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Association between adipocyte fatty acid–binding protein levels and childhood obesity in Korean children

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Abstract

Adipocyte fatty acid–binding protein (A-FABP) is a newly recognized adipokine that plays a role in the development of obesity and insulin resistance in adults. We investigated the association between A-FABP levels and obesity and insulin resistance in school-aged children. One hundred sixty-one 9-year–old Korean children (80 boys and 81 girls) voluntarily participated in this study at school-based health examinations. Weight, height, waist circumference, and blood pressure were measured. Fasting plasma glucose, triglycerides, high-density lipoprotein cholesterol, insulin, and A-FABP levels were measured; and insulin resistance was estimated by the homeostasis model assessment. Subjects with higher body mass index (BMI) percentiles had correspondingly higher concentrations of A-FABP in both boys and girls. Subjects within the highest quartile of A-FABP levels had correspondingly poor metabolic risk profiles (BMI, waist circumference, triglycerides, high-density lipoprotein cholesterol, fasting insulin, and homeostasis model assessment of insulin resistance) compared with those in the lowest A-FABP quartile ($P < .01$). Serum A-FABP concentrations were significantly correlated with BMI ($r = 0.58$, $P < .01$) and waist circumference ($r = 0.51$, $P < .01$). However, the significant correlation between serum A-FABP and insulin resistance faded after adjustment for BMI. Adipocyte fatty acid–binding protein was closely associated with obesity or abdominal obesity in children; however, the independent relationship between A-FABP and insulin resistance in children is still unclear and remains to be determined.

1. Introduction

Obesity is strongly associated with insulin resistance and increases the risk of developing the metabolic syndrome [1]. Adipose tissue is not simply an energy storage organ but also a major endocrine organ, producing and releasing a variety of adipokines into the bloodstream [2]. Although the mechanistic connections between obesity and insulin resistance are not fully understood, newly discovered adipokines may play a central role in the development of insulin resistance and the metabolic syndrome [3,4].

Adipocyte fatty acid–binding protein (A-FABP) belongs to the fatty acid–binding protein family, which accounts for an estimated 6% of total cellular proteins [5], and may represent important regulators of systemic insulin sensitivity and lipid and glucose metabolism [6]. Animal studies have suggested that A-FABP may be a link between various components of the metabolic syndrome, systemic chronic inflammation, and obesity [7,8]. A recent study demonstrated that orally available small molecule inhibitors of FABP were effective in treating diabetes and atherosclerosis in mice [9]; however, the clinical relevance of these findings remains to be confirmed in humans.

Adipocyte fatty acid–binding protein is originally known as *cytoplasmic protein*. However, a recent study showed that a significant portion of this protein is released from adipocytes into the bloodstream [10]. While circulating, A-FABP serves as a plasma biomarker of obesity and the metabolic syndrome in adults [10,11]; and consistent with this hypothesis, in prospective studies, A-FABP predicted the development of type 2 diabetes mellitus and the metabolic syndrome in adults [12,13]. However, the clinical implications of A-FABP levels in children are far from clear. Little research has addressed the relationships between these metabolic variables, particularly before puberty. Athero-

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Table 1
Clinical characteristics of the study subjects

Variables	Boys	Girls
	n = 80	n = 81
	Mean ± SD	Mean ± SD
BMI (kg/m^2)	18.6 ± 3.3	17.8 ± 3.1
Waist circumference (cm)*	62.3 ± 8.7	58.3 ± 8.0
Systolic blood pressure (mm Hg)	112.8 ± 13.6	112.0 ± 17.4
Diastolic blood pressure (mm Hg)	71.5 ± 13.2	72.3 ± 12.8
Fasting plasma glucose (mg/dL)	78.5 ± 8.2	77.3 ± 5.9
Triglyceride (mg/dL)	87.4 ± 48.6	92.6 ± 39.2
HDL cholesterol (mg/dL)	62.5 ± 12.6	60.0 ± 13.7
Fasting insulin (μIU/mL)	4.9 ± 7.1	3.4 ± 4.0
HOMA-IR	1.0 ± 1.6	0.6 ± 0.7
A-FABP (ng/mL)	12.4 ± 7.1	12.9 ± 8.9

Data are shown as mean ± SD. Triglycerides, insulin, HOMA-IR, and A-FABP levels were logarithmically transformed before statistical analysis.
* P less than .05 by t test.

sclerosis and features of the metabolic syndrome are beginning to be seen in childhood [14]. Because overweight children often become obese adults [15], the early onset of the metabolic syndrome gives rise to prolonged exposure to adverse cardiovascular risk factors. Accordingly, we investigated the association between circulating A-FABP levels and obesity and insulin resistance in prepubertal Korean children.

2. Methods and procedures

2.1. Study subjects

We recruited 161 Korean children aged 9 years (80 boys and 81 girls) who voluntarily participated in this study while being examined at school-based health examinations. Written informed consent was obtained from their parents. The study design was approved by Guro Hospital's ethics committee. We recorded past medical history and medication use that could affect cardiovascular function and metabolism. All subjects had no prior history of cardiovascular disease, diabetes, hypertension, or endocrine disorders; all subjects were nonsmokers.

2.2. Anthropometric and laboratory measurements

Anthropometric measurements were taken from lightly clothed subjects without shoes. Height and weight were measured by an automatic height-weight scale, and body mass index (BMI, in kilograms per square meter) was calculated. Waist circumference was measured at the midpoint between the lower border of the rib cage and the top of the lateral border of the iliac crest. Blood pressure was measured by a standard brachial cuff technique. *Obesity* was defined according to appropriate BMI cutoff points for age and sex [16]. Subjects were classified as healthy weight (fifth ≤ BMI percentile < 85th), at risk of overweight (85th ≤ BMI percentile < 95th), and overweight (≥95th BMI percentile) according to Korean growth charts [17].

Plasma was obtained from each subject after an 8-hour overnight fast. Fasting plasma glucose, triglycerides, and high-density lipoprotein (HDL) cholesterol levels were analyzed using an autoanalyzer (LX20; Beckman Coulter, Fullerton, CA). Plasma insulin levels were measured by radioimmunoassay (Diagnostic Products, Los Angeles, CA) (intra-and interassay coefficients of variation: 3.1%-9.3% and 4.9%-10.0%, respectively). Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as fasting insulin (in microunits per milliliter) × fasting glucose

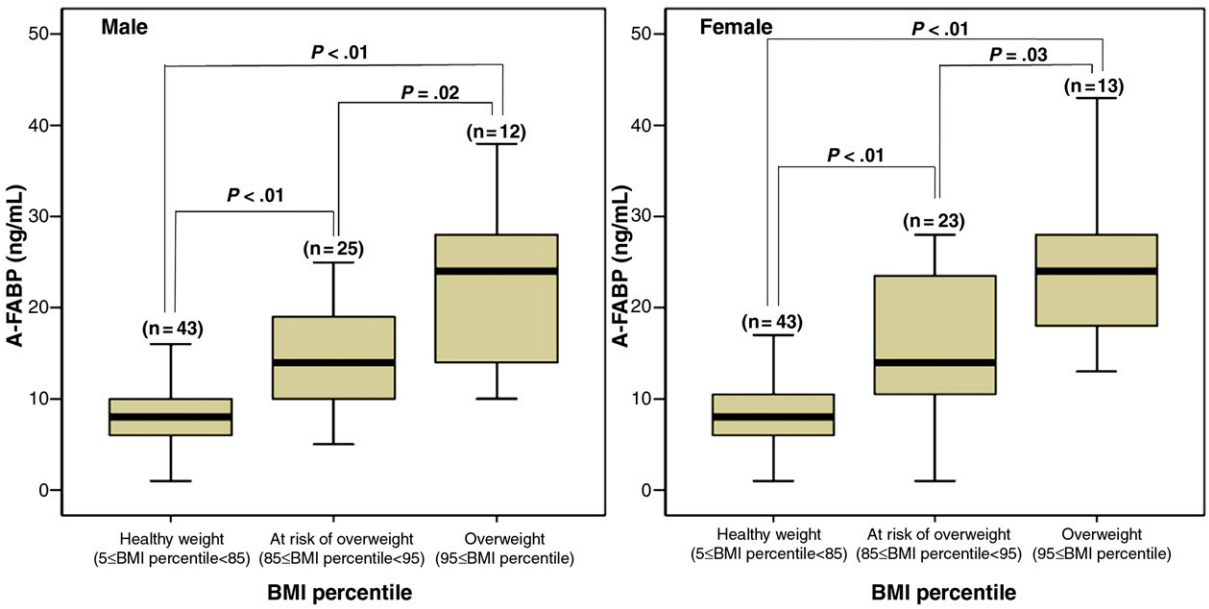

Fig. 1. The A-FABP concentrations according to BMI percentile in boys and girls.

(in milligrams per deciliter)/405 [18]. Plasma A-FABP levels were measured by enzyme-linked immunosorbent assay (BioVendor Research and Diagnostic Products, Candler, NC) (intra-and interassay coefficients of variation: 3.9%-6.6% and 2.6%-5.1%, respectively).

2.3. Statistical analysis

Data were tested for normal distribution; and variables such as triglycerides, insulin, HOMA-IR, and A-FABP levels were logarithmically transformed to approach a normal distribution before analysis. Metabolic parameters were compared between sexes using Student *t* test. A comparison of A-FABP levels according to BMI percentile was performed using 1-way analysis of variance. The A-FABP levels were grouped into quartiles so that each subject was classified as being in the first (lowest), second, third, or fourth (highest) quartile of A-FABP levels. Analysis of covariance was used to compare metabolic risk factors ranked according to A-FABP quartile, with adjustment for sex. The least significant difference test was used to compare multiple groups. Correlations between BMI, HOMA-IR, and A-FABP levels were calculated by Pearson correlations coefficients. All analyses were performed using SPSS (version 12.0; Chicago, IL). For all tests, *P* values less than .05 were considered statistically significant.

3. Results

Clinical characteristics of the study subjects of 161 children are summarized in Table 1. Among metabolic variables, except waist circumference, there was no significant difference according to sex. Waist circumference was significantly higher in boys compared with girls ($P < .05$). There was no significant difference in A-FABP (in nanograms per milliliter) concentrations according to sex. Fig. 1 demonstrates that subjects with higher BMI percentiles had correspondingly higher concentrations of A-FABP in both sexes. The A-FABP concentrations (±SD) of healthy-weight, at risk of overweight, and overweight individuals were 8.5 ± 3.7, 14.4 ± 5.2, and 22.3 ± 8.7 ng/mL in boys ($P < .01$) and 7.8 ± 4.3, 16.0 ± 7.9, and 24.4 ± 8.7 ng/mL in girls ($P < .01$).

Table 3
Correlations of A-FABP concentrations with parameters of obesity and insulin resistance in the study subjects

Variables	Correlations			
	Sex adjusted		Sex and BMI adjusted	
	r	*P*	*r*	*P*
BMI	0.58	<.01		
Waist circumference	0.51	<.01		
Triglyceride	0.27	<.01	0.10	.17
HDL cholesterol	−0.23	<.01	−0.17	.03
Fasting insulin	0.34	<.01	0.10	.17
HOMA-IR	0.31	<.01	0.08	.32

Table 2 shows parameters of obesity and insulin resistance according to the quartiles of serum A-FABP level. Subjects in the highest quartile of A-FABP level had worse metabolic risk profiles (BMI, waist circumference, triglycerides, HDL cholesterol, insulin, and HOMA-IR) compared with those in the lowest quartile of A-FABP level ($P < .01$). There were no differences in diastolic blood pressure and fasting plasma glucose levels according to the quartile of A-FABP levels.

Table 3 indicates the correlations between A-FABP and the parameters that showed a significant difference in Table 2, as serum A-FABP is significantly correlated with BMI ($r = 0.58$), waist circumference ($r = 0.51$), triglyceride ($r = 0.27$), HDL cholesterol ($r = -0.23$), fasting insulin ($r = 0.34$), and HOMA-IR ($r = 0.31$). After adjustment for BMI, the significant correlation between A-FABP levels and HDL cholesterol remained; but the significance of the other associations disappeared. Fig. 2 shows the correlations between the A-FABP and obesity indices in both boys and girls. Strong positive correlations were also observed between BMI ($r = 0.67$, $P < .01$ in boys; $r = 0.54$, $P < .01$

Table 2
Associations between A-FABP concentrations and parameters of obesity and insulin resistance in the study subjects

Variables	Quartile of FABP (ng/mL)				*P*
	1st (~7)	2nd (7~10)	3rd (10~16)	4th (≥16)	
BMI (kg/m^2)	15.7 ± 1.5	16.7 ± 2.7	18.9 ± 2.6*,†	21.6 ± 2.2*,†,‡	<.01
Waist circumference (cm)	54.6 ± 3.9	56.4 ± 6.3	62.6 ± 7.6 *,†	67.6 ± 8.9 *,†,‡	<.01
Systolic blood pressure (mm Hg)	106.3 ± 19.5	113.6 ± 16.4*	114.4 ± 12.8*	115.0 ± 12.1*	.05
Diastolic blood pressure (mm Hg)	68.5 ± 10.6	72.3 ± 14.9	73.5 ± 14.0	73.1 ± 12.1	.28
Fasting plasma glucose (mg/dL)	79.7 ± 6.5	78.2 ± 7.9	76.4 ± 5.9	77.2 ± 7.8	.19
Triglyceride (mg/dL)	73.7 ± 25.6	79.7 ± 36.3	93.8 ± 40.4*	113.4 ± 58.6*,†	<.01
HDL cholesterol (mg/dL)	64.4 ± 13.1	62.3 ± 11.8	62.8 ± 14.6	55.4 ± 11.6 *,†,‡	.01
Fasting insulin (μIU/mL)	1.9 ± 0.9	3.0 ± 6.2	3.5 ± 3.4*	7.4 ± 8.3 *,†,‡	<.01
HOMA-IR	0.3 ± 0.1	0.7 ± 1.5	0.6 ± 0.6	1.4 ± 1.8 *,†,‡	<.01

Data are shown as mean ± SD.

* *P* less than .05 vs first quartile.

† *P* less than .05 vs second quartile.

‡ *P* less than .05 vs third quartile.

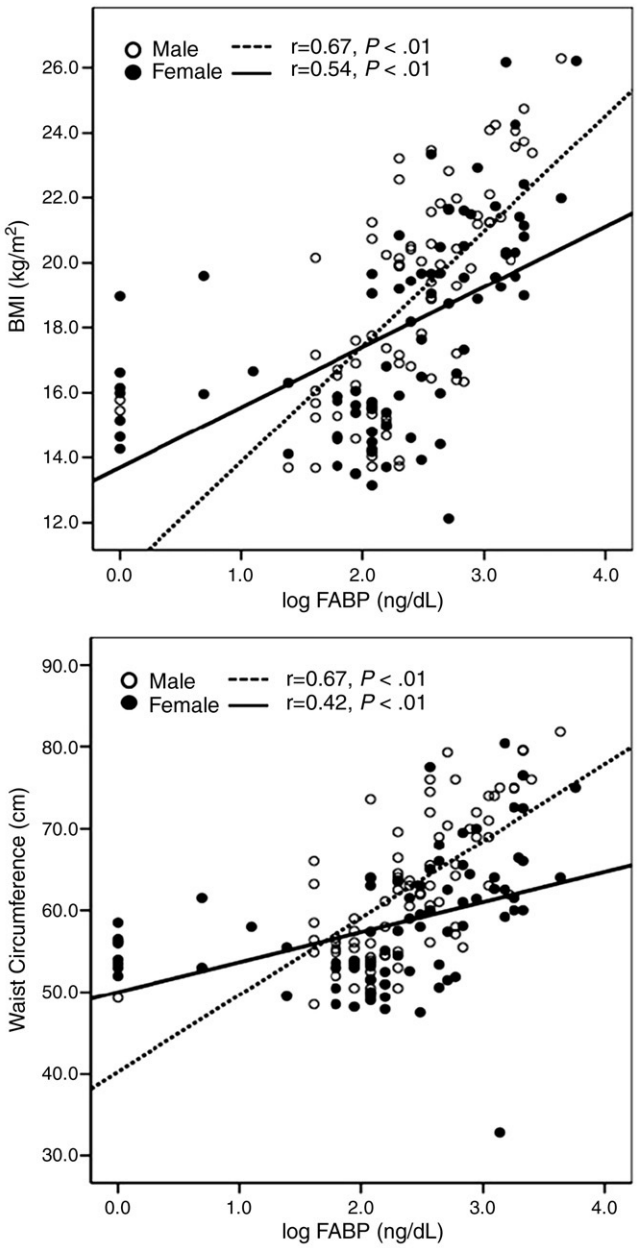

Fig. 2. Correlations between A-FABP concentrations and BMI and waist circumference in boys and girls.

in girls) and waist circumference ($r = 0.67$, $P < .01$ in boys; $r = 0.42$, $P < .01$ in girls).

4. Discussion

Our study demonstrates that circulating A-FABP levels are closely associated with obesity and abdominal obesity in Korean children. According to the worldwide trends in childhood obesity, obesity has increased more dramatically in developed countries and urban populations [19]. As the prevalence of obesity in Korean children and adolescents increased significantly [20], the incidence of metabolic syndrome and insulin resistance is expected to increase in Korean children. In overweight children and those at risk of overweight, A-FABP concentrations were markedly elevated in both boys and girls as compared with healthy-weight children.

The positive association between serum A-FABP concentrations and indicators of obesity (BMI and waist circumference) in children suggests that adipose tissue is probably the primary source of A-FABP secreted into the circulation. The physiologic functions of circulating A-FABP are still being characterized. Circulating A-FABP predicted the development of the metabolic syndrome independently of adiposity and insulin resistance in adults [12]. Although accumulating evidence from animal experiments indicates a role for A-FABP as a central regulator of systemic insulin sensitivity, lipid metabolism, and inflammation [5,6], its relevance in humans remains to be determined, particularly in children. Our data suggest that A-FABP is associated with childhood obesity, but it is unclear if A-FABP has any independent association with the risk factors associated with the metabolic syndrome in children. Similar results were observed in another study [21]. Further investigation is needed to confirm that serum A-FABP is related to disease susceptibility of infectious and inflammatory disease in obese children.

We found no sex difference in A-FABP concentration in our study subjects; however, women had higher values of A-FABP than men in adult studies [12,13]. This difference may be secondary to a relatively higher percentage of body fat and/or differing subcutaneous fat distribution pattern in women [22]. A prior study reported that A-FABP levels decreased significantly in obese children who achieved a substantial weight reduction after 1 year in contrast to obese children without weight loss [23]. Furthermore, decreased expression of A-FABP in human subcutaneous adipose tissue was reported after weight loss [24]. Taken together, available evidence suggests that the distribution and volume of subcutaneous adipose tissue may be major determinants of circulating A-FABP concentrations.

The existing literature indicates that approximately one third of overweight and obese children are also hypertensive [25,26]. The previous studies found that, in obese adults and patients with metabolic syndrome, A-FABP concentrations correlated positively with blood pressure [10,12]. In this study, blood pressure did not differ significantly according to the quartiles of serum A-FABP. These findings were consistent with the results of previous studies in which blood pressure showed no overlap with other components of the metabolic syndrome in children [27-29].

A recent study reported that A-FABP predicts the development of type 2 diabetes mellitus [13]. Another study showed a significant association between A-FABP and fasting glucose [12]. However, our study did not show any association between A-FABP and fasting glucose. In addition, we could not determine any significance between A-FABP and the parameters of insulin resistance after adjustment for BMI. Only HDL cholesterol remained significantly correlated with A-FABP. Therefore, we

conclude that the impact of A-FABP on the metabolic parameters might be weaker in children than in adults. To reach a final determination, further studies will be needed.

Our study had limitations. First, BMI percentiles were used to classify patients' obesity. Although generally accepted as a surrogate measure of obese status, BMI remains an indirect measure of fat mass. Second, the source of circulating FABP has not been established. Although macrophages as well as adipocytes express FABP [30], the main source of plasma A-FABP may be the adipocyte because it expresses A-FABP at high levels. Third, the cross-sectional design of this study limits the interpretation of its results, especially with regard to cause-effect interactions. This study was conducted in Korean children. However, because there may be differences in A-FABP expression based on genetic background, our conclusion needs to be drawn with additional studies on children of different races.

In summary, in our study, serum A-FABP levels were closely associated with obesity and abdominal obesity in Korean children. The relationship between A-FABP and insulin resistance became weaker after adjustment for adiposity. The independent associations between A-FABP and insulin resistance in children remain to be determined.

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