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Serum fatty acid binding protein 4, free fatty acids, and metabolic risk markers

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Abstract

Fatty acid binding protein (FABP) 4 chaperones free fatty acids (FFAs) in the adipocytes during lipolysis. Serum FFA relates to metabolic syndrome, and serum FABP4 is emerging as a novel risk marker. In 36 overweight/obese women, serum FABP4 and FFA were measured hourly during 5-hour oral glucose tolerance test. Insulin resistance was determined using frequently sampled intravenous glucose tolerance test. Serum lipids and inflammation markers were measured at fasting. During oral glucose tolerance test, serum FABP4 decreased by 40%, reaching its nadir at 3 hours (from 45.3 ± 3.1 to 31.9 ± 1.6 ng/mL), and stayed below the baseline at 5 hours (35.9 ± 2.2 ng/mL) ($P < .0001$ for both, compared with the baseline). Serum FFA decreased by 10-fold, reaching a nadir at 2 hours (from 0.611 ± 0.033 to 0.067 ± 0.004 mmol/L), then rebounded to 0.816 ± 0.035 mmol/L at 5 hours ($P < .001$ for both, compared with baseline). Both fasting FABP4 and nadir FABP4 correlated with obesity. Nadir FABP4 correlated also with insulin resistance parameters from frequently sampled intravenous glucose tolerance test and with inflammation. Nadir FFA, but not fasting FFA, correlated with the metabolic syndrome parameters. In conclusion, fasting FABP4 related to metabolic risk markers more strongly than fasting FFA. Nadir FABP4 and nadir FFA measured after glucose loading may provide better risk assessment than the fasting values.
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Insulin resistance, hyperinsulinemia, impaired glucose tolerance or diabetes, hypertension, elevated triglyceride, and low high-density lipoprotein (HDL) concentrations comprised the original definition of metabolic syndrome (METS) [1]. Since then, several other abnormalities of coagulation, vascular function, and inflammation have been associated with this syndrome [2]. New evidence from population studies and experimental animal models indicates that serum fatty acid binding protein 4 (FABP4) is a powerful new risk marker for predicting METS and atherosclerosis [3,4]. In white and Asian populations, serum FABP4 correlated directly with obesity, insulin resistance, and dyslipidemia. In Asians, FABP4 levels prospectively predicted incidence of the METS developing over the next 5 years. This was independent of adiposity and insulin resistance [5,6]. In a predominantly white population, the T-87C polymorphism in the FABP4 gene was associated with lower plasma triglyceride concentrations and decreased risk of risk for coronary heart disease [7].

The exact role of FABP4 in METS is not clear. Experimental evidence supports that FABP4 plays mechanistic roles in obesity, insulin resistance, and atherogenesis. It is expressed both in the adipose tissue and macrophages and thus may integrate the metabolic and inflammatory responses that lead to atherosclerosis [3,8]. Mice deficient in FABP4 were resistant to diet-induced insulin resistance despite gaining weight [9]. Treatment with a pharmacologic inhibitor of FABP4 improved insulin sensitivity in both genetic and diet-induced mouse models [10]. Elimination of FABP4 from macrophages protected apolipoprotein (apo) E–deficient mice from diet-induced atherosclerosis without improving insulin resistance [11].

Institutional approval: The study was approved by the Human Subjects Committee of the University of California at Davis, and all subjects signed the approved informed consent.

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This study was designed to test the null hypothesis that there will be no difference between the serum FABP4 and free fatty acid (FFA) as they relate to METS risk markers. This hypothesis was based on the evidence supporting that serum FFA correlates with cardiovascular disease [12], endothelial dysfunction [13], obesity, insulin resistance [14], dyslipidemia [12], and tumor necrosis factor (TNF)–α [15].

In addition, to gain information about in vivo regulation of serum FABP4 and FFA, FABP4 response to oral glucose load was determined. It is known that administration of glucose orally or intravenously stimulates insulin secretion, inhibits lipolysis in the adipose tissue, and consequently decreases serum FFA concentrations [16,17]. We anticipated that serum FABP4 may also decline simultaneously because FABP4 chaperones FFA from the hormone-sensitive lipase to the adipocyte membrane during lipolysis to facilitate efflux [18,19].

1. Study design

1.1. Subjects

Thirty-six women between the ages of 18 and 45 years, with body mass index (BMI) from 27 to 40 kg/m^2, were recruited after signing informed consents approved by the Human Subjects Committee of the University of California at Davis (UC Davis). Subjects were not recruited based on fulfilling any of the METS criteria. All participants were examined by the principal investigator (SEK-K). Patients using oral contraceptives, insulin sensitizers, lipid-lowering medications, or any other medicines or supplements affecting weight or insulin sensitivity during the preceding 2 months; having diabetes mellitus, untreated hypothyroidism, and any other systemic illnesses such as renal, hepatic, and gastrointestinal diseases; smoking; and drinking more than 2 servings of alcoholic drinks a week were excluded. Pregnant women, women who delivered during the previous 12 months, and lactating women were excluded. The studies were carried out at the Clinical and Translational Science Center (CTSC): Clinical Research Center of the UC Davis. The subjects were on their habitual diets and weight stable.

2. Anthropometric measurements

Weight was determined in light clothing using Tanita BWB800-P Digital Medical Scale (Arlington Heights, IL). Height without shoes was measured using an Ayrton Model S100 stadiometer (Snoqualmie, WA). Body composition was determined using bioelectrical impedance (Biostat, British Isles, United Kingdom) [20].

3. Oral glucose tolerance test

The nutritional intake was assessed by analyzing the 7-day food records with Food Processor software (ESHA Research, Salem, OR). All subjects consumed adequate carbohydrate before testing. The studies were initiated after an overnight fast, between 7:00 AM and 8:00 AM. An intravenous catheter was placed in the forearm. After obtaining the baseline blood samples, the participants ingested 75 g of glucose (Glucola, Fisher Healthcare, Houston, TX) at 0 minute; and additional blood samples were obtained every 30 minutes thereafter for 5 hours. The subjects remained supine in bed throughout the testing to avoid confounding effects of physical activity on blood glucose. The samples for glucose were collected in sodium fluoride–containing tubes on ice. Other samples were collected either in serum separation tubes, or in EDTA- or heparin-containing tubes. Glucose and insulin were assayed in all samples. Free fatty acids and FABP4 were assayed in hourly samples.

3.1. Frequently sampled intravenous glucose tolerance test

This was conducted approximately 1 week after the oral glucose tolerance test (OGTT). After an overnight fast, an intravenous catheter was placed in each forearm, one for blood sampling and the other for administering glucose and insulin. The catheters were kept open with isotonic sodium chloride solution drip. Heating pads were used to maximize the blood flow. Three blood samples were obtained at times −20, −10, and 0 minute(s). Glucose (0.3 U/kg as 25% dextrose) was given intravenously at time 0. Intravenous insulin at 0.03 U/kg (Humulin Regular; Eli Lilly, Indianapolis, IN) was administered at time 20 minutes. Blood samples were obtained at times 0, 2, 3, 4, 5, 6, 8,10, 12, 14, 16, 19, 22, 23, 24, 25, 27, 30, 35, 40, 50, 60, 70, 80, 90, 100, 120, 140, 160, and 180 minutes. The samples were analyzed for glucose and insulin. The results were entered to the MiniMod-Millenium (Los Angeles, CA) for the calculations of the acute insulin response, β-cell function, insulin sensitivity index (SI), and disposition index [21].

4. Laboratory assays

Glucose was measured using YSI 2300 STAT Plus Glucose & Lactate Analyzer (YSI Life Sciences, Yellow Springs, OH); triglyceride, cholesterol, HDL cholesterol, apo B, and FFA were measured using Poly-Chem System clinical chemistry analyzer (Cortlandt Manor, NY). The coefficients of variations (CVs) for these assays were 1% for glucose, 3.5% for cholesterol, 4% for triglyceride, 3.6% for direct HDL, 4.7% for apo B, and 4.1% for FFA. Insulin, leptin, and adiponectin were measured using radioimmunoassay kits (Linco Research, St Charles, MO) with CVs of 8.2%, 4.3%, and 6.5%, respectively. The homeostatic model assessment (HOMA) was calculated using the following formula: fasting insulin (in microunits per milliliter) × fasting glucose (in millimoles per liter)/22.5; FABP4 was measured using an enzyme-linked immunosorbent assay kit (BioVendor, Candler, NC) with a CV of 5%. Inflammatory markers were measured by the CTSC Laboratory under the supervision of

Dr S Devaraj. The highly sensitive C-reactive protein (hs-CRP) was measured with a highly sensitive latex-enhanced immunonephelometric assay as reported previously [22]. Both interassay and intraassay CVs were less than 5% [23]. Interleukin (IL)-6, IL-1β, and TNF-α were measured using the High Sensitivity Human Cytokine Panel-3 Plex (Milliplex) kit (Millipore, St Charles, MO) with a CV of 11%.

5. Statistical methods

All statistical analyses were performed using SAS, Version 9.1 (SAS Institute, Cary, NC). Measurements were log transformed as necessary to improve the normality of residuals and homoscedasticity of errors. Arithmetic means ± SD were calculated for levels of serum measures. Mean differences (with a 95% confidence interval) in response between 2 time points were compared using paired *t* test. Separate analyses were performed for each variable. A significance level of .05 was used to determine statistical significance of observed differences. Pearson correlation coefficients were calculated to assess the magnitude and direction of a linear association between 2 given variables. Multiple comparisons were controlled by the Sidak method where appropriate. An adjusted *P* value less than .05 using the Sidak method was considered as significant. Trajectory of 5-hour change in response levels was estimated by a repeated-measures analysis of variance. Individual trajectories of FABP4 and FFA changes in response level over 6 time points, evenly spaced, were estimated from linear random-effects models. Each response level was entered as the dependent variable (*Y*), and time (in minutes) was entered as the independent variable. To account for between-subject heterogeneity in the changes of response levels, time was modeled as random effect.

6. Results

Baseline characteristics of the subjects are shown in Table 1.

Table 1
Baseline characteristics of the subjects, obtained after overnight fasting (N = 36, mean ± SEM)

Age (y)	32.2 ± 1
Weight (kg)	99.1 ± 3.0
BMI (kg/m^2)	35.2 ± 0.9
Fat mass (kg)	45.3 ± 2.2
Lean mass (kg)	53.8 ± 1.0
Glucose (mg/dL)	100.0 ± 1.9
Insulin (mU/mL)	19.1 ± 1.5
HgBA1 (%)	5.7 ± 0.1
HOMA	4.0 ± 0.3
Leptin (ng/mL)	25.7 ± 1.7
Adiponectin (ng/mL)	10.5 ± 0.9
FFA (mmol/L)	0.624 ± 0.043
Triglyceride (mg/dL)	106 ± 10
Cholesterol (mg/dL)	182 ± 6
LDL-C (mg/dL)	122 ± 5
HDL-C (mg/dL)	39 ± 1
Apo B (mg/dL)	77 ± 4
hs-CRP (mg/L)	7.5 ± 1.3
TNF-α (pg/mL)	267 ± 46
IL-1β (pg/mL)	176 ± 33
IL-6 (pg/mL)	63 ± 11

LDL-C indicates low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; HgBA1, glycosylated hemoglobin.

6.1. Changes in glucose, insulin, FFA, and FABP4 during OGTT

Serum glucose increased from 100 ± 2 mg/dL to the peak value of 164 ± 6 mg/dL in 1 hour ($P < .0001$) and returned to the baseline (97 ± 4 mg/dL) in 3 hours. Serum insulin increased from the baseline of 19.3 ± 1.5 to 108.2 ± 10.1 μU/mL within 30 minutes (.0001), reached a peak of 123.8 ± 11.8 μU/mL at 90 minutes, and returned to the baseline at 4 hours.

As shown in Fig. 1, serum FABP4 reduced from the baseline of 45.3 ± 3.1 to 39.3 ± 2.8 ng/mL in 1 hour and to a nadir of 31.9 ± 1.6 g/mL in 3 hours, and stayed below the baseline for the rest of the OGTT ($P < .0001$ for all time points). Most subjects had their lowest (nadir) FABP4 during the second or the third hour. Serum FFA reduced from the baseline of 0.611 ± 0.033 to 0.181 ± 0.013 mmol/L in 1 hour and to a nadir of 0.067 ± 0.004 mmol/L in 2 hours ($P < .0001$ for both). Serum FFA rebounded to 0.816 ± 0.035 mmol/L at 5 hours ($P < .001$, as compared with the baseline).

6.2. Relationships among FABP4 and FFA concentrations and other study parameters

Correlations among FABP4, FFA, and various anthropometric, insulin resistance, and inflammatory parameters were calculated as shown in Table 2.

Fasting FABP, nadir FABP4, and the decrease (Δ) correlated directly with several of the anthropometric parameters and leptin. The nadir FABP4 showed a significant correlation with IL-1β and tended to correlate ($P < .1$) with hs-CRP, IL-6, and TNF-α. Fasting FABP4 also tended to correlate with hs-CRP and IL-6 ($P < .1$). The nadir FABP4 correlated directly with pancreatic insulin secretion and inversely with sensitivity index (SI) measured by intravenous glucose tolerance test (IVGTT). In general, nadir FABP4 showed the strongest correlations with the insulin resistance and inflammation. None of the FABP4 fractions correlated with plasma lipids/lipoproteins (triglyceride, cholesterol, low-density lipoprotein cholesterol, HDL cholesterol, or apo B).

Fasting FFA and the Δ FFA did not correlate with FABP4 or any of the METS variables. On the other hand, nadir FFA measured during the second hour of OGTT correlated directly with weight, BMI, fat mass, fasting insulin, HOMA, and pancreatic β-cell function measured by IVGTT, and inversely with adiponectin. None of the FFA fractions correlated with the inflammatory markers or serum

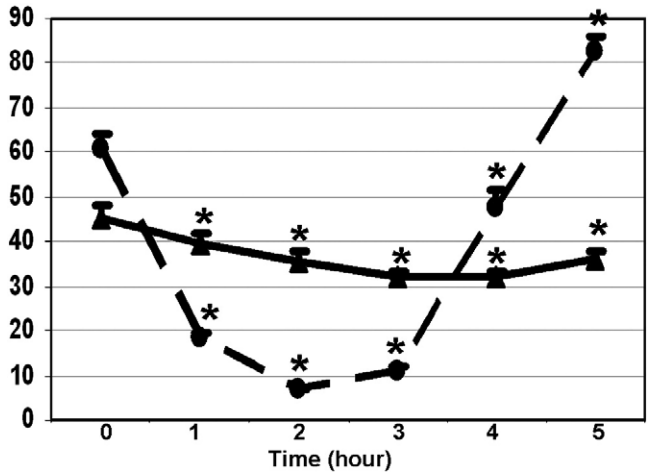

Fig. 1. Changes in FABP4 (nanograms per milliliter, ▲—▲) and FFAs (100 × millimoles per liter, ●- - -●) during OGTT. Significant changes (.05 < P < .0001) from the baseline are marked with "*" (N = 36, mean ± SEM).

lipids, although correlation of the nadir FFA with HDL cholesterol approached statistical significance (r = −0.3061, P = .08).

7. Discussion

The study yielded the following new information: First, at fasting, serum FABP4 related to several of the metabolic risk markers better than FFA. Second, FABP4 and FFA concentrations measured 2 to 3 hours after oral glucose loading related to obesity, inflammation, and insulin resistance better than the fasting values.

The fasting FABP4 correlated with obesity and fasting insulin. Similar relationships have been previously reported in type 2 diabetes mellitus patients [24]. In this report, FABP4 also correlated directly with adiponectin; and this finding was surprising because adiponectin increases insulin sensitivity, whereas serum FABP4 is associated with insulin resistance [25-27]. In our study, fasting FABP4 showed a weak inverse correlation with adiponectin (r = −0.3185, P = .07). In HIV-positive patients, serum FABP4 correlated with BMI, fasting glucose, insulin, and CRP [28]. In women with polycystic ovary syndrome, serum FABP4 correlated positively with BMI and negatively with HDL cholesterol [29]. In hyperlipidemic patients, serum FABP4 correlated with fasting glucose, but not with lipids [30]. In our study, none of the FABP4 fractions correlated with plasma lipids or apo B either.

It was clear that fasting FABP4 related to the risk markers more than the fasting FFA. Although literature indicates that fasting FFA correlated with coronary artery disease [12], endothelial dysfunction [13], obesity, insulin resistance [14], dyslipidemia [12], and TNF-α [15], we did not observe similar correlations. One explanation may be that the reports showing positive correlations with FFA involved large populations [12,17], animal experiments [14], or case-control studies [15].

A novel aspect of our study is that we measured dynamic changes in serum FABP4 and FFA after oral glucose loading.

Table 2
Correlations among FFA, FABP4, anthropometric parameters, insulin resistance indicators, and inflammatory markers

	FFA			FABP4		
	Fasting	Nadir	Decrease	Fasting	Nadir	Decrease
Fasting FFA anthropometric		−0.1572	**0.9929**	−0.0579	0.0059	−0.0762
Weight	−0.0219	**0.5471**	−0.0871	**0.4546**	**0.4186**	**0.3322**
BMI	−0.0469	**0.4814**	−0.1036	**0.5107**	**0.4178**	**0.4033**
Fat mass	−0.0393	**0.5240**	−0.1013	**0.4349**	**0.3763**	0.3316
Lean mass	0.0243	**0.4926**	−0.0356	**0.3648**	**0.4099**	0.2242
Leptin	−0.0205	0.2205	−0.0465	**0.4441**	0.2316	**0.4262**
Insulin resistance						
Fasting						
Insulin	0.0016	**0.4727**	−0.0553	**0.4773**	**0.5109**	**0.3791**
HOMA	0.0476	**0.3813**	0.0005	0.3574	0.2896	0.0072
Adiponectin	0.1134	**−0.4007**	0.1587	−0.3185	−0.2142	−0.2781
FS-IVGTT						
$AIR_{Glucose}$	−0.1329	0.3062	−0.1663	0.3032	**0.4718**	0.1112
β-Cell function	−0.0414	**0.4092**	−0.0863	0.1655	**0.3781**	−0.0085
SI	−0.1703	−0.2448	−0.1364	−0.3162	**−0.3405**	−0.2028
Inflammation						
hs-CRP[a]	0.0154	0.1872	−0.0075	0.2906*	0.3253*	0.1881
IL-6[a]	0.0535	0.2479	0.0223	0.3081*	0.3101*	0.2100
IL-1β[a]	−0.0064	0.1943	−0.0296	0.2797	**0.3484**	0.1523
TNF-α[a]	−0.0002	0.1851	−0.0224	0.2824	0.3005*	0.1832

The *nadir* refers to the lowest FFA or FABP4 value reached during the second or third hour of the OGTT, and Δ refers to the decrease between the fasting and nadir values. Coefficients of variations with P less than .05 to .0001 are bolded (N = 36). AIR indicates acute insulin response.

[a] The data for the inflammatory markers were log transformed.

* P less than .1.

Serum FABP4 decreased by 40% and FFA decreased approximately 10-fold during the second to third hour of OGTT. Both the fasting FABP4 and the nadir FABP4 correlated with obesity, although the nadir FABP4 showed stronger correlations with insulin resistance and inflammation. Interestingly, only the nadir FFA correlated with the anthropometric and metabolic variables, whereas the fasting FFA did not relate to any of these parameters. This finding is noteworthy, especially in the light of the recent report from Boston and Moate [16] that described a minimal model of FFA kinetics using frequently sampled (FS)–IVGTT. In this model, fasting FFA concentrations did not relate to the rate of lipolysis; and the nadir FFA occurred when the rate of lipolysis equaled the rate of oxidation. It is conceivable that, in obesity and insulin resistance, lipolysis is not suppressed efficiently in the adipose tissue. Consequently, obese and insulin-resistant individuals exhibit higher nadir FFA values [10,18,19]. In agreement with this explanation, we found that the nadir FABP4 and FFA correlated with the anthropometric parameters and insulin resistance directly. We did not measure FABP4 during FS-IVGTT for several reasons: First, this test requires administration of glucose at 0 minute and insulin at 20 minutes. Because our study was the first to measure FABP4 in a dynamic setting and the half-life of FABP4 is not known, we anticipated that 20 minutes may not be long enough to see a response to intravenous glucose. Second, the dose of intravenous glucose and insulin is calculated based on weight and varies from individual to individual. We anticipated that varying doses of glucose and insulin may modify FABP4 response. Third, each FS-IVGTT yields 31 samples; and the cost of the FABP4 assay would be prohibitive. Finally, OGTT is a widely used test; and the findings obtained from OGTT can find wider clinical and research application.

In summary, the literature indicates that FABP4 may predict the development of METS prospectively and independently of adiposity and insulin resistance [5,6]. Our findings suggest that the predictive value may be improved by measuring FABP4 not only at fasting state but also after glucose loading.

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