (0.9–1.1)	1.2 (1.1–1.2)	<.001
A-FABP (ng/ml)	8.6 (6.8–11.2)	11.7 (9.5–15)	<.001
hsCRP (mg/dl)	0.04 (0.02–0.12)	0.13 (0.06–0.17)	.008
TNF-α (pg/ml)	3.29±1.81	4.09±1.36	<.001

Values are expressed as mean±SD, median (25th–75th percentile), or percentage.

TNF-α and live profile enzymes AST, ALT, GGT and ALP were significantly higher in the NAFLD group ($P<.001$). In addition, serum A-FABP level was also significantly higher in the NAFLD than the non-NAFLD group ($P<.001$) (Table 1). When subjects were grouped into A-FABP tertiles, the rising (second and third) tertiles of A-FABP had higher values of all parameters defining metabolic syndrome (BMI, systolic BP, diastolic BP, FPG and TG) than the first tertile and a higher prevalence of metabolic syndrome (7.4%, 16.7%, and 30.1% for first, second and third tertiles respectively, $P<.001$). In addition, rising

Table 2
Characteristics of subjects according to A-FABP tertile

	A-FABP tertile			*P*
	<7.72 ng/ml	7.72-11.18 ng/ml	>11.18 ng/ml	
Age (years)	39 (35–45)	40 (36–45)	41 (37–45)	.148
Sex (male %)	61.1%	69.0%	66.9%	.294
Smokers (%)	11.1%	18.0%	19.8%	.084
BMI (kg/m^2)	22.1±23.6	23.6±2.4#	25.1±2.9# ¶	<.001
Systolic BP (mmHg)	110 (100-120)	110 (100-120)	120 (110-120)	.002
Diastolic BP (mmHg)	70 (60-80)	70 (70-80)	80 (70-80)	.002
FPG (mg/dl)	92 (88-97)	92 (88-98)	94 (89-100)	.032
Total Cholesterol (mg/dl)	191.7±203.7	203.7±36.0**	206.9±33.6#	<.001
LDL-C (mg/dl)	106.7±116.4	116.4±26.5**	120.1±27.1#	<.001
HDL-C (mg/dl)	56.6±53.6	53.6±10.4*	52.8±11.3**	.005
TG (mg/dl)	88 (65.8-129.0)	113.5 (82.0-159.8)	125 (95.0-178.0)	<.001
Metabolic syndrome (%)	7.4%	16.7%	30.1%	<.001
Fasting insulin (μU/ml)	5.3 (4-7.6.0)	5.9 (4.4-7.7)	7.2 (5.0-9.6)	<.001
HOMA-IR	1.2 (0.9-1.8)	1.3 (1.0-1.9)	1.7 (1.2-2.3)	<.001
AST (IU/L)	24 (21-28)	25.5 (21-31)	24 (21-29)	.222
ALT (IU/L)	20 (17-27)	25 (18-35)	24 (18-36)	<.001
ALP (IU/L)	49 (38-59)	51 (41-61)	51 (42-61)	.381
GGT (IU/L)	15 (10-24)	19 (13-32)	20 (14-40)	<.001
Serum creatinine (mg/dl)	1 (0.9-1.1)	1.1 (0.9-1.2)	1.1 (1.0-1.2)	<.001
hsCRP (mg/dl)	0.03 (0.02-0.05)	0.06 (0.03-0.15)	0.12 (0.05-0.20)	.003
TNF-α (pg/ml)	2.79±1.75	3.64±1.67#	3.88±1.65#	<.001

Values are expressed as mean±S.D., median (25th–75th percentile), or percentage.
*$P<.05$; **$P<.01$; #$P<.001$ vs. Tertile 1.
†$P<.05$; ‡$P<.01$; ¶$P<.001$ between Tertiles 2 and 3.

Table 3
Correlations between A-FABP and metabolic syndrome, HOMA-IR, TNF-α

	A-FABP	
	r	*P*
Metabolic syndrome	0.16	<.001
HOMA-IR	0.18	<.001
TNF-α	0.17	<.001

Model was adjusted for sex and age.

(second and third) tertiles of A-FABP also had higher values of HOMA-IR, AST, ALT, GGT, serum creatinine, hsCRP and TNF-α (Table 2). As shown in Table 3, A-FABP showed significant positive correlation with metabolic syndrome, HOMA-IR and TNF-α when adjusted for age and sex ($P<.001$).

In multiple logistic regression analysis to calculate odds ratios (ORs) for the risk of NAFLD after adjustment for age and sex (Model 1, Table 4), the highest tertile of A-FABP had a greatly increased likelihood of having NAFLD compared with the lowest tertile (OR 7.36, CI 3.80–14.27, $P<.001$). After adjustment for HOMA-IR and metabolic syndrome in addition to age and sex (Model 2, Table 4), the OR for the risk of NAFLD in the highest tertile of A-FABP was attenuated but maintained significance (OR 4.52, CI 2.22–9.20, $P<.001$). Moreover, the OR in the highest tertile of A-FABP remained significant after adjustment for age, sex, and all of the variables of Table 2 that showed a significant relationship with A-FABP (OR 2.86, CI 1.11–7.35, $P<.05$).

Thus, together with BMI and FPG, high serum level of A-FABP was independently associated with the risk of NAFLD (Model 3, Table 4).

4. Discussion

NAFLD is regarded as a representative metabolic disorder and insulin resistance syndrome has been identified as a crucial pathophysiological factor of this disease [15,16]. Accumulating evidence from previous studies suggests that adipocyte-specific fatty acid-binding protein (A-FABP) is closely associated with metabolic syndrome and plays a key role in the development of metabolic disorder [4,9]. However, it is not clear whether A-FABP plays a similar role in NAFLD, which shares mechanisms of insulin resistance with metabolic syndrome, and there are few studies on the relationship between A-FABP and NAFLD. In the present study, we demonstrated that serum A-FABP levels were significantly higher in the NAFLD group than the non-NAFLD group, and we were able to verify these results and obtain ORs from various models of multiple logistic regression analysis after dividing serum levels of A-FABP into tertiles. Subjects in the highest tertile of A-FABP were 2.86 times more likely to have NAFLD compared with those in the lowest tertile after adjustment for all parameters related to metabolic syndrome.

Table 4
Multiple logistic regression analysis showing OR for the risk of NAFLD

Model	Parameters	OR	95% CI	*P*-value
Model 1	A-FABP Tertile 1 vs. 2	2.32	1.16–4.61	.017
	A-FABP Tertile 1 vs. 3	7.36	3.80–14.27	<.001
Model 2	Metabolic syndrome	2.69	1.47–4.91	.001
	HOMA-IR	2.14	1.52–3.00	<.001
	A-FABP Tertile 1 vs. 2	1.99	0.95–4.17	.067
	A-FABP Tertile 1 vs. 3	4.52	2.22–9.20	<.001
Model 3	BMI	1.26	1.08–1.48	.004
	FPG	1.07	1.00–1.14	.048
	A-FABP Tertile 1 vs. 2	1.3	0.52–3.28	.578
	A-FABP Tertile 1 vs. 3	2.86	1.11–7.35	.03

Model 1: Variables included in the original model are age and sex.
Model 2: Variables included in the original model are age, sex, HOMA-IR and metabolic syndrome.
Model 3: Variables included in the original model are age, sex, BMI, systolic BP, diastolic BP, FPG, total cholesterol, LDL-C, HDL-C, TG, metabolic syndrome, fasting insulin, HOMA-IR, AST, ALT, GGT, serum creatinine and TNF-α.

Notably, serum level of A-FABP was independently associated with BMI and FPG together with NAFLD in the final step of Model 3. BMI and FPG are the two most important non-invasive markers for staging of NAFLD [17–19]. Interestingly, A-FABP showed a stronger association with NAFLD than BMI or FPG in the present study; therefore, we propose that A-FABP might be an additional non-invasive biomarker for predicting development of NAFLD. Recently, Koh et al. reported that serum A-FABP levels are associated with NAFLD in a study of a restricted population of Type 2 diabetic patients [20]. Our data showed similar results in an extended population of apparently healthy subjects, allowing us to generalize this concept. As in previous studies, we showed positive correlations between A-FABP and metabolic syndrome and HOMA-IR, a hallmark of metabolic disorder, rather than individual components of metabolic syndrome. In addition, a positive correlation between A-FABP and TNF-α was demonstrated in the present study. TNF-α is the prototypic proinflammatory cytokine in many types of liver injury and enhanced liver TNF-α expression is observed in animal models and humans with progressive NAFLD [1,2].

There are several potential limitations to the present study. First, this research was a cross-sectional study; therefore, we could not conclusively exclude a causal relationship between serum A-FABP levels and the development of NAFLD. Further longitudinal studies are needed to investigate this association. Secondly, fatty liver disease was assessed by ultrasonography instead of pathological confirmation, and grouping by severity of NAFLD was not performed because of the small sample size for moderate and severe NAFLD.

Recently, Milner et al. [21] reported that increased serum A-FABP was a predictive factor for intrahepatic inflammation and fibrosis among histologically confirmed NAFLD with abnormal liver function, and they also reported an association between high serum A-FABP and the progression of the disease.

Although liver biopsy is the gold standard for diagnosis and accurate staging of NAFLD, it is impractical to use such an invasive method for the assessment of NAFLD because most patients with NAFLD are asymptomatic in clinical practice. Moreover, the subjects in this study were apparently healthy individuals undergoing routine medical check-up. The decision of whether to perform a liver biopsy is the most controversial consideration in the evaluation of patients with suspected NAFLD. However, ultrasonography has been reported to have 87–100% sensitivity and 84–89% specificity in detection of fatty infiltration of the liver in several studies [22,23]. Also, liver biopsy is costly, takes time and involves its risks such as pain and bleeding. In this regard, measuring serum A-FABP, a noninvasive method, among apparently healthy person will provide a convenient and economical tool to screen NAFLD.

In summary, together with BMI and FPG, high serum level of A-FABP was independently associated with the risk of development of NAFLD and showed significant correlation with TNF-α in apparently healthy subjects. We suggest that A-FABP levels might predict NAFLD development and that A-FABP might be a valuable noninvasive biomarker for inflammation and fibrosis in progressive NAFLD. Further prospective studies are warranted to confirm the role of A-FABP as a biomarker for NAFLD in apparently healthy individuals.

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