Int J Clin Exp Pathol 2017;10(8):8727-8734
www.ijcep.com /ISSN:1936-2625/IJCEP0056711

Original Article

Positive correlation of serum adipocyte fatty acid binding protein levels with metabolic syndrome in kidney transplantation patients

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Received May 3, 2017; Accepted May 25, 2017; Epub August 1, 2017; Published August 15, 2017

Abstract: Adipocyte fatty acid binding protein (A-FABP) is significantly expressed in white and brown adipose tissue, monocytes, and macrophages and is a central regulator of systemic insulin sensitivity. Metabolic syndrome (MetS) is a risk factor for post-transplant diabetes mellitus (PTDM), chronic graft dysfunction, graft loss, and patient death in kidney transplantation (KT) patients. This study was undertaken to evaluate the relationship between MetS and fasting serum A-FABP concentration in KT patients. Fasting blood samples were obtained from 70 KT patients. Serum A-FABP levels were measured using a commercial enzyme-linked immunosorbent assay kit. MetS and its components were defined using the diagnostic criteria of the International Diabetes Federation. Twenty-two patients (31.4%) had MetS. KT patients with hypertension ($P = 0.011$), diabetes ($P = 0.002$), body weight ($P = 0.004$), body mass index (BMI, $P = 0.001$), waist circumference ($P < 0.001$), body fat mass ($P < 0.001$), systolic blood pressure (SBP, $P = 0.017$), total cholesterol (TCH, $P = 0.028$), triglycerides (TG, $P = 0.001$), blood urea nitrogen (BUN, $P = 0.003$), insulin ($P < 0.001$), homeostasis model assessment of insulin resistance (HOMA-IR, $P < 0.001$), and A-FABP level ($P < 0.001$) were higher, while high-density lipoprotein cholesterol (HDL-C, $P = 0.010$) was lower in KT patients with MetS. Moreover, SBP ($\beta = 0.347$, adjusted R^2 change = 0.108, $P = 0.001$) and logarithmically transformed triglycerides (log-TG, $\beta = 0.393$, adjusted R^2 change = 0.189, $P < 0.001$) were associated with A-FABP levels in a multivariable forward stepwise linear regression analysis among KT patients. The results of our study showed that the fasting A-FABP level was positively associated with MetS in KT patients. SBP and log-TG were independent predictors of the serum A-FABP level among KT patients.

Keywords: Adipocyte fatty acid binding protein, metabolic syndrome, kidney transplantation

Introduction

Fatty acid binding protein (FABP), which was first discovered in 1972, has at least nine members [1]. This intracellular lipid chaperone coordinates the import, storage, and export of fatty acid, cholesterol, and phospholipids [2-6]. It influences the lipid-mediated transcriptional regulation in the nucleus and is strongly linked to metabolic and inflammatory activations [2-6]. As one of the members of FABP, adipocyte FABP (A-FABP), which is also known as FABP4 or adipocyte P2 (aP2) is expressed in adipocytes, macrophages, and dendritic cells [7]. The expression of A-FABP is highly regulated during differentiation of adipocytes, and its mRNA expression is transcriptionally controlled by fatty acids, PPAR-γ agonists, oxidized low-density lipoprotein (LDL), and insulin [2, 3, 8, 9]. A-FABP deficiency would lead to insulin resistance in obesity and decrease lipolysis [10, 11]. Other animal experiments revealed that total A-FABP deficiency granted protection against atherosclerosis [3, 12]. These results showed significance for A-FABP in the development of major components of the metabolic syndrome (MetS).

MetS is a severe health condition affecting more than 20% of adults in the West and is also a serious challenge in Taiwan [13, 14]. The common causes of MetS include obesity, physical

inactivity, dietary habits, and genetic factors. MetS can lead to cardiovascular disease, diabetes, chronic kidney disease (CKD), and diseases resulting from fatty buildup in artery walls [15-17]. MetS is also a risk factor for post-transplant diabetes mellitus (PTDM), chronic graft dysfunction, graft loss, and patient death in KT patients [18, 19]. Our previous studies have demonstrated that serum A-FABP was positively associated with MetS in patients with coronary artery disease (CAD), hemodialysis (HD) patients, and type 2 diabetes mellitus (DM) patients [20-22]. The aim of this study was to confirm the relationship between MetS and fasting A-FABP concentration in KT patients and to find out the independent factors of MetS and serum A-FABP level in KT patients.

Materials and methods

Patients

This was a prospective, cross-sectional study conducted at a medical center in Hualien, Taiwan from May to August 2013 where 70 KT patients were enrolled. The study was approved by the Protection of Human Subjects Institutional Review Board of Tzu-Chi University and Hospital and is consistent with the Declaration of Helsinki. All patients provided their informed consent before participating in this study. Blood pressure (BP) was measured by trained staff in the morning using standard mercury sphygmomanometers with appropriate cuff sizes after the patient sat for at least 10 min. Systolic BP (SBP) and diastolic BP (DBP) were taken 3 times at 5-min intervals and were averaged for analysis. Patients who were diagnosed with hypertension were defined as SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg or having received any anti-hypertensive medication in the previous 2 weeks. Patients were excluded if they had an acute infection, acute myocardial infarction, heart failure, acute transplant rejection status, and malignancy at the time of blood sampling, or if they refused to provide informed consent for the study.

Anthropometric analysis

Participants' body weight was measured in light clothing and without shoes to the nearest 0.5 kg, and body height was measured to the nearest 0.5 cm. Waist circumference was measured using a tape measure around the waist from the point between the lowest ribs and the hip bones with the hands on the hips. Body mass index (BMI) was calculated as the weight in kilograms divided by the height in meters squared. 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, USA). Measurements were carried out by the same operator [20-22].

Biochemical investigations

Fasting blood samples (approximately 5 ml) of all participants were immediately centrifuged at 3000 *g* for 10 min. Serum levels of blood urea nitrogen (BUN), creatinine (Cre), fasting glucose, total cholesterol (TCH), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were measured using an auto-analyzer (Siemens Advia 1800, Siemens Healthcare GmbH, Henkestr, Germany) [20-22]. Serum A-FABP levels were measured using a commercially available enzyme immunoassay (EIA; SPI-BIO, Montigny le Bretonneux, France) [20-23]. Serum insulin levels were measured using the commercially available enzyme-linked immunosorbent assay (ELISA) (Labor Diagnostika Nord, Nordhorn, Germany) [22]. Insulin resistance was evaluated using a homeostasis model assessment of insulin resistance (HOMA-IR) as follows: HOMA-IR = fasting plasma glucose (mg/dl) × fasting serum insulin (μU/ml)/405 [22]. The estimated glomerular filtration rate (GFR) was calculated using the Modification of Diet in Renal Disease (MDRD) equation in this study.

Metabolic syndrome and its components

The prevalence of MetS was defined using the International Diabetes Federation definition [24]. People 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 met two or more of the following criteria: fasting serum glucose ≥ 100 mg/dl, TG ≥ 150 mg/dl, HDL-C level < 40 mg/dl in men or < 50 mg/dl in women, or BP ≥ 130/85 mmHg. The use of anti-hypertensive drugs was considered as indicative of high blood pressure in this analysis. Type 2 DM was determined according to World Health

Table 1. Clinical variables of the 70 kidney transplantation patients with or without metabolic syndrome

Items	All patients (n = 70)	No metabolic syndrome group (n = 48)	Metabolic syndrome group (n = 22)	*P* value
Age (years)	51.94 ± 9.88	51.42 ± 10.23	53.09 ± 9.18	0.514
Post-KT duration (months)	72.23 ± 43.99	76.04 ± 43.71	63.91 ± 44.45	0.287
Height (cm)	162.10 ± 8.26	162.23 ± 7.97	161.82 ± 9.05	0.848
Body weight (kg)	62.20 ± 11.58	59.58 ± 10.12	67.91 ± 12.72	0.004*
Waist circumference (cm)	84.77 ± 10.88	81.07 ± 9.79	92.84 ± 8.65	< 0.001*
Body mass index (kg/m^2)	23.63 ± 3.98	22.58 ± 3.23	25.94 ± 4.54	0.001*
Body fat mass (%)	29.08 ± 6.46	26.93 ± 5.73	33.77 ± 5.50	< 0.001*
Systolic blood pressure (mmHg)	138.23 ± 16.33	135.10 ± 16.78	145.05 ± 13.24	0.017*
Diastolic blood pressure (mmHg)	85.96 ± 11.10	85.06 ± 11.32	87.91 ± 10.59	0.323
Total cholesterol (mg/dl)	195.47 ± 46.34	187.27 ± 33.03	213.36 ± 64.22	0.028*
Triglyceride (mg/dl)	108.00 (79.75-167.00)	95.00 (72.00-148.00)	156.00 (98.25-376.25)	0.001*
HDL-C (mg/dl)	50.53 ± 15.23	53.67 ± 15.27	43.68 ± 12.99	0.010*
LDL-C (mg/dl)	108.79 ± 39.94	113.81 ± 36.08	97.84 ± 46.32	0.121
Fasting glucose (mg/dl)	93.50 (86.00-110.00)	93.50 (85.00-100.50)	95.50 (88.75-179.00)	0.122
Blood urea nitrogen (mg/dl)	22.50 (17.00-32.50)	19.00 (15.25-29.75)	26.00 (22.75-41.25)	0.003*
Creatinine (mg/dl)	1.59 (1.20-2.10)	1.50 (1.10-2.10)	1.70 (1.48-1.95)	0.498
Glomerular filtration rate (ml/min)	44.86 ± 21.07	47.19 ± 23.50	39.77 ± 13.52	0.173
Insulin (uIU/ml)	6.16 (4.44-8.83)	5.47 (4.21-6.94)	11.14 (6.17-12.78)	< 0.001*
HOMA-IR	1.49 (1.13-2.32)	1.34 (0.98-1.71)	2.59 (1.54-5.27)	< 0.001*
A-FABP (ng/ml)	39.81 ± 31.60	27.99 ± 23.34	65.59 ± 32.35	< 0.001*

Values for continuous variables are given as means ± standard deviation and tested by Student's *t*-test; variables not normally distributed given as medians and interquartile range and are tested by Mann-Whitney U test. KT, kidney transplantation; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance. *$P < 0.05$ was considered statistically significant after the Student's *t*-test or Mann-Whitney U test.

Organization criteria, and a patient was considered as having DM if their fasting plasma glucose was ≥ 126 mg/dl or if they were using anti-diabetic therapy [25].

Statistical analysis

Data were tested for the normal distribution using the Kolmogorov-Smirnov test. Normally distributed data are expressed as the mean ± standard deviation (SD), and comparisons between patients were performed using the Student's independent t-test (two-tailed). Non-normally distributed data are expressed as medians and interquartile ranges, and comparisons between patients were performed using the Mann-Whitney U test (TG, fasting glucose, BUN, Cre, insulin, and HOMA-IR). Data expressed as the number of patients were analyzed by the χ^2 test. Because TG, fasting glucose, BUN, Cre, insulin, and HOMA-IR data were not normally distributed, we performed base 10 logarithmic transformations to achieve normality. Clinical variables that correlated with serum A-FABP levels in KT patients were evaluated using univariate linear regression analysis. Variables that were significantly associated with A-FABP levels in KT patients were tested for independence in multivariate forward stepwise regression analysis. Data were analyzed using SPSS for Windows (version 19.0; SPSS Inc., Chicago, IL, USA). A *P*-value of < 0.05 was considered statistically significant.

Results

The clinical characteristics of KT patients with or without MetS are presented in **Table 1**. Twenty-two KT patients (31.4%) had MetS. KT patients with MetS had significantly higher serum fasting A-FABP levels than those without MetS ($P < 0.001$). Compared with KT patients without MetS, those with MetS showed a much higher body weight ($P = 0.004$), waist circumference ($P < 0.001$), BMI ($P = 0.001$), body fat mass ($P < 0.001$), SBP ($P = 0.017$), TCH ($P = 0.028$), TG ($P = 0.001$), BUN ($P = 0.003$), insulin ($P < 0.001$), and HOMA-IR ($P < 0.001$), while HDL-C ($P = 0.010$) was lower.

Table 2. Baseline characteristics of the 70 kidney transplantation patients with or without metabolic syndrome

Characteristic		No metabolic syndrome group (%)	Metabolic syndrome group (%)	*P* value
Gender	Male	29 (60.4)	8 (36.4)	0.061
	Female	19 (39.6)	14 (63.6)	
Diabetes	No	38 (79.2)	9 (40.9)	0.002*
	Yes	10 (20.8)	13 (59.1)	
Hypertension	No	31 (64.6)	7 (31.8)	0.011*
	Yes	17 (35.4)	15 (68.2)	
Transplantation model	Cadaveric	42 (87.5)	19 (86.4)	0.895
	Living	6 (12.5)	3 (13.6)	
Tacrolimus use	No	18 (37.5)	11 (50.0)	0.324
	Yes	30 (62.5)	11 (50.0)	
Mycophenolate mofetil or mycophenolic acid use	No	13 (27.1)	8 (36.4)	0.432
	Yes	35 (72.9)	14 (63.6)	
Steroid use	No	11 (22.9)	2 (9.1)	0.167
	Yes	37 (77.1)	20 (90.9)	
Rapamycin use	No	39 (81.2)	17 (77.3)	0.699
	Yes	9 (18.8)	5 (22.7)	
Cyclosporine use	No	39 (81.2)	15 (68.2)	0.227
	Yes	9 (18.8)	7 (31.8)	

*$P < 0.05$ was considered statistically significant. Data are expressed as number of patients, and analysis was carried out using the chi-square test.

Table 3. Clinical characteristics and adipocyte fatty acid binding protein levels of the 70 kidney transplantation patients

Characteristic		Number (%)	A-FABP (ng/ml)	*P* value
Gender	Male	37 (52.9)	32.79 ± 29.78	0.049*
	Female	33 (47.1)	47.67 ± 32.17	
Diabetes	No	47 (67.1)	30.32 ± 27.57	< 0.001*
	Yes	23 (32.9)	59.19 ± 30.94	
Hypertension	No	38 (54.3)	30.27 ± 23.05	0.005*
	Yes	32 (45.7)	51.14 ± 36.67	
Transplantation model	Cadaveric	62 (88.6)	37.85 ± 31.34	0.150
	Living	8 (11.4)	55.00 ± 31.38	
Tacrolimus use	No	29 (41.4)	43.33 ± 31.12	0.436
	Yes	41 (58.6)	37.31 ± 32.08	
Mycophenolate mofetil or Myfortic use	No	21 (30.0)	47.99 ± 27.22	0.157
	Yes	49 (70.0)	36.30 ± 32.94	
Steroid use	No	13 (18.6)	26.05 ± 20.63	0.082
	Yes	57 (81.4)	42.95 ± 32.94	
Rapamycin use	No	56 (80.0)	36.16 ± 31.75	0.388
	Yes	14 (20.0)	40.38 ± 31.24	
Cyclosporine use	No	54 (77.1)	39.78 ± 32.06	0.990
	Yes	16 (22.9)	39.89 ± 31.02	

*$P < 0.05$ was considered statistically significant for the Student's *t*-test.

Clinical characteristics and immunosuppressive drugs used in KT patients with or without MetS are presented in **Table 2**. Comorbid conditions included diabetes (n = 23; 32.9%), and

Table 4. Correlation between serum adipocyte fatty acid binding protein levels and clinical variables among 70 kidney transplantation patients

Variables	A-FABP (ng/mL)				
	Univariate		Multivariate		
	r	*P* value	Beta	Adjusted R^2 change	*P* value
Age (years)	0.144	0.234	-	-	-
Gender (female)	0.237	0.049*	-	-	-
Diabetes	0.432	< 0.001*	-	-	-
Hypertension	0.331	0.005*	-	-	-
Post-KT duration (months)	-0.045	0.709	-	-	-
Height (cm)	-0.211	0.079	-	-	-
Body weight (kg)	0.163	0.178	-	-	-
Waist circumference (cm)	0.326	0.006*	-	-	-
Body mass index (kg/m^2)	0.311	0.009*	-	-	-
Body fat mass (%)	0.274	0.022*	-	-	-
Systolic blood pressure (mmHg)	0.409	< 0.001*	0.347	0.108	0.001*
Diastolic blood pressure (mmHg)	0.138	0.253			
Total cholesterol (mg/dL)	0.248	0.039*	-	-	-
Log-triglyceride (mg/dL)	0.448	< 0.001*	0.393	0.189	< 0.001*
HDL-C (mg/dL)	-0.119	0.325	-	-	-
LDL-C (mg/dL)	-0.059	0.628	-	-	-
Log-glucose (mg/dL)	0.261	0.029*	-	-	-
Log-blood urea nitrogen (mg/dL)	0.283	0.017*	-	-	-
Log-creatinine (mg/dL)	0.097	0.425	-	-	-
Glomerular filtration rate (mL/min)	-0.237	0.049*	-	-	-
Log-insulin (uIU/mL)	0.322	0.007*	-	-	-
Log-HOMA-IR	0.392	0.001*	-	-	-

Data on triglyceride, glucose, blood urea nitrogen, creatinine, insulin, and HOMA-IR levels showed a skewed distribution and therefore were log-transformed before analysis. Data analysis was performed using univariate linear regression analyses or multivariate stepwise linear regression analysis (adopted factors: gender, diabetes, hypertension, waist circumference, body mass index, body fat mass, systolic blood pressure, log-triglyceride, log-glucose, log-blood urea nitrogen, glomerular filtration rate, log-insulin, and log-HOMA-IR). KT, kidney transplantation; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance. *$P < 0.05$ was considered statistically significant.

hypertension (n = 32; 45.7%). Prescribed therapeutic agents included tacrolimus (n = 41; 58.6%), mycophenolate mofetil or mycophenolic acid (n = 49; 70.0%), steroids (n = 57; 81.4%), rapamycin (n = 14; 20.0%), and cyclosporine (n = 16; 22.9%). Hypertension (P = 0.011) and diabetes (P = 0.002) were more frequent in KT patients with MetS than in those without MetS. There were no significant differences in gender, transplantation model, or the use of tacrolimus, mycophenolate mofetil or mycophenolic acid, steroids, rapamycin, or cyclosporine medications between KT patients with and without MetS.

Clinical characteristics and serum A-FABP values for the 70 KT patients are presented in **Table 3**. A-FABP level was statistically significantly higher in female KT patients (P = 0.049), diabetes KT patients (P < 0.001), and hypertensive KT patients (P = 0.005). No statistically significant differences in A-FABP levels were found between transplantation models or in the use of tacrolimus, mycophenolate mofetil or mycophenolic acid, steroids, rapamycin, or cyclosporine.

Univariate linear analysis of clinical variables associated with fasting serum A-FABP levels in KT patients is presented in **Table 4**. Female gender (r = 0.237; P = 0.049), KT patients with diabetes (r = 0.432; P < 0.001), hypertensive KT patients (r = 0.331; P = 0.005), waist circumference (r = 0.326; P = 0.006), BMI (r = 0.311; P = 0.009), body fat mass (r = 0.274; P = 0.022), SBP (r = 0.409; P < 0.001), TCH (r = 0.248; P = 0.039), logarithmically transformed TG (log-TG, r = 0.448; P < 0.001), log-glucose (r = 0.261; P = 0.029), log-BUN (r = 0.283; P = 0.017), log-insulin (r = 0.322; P = 0.007), and log-HOMA-IR (r = 0.392; P = 0.001) were positively correlated, while GFR (r = -0.237; P = 0.049) was negatively correlated with serum A-FABP levels in this study.

Multivariate forward stepwise linear regression analysis of the variables significantly associat-

ed with fasting serum A-FABP levels revealed that SBP (β = 0.347, adjusted R^2 change = 0.108, P = 0.001) and log-TG (β = 0.393, adjusted R^2 change = 0.189, P < 0.001) was independent predictors of these values for KT patients (**Table 4**).

Discussion

This study showed that serum fasting A-FABP levels were higher in KT patients with MetS. In addition, A-FABP level was statistically significantly higher in KT female patients and those with DM and hypertension. Furthermore, SBP and TG were independent predictors of serum fasting A-FABP level in KT patients.

MetS, which was first described in 1989, was characterized by abdominal obesity, hypertension, hyperglycemia, elevated TG levels, and low HDL-C levels [26, 27]. In KT patients, MetS was an independent risk factor for chronic allograft dysfunction, graft failure, new-onset DM, and cardiovascular disease [28]. In this study, the prevalence of MetS in KT patients was 31.4%, in accordance with a study done in Hong Kong, which showed the prevalence of MS to be 32% in Chinese KT patients [29]. In our study, KT patients who had MetS had significantly higher levels of A-FABP as well as higher body weight, waist circumference, BMI, body fat mass, waist circumference, SBP, TCH levels, TG levels, BUN levels, insulin levels, and HOMA-IR and lower HDL-C levels. Our results also revealed that KT patients with MetS were more susceptible to comorbid DM and hypertension than those without MetS. PTDM was a complication after solid-organ transplantation, which was associated with decreased graft and patient survival. Risk factors of PTDM included patient age and glucocorticoid, cyclosporine, and tacrolimus use [30]. Although immunosuppressive agents were said to increase the incidence of MetS after KT [31], our study revealed no relationship between immunosuppressive agents and those who had MetS in KT patients. In addition, neither transplantation model nor gender differences were found in KT patients with MetS, though some studies on KT patients may have revealed gender-based predispositions to MetS [28].

Serum A-FABP, the predominant cytosolic protein on the adipocyte, was an early marker for adiposity associated with MetS [32]. It played a crucial role in insulin resistance and modulation of systemic lipid and glucose metabolism [33]. Our study revealed significantly higher serum A-FABP levels in female KT, DM KT and hypertensive KT patients. Several studies produced the same results of higher A-FABP levels in female populations [33-35], because females have comparatively higher percentages of body fat than males [36]. No relationship was found between serum A-FABP levels and the other factors, including the transplantation model and immunosuppressive agents used.

Our study revealed a positive association between serum A-FABP levels and the indicators of adiposity including waist circumference, BMI, and body fat mass. It was suggested that adipocytes were the major site for A-FABP secretion in KT patients. The involvement of serum A-FABP in the development of hyperinsulinemia, hyperglycemia, and insulin resistance [32, 36] is consistent with our results of a positive correlation between A-FABP and log-insulin, log-glucose, log HOMA-IR, and DM. A previous study demonstrated that serum A-FABP level was positively correlated with TG [37], and a similar finding was obtained in this study. The positive correlation between A-FABP and Cre as well as the negative correlation between A-FABP and GFR were noted in type 2 DM patients [32]. Our results revealed a coherent negative correlation in A-FABP and GFR, but no relationship was found in A-FABP and Cre. A-FABP played an important role in obesity-related cardiovascular disease and endothelial dysfunction by increasing cholesterol and TG accumulation; therefore, it was positively associated with atherosclerosis [23, 36]. After multivariate forward stepwise linear regression analysis of the significant variables showed that SBP and TG were independent predictors of fasting serum A-FABP levels.

Our study has some limitations. First, this was a cross-sectional study; therefore, our findings should be investigated in long-term prospective studies before a causal relationship between serum A-FABP levels and MetS in KT patients can be established. Second, A-FABP usually acts at the interface of inflammatory pathways such as tumor necrosis factor alpha (TNF-α), high sensitivity C-reactive protein (hs-CRP), and interleukin-6 (IL-6). However, our study did not investigate their influence on these inflammatory markers. Further studies should examine

the association between serum A-FABP levels and inflammatory cytokines in KT patients.

In conclusion, the present study showed that the serum A-FABP level was positively associated with MetS in KT patients. In addition, SBP and TG are positively correlated with serum fasting A-FABP level in KT patients.

Acknowledgements

This study was supported by a grant from the Buddhist Tzu Chi General Hospital, Hualien, Taiwan (TCRD102-26).

Disclosure of conflict of interest

None.

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