

# Contribution of serum adipocyte fatty acid-binding protein levels to the presence of microalbuminuria in a Chinese hyperglycemic population

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## Keywords

Adipocyte fatty acid-binding protein, Microalbuminuria, Urinary albumin-to-creatinine ratio

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## ABSTRACT

**Aims/Introduction:** Individuals with type 2 diabetes mellitus are vulnerable to micro- and macrovascular complications in the presence of microalbuminuria. Adipocyte fatty acid-binding protein (A-FABP) was proposed as an indicator for albuminuria in patients with diabetes. The present study aimed to explore the associations between serum A-FABP levels and microalbuminuria in the hyperglycemic population.

**Materials and Methods:** Serum A-FABP levels were detected using sandwich enzyme-linked immunosorbent assay. Microalbuminuria was identified by urinary albumin-to-creatinine ratio (UACR), when the value was between 30–300 mg/g. The participants were divided into the subgroups based on sex and the status of impaired glucose regulation or newly diagnosed type 2 diabetes mellitus.

**Results:** A total of 939 participants, consisting of 436 men and 503 women, were enrolled. Serum levels of A-FABP were much higher in participants with microalbuminuria than those without microalbuminuria. This result held true for all subgroups (all  $P < 0.05$ ). For Spearman's correlation analyses, serum A-FABP levels showed a positive relationship with the UACR in men and women (both  $P < 0.01$ ). Multiple stepwise regression analysis showed that serum A-FABP levels were independently and positively correlated with UACR in both sexes (men: standardized  $\beta = 0.256$ ,  $P < 0.001$ ; women: standardized  $\beta = 0.155$ ,  $P = 0.001$ ). This relationship remained significant in every subgroup (all  $P < 0.01$ ).

**Conclusions:** For hyperglycemic individuals, serum A-FABP levels increased in the presence of microalbuminuria. Serum A-FABP levels were identified as an independent factor positively associated with the UACR.

## INTRODUCTION

Diabetic kidney disease (DKD) is one of the most prevalent microvascular complications of diabetes mellitus, as well as the leading cause of end-stage renal disease<sup>1</sup>. Based on the finding of elevated urinary albumin excretion, DKD is divided into microalbuminuria and macroalbuminuria<sup>2</sup>. The presence of microalbuminuria indicates generalized vascular endothelial damage and early atherosclerosis. Additionally,

microalbuminuria predisposes patients with diabetes mellitus to developing micro- and macrovascular complications, such as nephropathy, myocardial infarction and stroke<sup>3</sup>.

Adipocyte fatty acid-binding protein (A-FABP; also termed fatty acid-binding protein 4 or adipocyte protein 2), an adipokine, is preferentially produced in and released from adipocytes during differentiation and intracellular lipid accumulation<sup>4,5</sup>. Since circulating A-FABP was first described by Xu *et al.*<sup>6</sup>, accumulating evidence has shown that increased concentrations of circulating A-FABP contribute to obesity, type 2 diabetes mellitus and metabolic syndrome<sup>7,8</sup>. In our previous research,

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A-FABP deficiency was found to protect mice from diabetes-induced cardiac injury<sup>9</sup>. Furthermore, findings from clinical studies suggested that A-FABP might serve as a serum biomarker for DKD stages and cardiovascular risks in patients with diabetes mellitus<sup>10,11</sup>.

Our previous epidemiological investigations<sup>12</sup> revealed the ascending prevalence of microalbuminuria among patients with impaired glucose regulation (IGR) and newly diagnosed type 2 diabetes mellitus, which suggested that DKD developed before blood glucose levels increased to levels that met the standard diagnostic criterion for diabetes mellitus. Hence, it is of great importance to explore the relationship between serum A-FABP levels and microalbuminuria for the early prevention and diagnosis of DKD and other diabetes-related cardiovascular diseases. However, few data are available regarding the association of serum A-FABP levels with microalbuminuria in patients with IGR and newly diagnosed type 2 diabetes mellitus. For a more accurate representation of urine albumin excretion in 24 h, the urinary albumin-to-creatinine ratio (UACR) is recommended by the American Kidney Foundation as the screening tool for patients with diabetes mellitus<sup>13</sup>. Using the UACR to define the presence of microalbuminuria in the present study, we aimed to investigate the relationship between serum A-FABP levels and microalbuminuria.

## MATERIALS AND METHODS

### Participants

The present study selected a total of 939 participants with IGR and newly diagnosed type 2 diabetes mellitus from the Shanghai Obesity Study, which investigated the onset and progression of metabolic syndrome and its related diseases<sup>14</sup>. Every participant presented with preserved kidney function (estimated glomerular filtration rate [eGFR]  $\geq 60$  mL/min/1.73 m<sup>2</sup>). All of the participants provided clinical data, and completed a standardized questionnaire to collect information on their disease history, medication usage, family history and smoking status. The present study excluded individuals with previously diagnosed type 2 diabetes mellitus, type 1 diabetes mellitus, other specific types of diabetes mellitus, gestational diabetes mellitus, macroalbuminuria, urinary tract infection, severe liver or renal dysfunction, hyperthyroidism or hypothyroidism, tumors, psychiatric disease and a history of cardiovascular disease, as well as those receiving antihypertensive therapy, lipid-lowering therapy, or replacement therapy with systemic corticosteroids or thyroxine at the time of the study.

The study was carried out in accordance with the Declaration of Helsinki, and was approved by the Ethics Committee of Shanghai Jiao Tong University Affiliated Sixth People's Hospital. Written informed consent was provided by all of the participants before enrollment in the present study.

### Anthropometric and biochemical assessments

Every participant underwent examination after at least 10 h of overnight fasting. Details on the measurement of

anthropometric parameters, which included bodyweight, height, waist circumference (W) and resting blood pressure (BP), were described previously<sup>14</sup>. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters.

Biochemical variables, such as fasting plasma glucose (FPG), 2-h plasma glucose (2hPG), glycated hemoglobin (HbA1c), fasting serum insulin (FINS), total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol, C-reactive protein (CRP) and serum A-FABP levels (intra- and interassay coefficients of variation of 6.6 and 8.7%, respectively) were detected using the standard methods<sup>14,15</sup>. Serum creatinine and urinary creatinine were determined by the sarcosine oxidase-PAP method on a 7600-120 Hitachi automatic analyzer (Hitachi, Tokyo, Japan). Immunonephelometry was used to detect urinary albumin (BN II System; Siemens, Marburg, Germany). UACR was calculated by dividing the urinary albumin by the urinary creatinine levels. The eGFR was calculated according to the Chronic Kidney Disease Epidemiology Collaboration equation<sup>16</sup>:  $eGFR = (141 \times \text{minimum} [\text{serum creatinine (mg/dL)/}k, 1]^\alpha \times \text{maximum} [\text{serum creatinine/}k, 1]^{-1.209} \times 0.993^{\text{age}} \times 1.018$  [if women]);  $k$  is 0.7 (women) or 0.9 (men);  $\alpha$  is  $-0.329$  (women) or  $-0.411$  (men). The insulin resistance index<sup>17</sup> was calculated by the homeostasis model assessment for insulin resistance (HOMA-IR):  $\text{HOMA-IR} = \text{FINS (mU/L)} \times \text{FPG (mmol/L)} / 22.5$ .

### Diagnostic criteria

According to 1999 World Health Organization criteria<sup>18</sup>, diabetes was diagnosed as  $\text{FPG} \geq 7.0$  mmol/L and/or  $2\text{hPG} \geq 11.1$  mmol/L, and IGR was diagnosed as  $6.1$  mmol/L  $\leq$   $\text{FPG} < 7.0$  mmol/L and/or  $7.8$  mmol/L  $\leq$   $2\text{hPG} < 11.1$  mmol/L. Microalbuminuria was defined as a UACR between 30–300 mg/g, and macroalbuminuria was defined as a UACR  $> 300$  mg/g<sup>2</sup>. Current smokers were defined as those who smoked regularly (at least once daily) and/or had smoked for a long time (at least 6 months)<sup>19</sup>.

### Statistical analysis

All statistical analyses were carried out using the Spss 16.0 statistical software package (SPSS Inc., Chicago, Illinois, USA). The normality of the data distribution was determined by the one-sample Kolmogorov–Smirnov test. Normally distributed data were expressed in the form of the mean  $\pm$  standard deviation, whereas skewed data were expressed in the form of the median with interquartile range (25–75%). Categorical variables were expressed as percentages (%). Comparisons between the two groups were carried out using an unpaired Student's  $t$ -test (normal distribution) or the Mann–Whitney  $U$ -test (skewed distribution) for continuous data, and the  $\chi^2$ -test for categorical variables<sup>20</sup>. Spearman's correlation coefficient analyses were carried out to examine the relationships of UACR with other variables. Multiple regression analysis was carried out to identify

factors independently affecting UACR with the method of stepwise selection. The probabilities of  $F$  were used for stepping methods criteria: 0.05 was the cut-off of entry, and 0.10 was the cut-off of removal<sup>21</sup>. The potential affecting factors of UACR, including age, BMI, W, SBP, DBP, HbA1c, HOMA-IR, TC, TG, HDL-c, low-density lipoprotein cholesterol, CRP, eGFR and smoking status, were defined as independent variables. All reported  $P$ -values were two-tailed, of which  $<0.05$  was considered statistically significant.

## RESULTS

### Clinical characteristics of the study participants

A total of 939 participants with an age range of 23–79 years (median 54.62 years [interquartile range 48.63–60.01]), including 436 men and 503 women, were enrolled in the present study. Women showed higher serum A-FABP levels than men (5.15 ng/mL [interquartile range 3.58–7.32] vs 3.46 ng/mL [2.47–4.89];  $P < 0.001$ ). Compared with men, women had higher levels of TC, HDL-c, eGFR and UACR (all  $P < 0.01$ ), but lower levels of BMI, W, systolic BP (SBP), diastolic BP (DBP), FPG and TG (all  $P < 0.01$ ). In addition, fewer women were current smokers ( $P < 0.01$ ). There were no sex differences in age and other biochemical parameters (all  $P > 0.05$ ). Men and women were divided into the subgroups according to the serum A-FABP levels. The median values of serum A-FABP levels in men and women were defined as the corresponding cut-off values, respectively. Participants with high levels of serum A-FABP showed lower eGFR than those with low levels of serum A-FABP in both men and women ( $P = 0.002$  and  $P < 0.001$ , respectively).

The participants diagnosed with microalbuminuria accounted for 8.94% (39) of men, and 7.95% (40) of women. The percentage of participants with microalbuminuria did not differ significantly between men and women ( $P = 0.585$ ). BMI, W, SBP, FPG levels, HOMA-IR, TG level, CRP levels and UACR were much higher in participants with microalbuminuria than in those with normoalbuminuria, which was observed in both men and women (all  $P < 0.05$ ). Additionally, men with microalbuminuria had higher levels of HbA1c than men with normoalbuminuria ( $P < 0.05$ ), and women with microalbuminuria were older and showed higher levels of 2hPG and FINS (both  $P < 0.05$ ), but lower levels of HDL-c ( $P < 0.05$ ) compared with women with normoalbuminuria (Table 1).

### Comparison of serum A-FABP levels between participants with microalbuminuria and normoalbuminuria

For men, participants with microalbuminuria had higher serum levels of A-FABP than those with normoalbuminuria (5.41 ng/mL [3.36–7.71] vs 3.40 ng/mL [2.42–4.63];  $P < 0.001$ ). Similar results were observed in women (serum A-FABP levels of 6.08 ng/mL [4.83–9.13] in women with microalbuminuria vs 5.00 ng/mL [3.44–7.12] in women with normoalbuminuria;  $P < 0.001$ ). Despite the significant sex difference in the ratio of participants with IGR to those with newly diagnosed type 2

diabetes mellitus ( $P < 0.01$ ), there was no difference in serum A-FABP levels between participants with IGR and those with newly diagnosed type 2 diabetes mellitus for either men or women (both  $P > 0.05$ ). Serum A-FABP levels were observed to be higher in participants with microalbuminuria, and this difference was found in men with IGR, men with newly diagnosed type 2 diabetes mellitus, women with IGR and women with newly diagnosed type 2 diabetes mellitus (all  $P < 0.05$ ; Figure 1).

### Associations between different variables and UACR

Spearman's correlation analyses showed that serum A-FABP levels were positively associated with UACR in both men and women ( $P = 0.005$  and  $P < 0.001$ , respectively). In addition, BMI, W, SBP, FPG, 2hPG, HbA1c, HOMA-IR, TG, CRP and eGFR also showed positive correlations with UACR in both sexes (all  $P < 0.05$ ). The positive associations of DBP ( $P = 0.031$ ) and TC ( $P < 0.001$ ) with UACR were observed only in men. In women, age (positive,  $P = 0.004$ ) and HDL-c levels (negative,  $P = 0.001$ ) were significantly related to UACR (Table 2).

### Multiple stepwise regression analyses of UACR

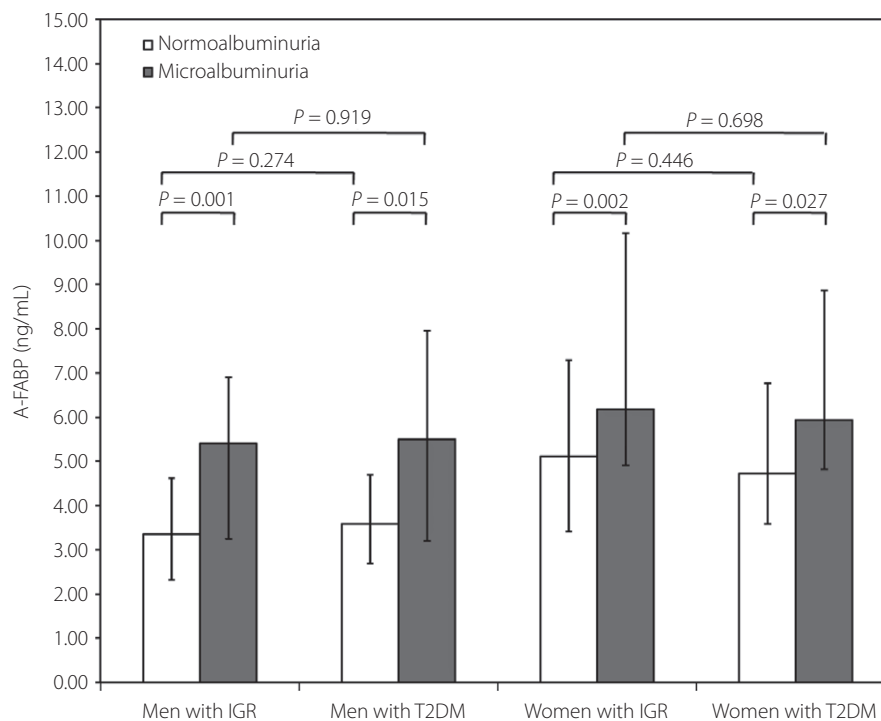
Multiple stepwise regression analysis defined UACR as a dependent variable and serum A-FABP levels as one of the independent variables. The additional independent variables included age, BMI, W, SBP, DBP, HbA1c, HOMA-IR, TC, TG, HDL-c, low-density lipoprotein cholesterol, CRP, eGFR and smoking status. The results identified serum A-FABP levels as an independent and positive factor associated with UACR in both men (standardized  $\beta = 0.256$ ,  $P < 0.001$ ) and women (standardized  $\beta = 0.155$ ,  $P = 0.001$ ). The independent and positive relationship between serum A-FABP levels and UACR remained significant even when the multiple stepwise regression analyses were carried out separately in men with IGR (standardized  $\beta = 0.258$ ,  $P < 0.001$ ), men with newly diagnosed type 2 diabetes mellitus (standardized  $\beta = 0.278$ ,  $P = 0.002$ ), women with IGR (standardized  $\beta = 0.157$ ,  $P = 0.003$ ) and women with newly diagnosed type 2 diabetes mellitus (standardized  $\beta = 0.302$ ,  $P = 0.003$ ; Table 3).

## DISCUSSION

In the present study, we observed that hyperglycemic individuals with microalbuminuria showed higher serum levels of A-FABP, and the serum A-FABP levels were identified as an independent factor positively associated with the UACR. Despite the significant sex difference in serum A-FABP levels, the relationship between serum A-FABP levels and the UACR held true for both men and women.

Accumulating clinical evidence showed that the presence of microalbuminuria was not only an early predictor of deteriorative renal function, but also a dominant risk factor for cardiovascular diseases in patients with diabetes mellitus<sup>2</sup>. A previous study carried out in the general population also supported an





**Figure 1** | Subgroup comparisons of serum adipocyte fatty acid-binding protein (A-FABP) levels between patients with microalbuminuria and those with normoalbuminuria. Serum A-FABP levels are expressed as median values with interquartile ranges. IGR, impaired glucose regulation; T2DM, type 2 diabetes mellitus.

association of microalbuminuria with all-cause mortality and specifically cardiovascular mortality<sup>22</sup>. Therefore, screening and diagnosis of microalbuminuria are of great importance for individuals with diabetes, and even those without diabetes, to prevent advanced kidney disease, cardiovascular events and death in the early phase. Clinical investigations discovered that serum A-FABP levels were much higher in diabetes patients with microalbuminuria and macroalbuminuria than in those with normoalbuminuria<sup>10</sup>; and across groups of patients with normoalbuminuria, microalbuminuria and macroalbuminuria, serum A-FABP levels showed an increasing trend<sup>11</sup>. In line with these clinical findings, the present study was carried out among a hyperglycemic population, and showed that serum A-FABP levels were increased significantly in participants with microalbuminuria.

Our previous epidemiological study showed that compared with individuals with normal glucose tolerance, individuals with newly diagnosed type 2 diabetes mellitus, even those with prediabetes (IGR), were more likely to develop microalbuminuria<sup>12</sup>. Nevertheless, there were limited data regarding the relationship between serum A-FABP levels and microalbuminuria, available only in patients with diabetes. Toruner *et al.*<sup>10</sup> selected a total of 87 patients with type 2 diabetes mellitus as their study population, and found that serum A-FABP levels were independently and positively associated with the albumin excretion rate, suggesting an involvement of increased serum

A-FABP levels in the occurrence and development of microalbuminuria among patients with type 2 diabetes mellitus. Furthermore, researchers from Hong Kong<sup>11</sup> also observed that, among patients with diabetes mellitus, serum A-FABP levels were shown to be independently associated with the severity of nephropathy for micro- and macroalbuminuria vs normoalbuminuria, respectively. Their findings raised the possibility that A-FABP might be used as a serum biomarker for stratifying nephropathy stages in patients with diabetes mellitus. Indirect evidence supporting an association between the serum A-FABP levels and microalbuminuria was reported by a study carried out in a rural population. In the study of Okazaki *et al.*<sup>23</sup>, urine A-FABP levels were correlated with serum A-FABP levels and UACR, respectively, providing a link between them. However, the overall results have not been entirely consistent. Another study with a small sample size<sup>24</sup> failed to find a relationship between serum A-FABP levels and microalbuminuria. After excluding the participants who received antihypertensive or lipid-lowering therapy at the time of the study to eliminate the influence of such medicines, the present study included, but was not restricted to, individuals with newly diagnosed type 2 diabetes mellitus. Individuals with IGR also were selected for inclusion in the study population. The results showed an independent and positive association between the serum A-FABP levels and the UACR in this hyperglycemic population. Given these clinical associations, we propose that the serum A-FABP

**Table 2** | Spearman's correlation analysis of the urinary albumin-to-creatinine ratio

Variable	Men		Women	
	r	P	r	P
Age	-0.048	0.318	0.127	0.004
BMI	0.113	0.018	0.163	<0.001
W	0.124	0.010	0.202	<0.001
SBP	0.251	<0.001	0.134	0.003
DBP	0.103	0.031	0.010	0.831
eGFR	0.188	<0.001	0.106	0.017
FPG	0.217	<0.001	0.120	0.007
2hPG	0.126	0.009	0.162	<0.001
HbA1c	0.217	<0.001	0.141	0.002
HOMA-IR	0.145	0.002	0.196	<0.001
TC	0.192	<0.001	0.034	0.445
TG	0.138	0.004	0.172	<0.001
HDL-c	0.048	0.317	-0.153	0.001
LDL-c	0.082	0.089	0.008	0.864
CRP	0.143	0.003	0.198	<0.001
A-FABP	0.134	0.005	0.174	<0.001

2hPG, 2-h plasma glucose; A-FABP, adipocyte fatty acid binding protein; BMI, body mass index; CRP, C-reactive protein; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FINS, fasting serum insulin; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HDL-c, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment-insulin resistance; IGR, impaired glucose regulation; LDL-c, low-density lipoprotein cholesterol; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus; TC, total cholesterol; TG, triglyceride; W, waist circumference; UACR, urinary albumin-to-creatinine ratio.

level can be used as an indicator of microalbuminuria not only in diabetes patients with early stage disease, but also for hyperglycemic individuals before the development of diabetes.

Hsu *et al.*<sup>25</sup> enrolled 738 normoalbuminuric patients with type 2 diabetes mellitus in their prospective study between 2003 and 2005, and followed them to the end of 2009. They discovered that patients who experienced advanced microalbuminuria had an increased HOMA-IR at baseline. From the lowest to the highest HOMA-IR quartiles, the incidences of microalbuminuria increased. Similarly, the present study uncovered a positive correlation between HOMA-IR and UACR in both sexes. Furthermore, HOMA-IR was an independent and positive factor associated with UACR in women. The results were suggestive of a critical role for insulin resistance in the onset and progression of microalbuminuria. Based on our previous findings that the serum A-FABP levels were independently and positively associated with insulin resistance<sup>14,26</sup>, insulin resistance was implicated as a central factor linking the serum A-FABP levels and microalbuminuria.

The underlying mechanism through which A-FABP might contribute to microalbuminuria remains to be determined. Tanaka *et al.*<sup>27</sup> retrospectively selected a total of 112 consecutive patients who had undergone renal biopsy to subsequently assess the expression of A-FABP protein and messenger ribonucleic acid, and such expression was finally found not only in peritubular capillaries, but also in endothelial cells and macrophages in the glomerulus. They further discovered that the ratio of the A-FABP-positive area to the total area within glomeruli was positively correlated with the urinary protein

**Table 3** | Multivariate linear regression analysis of the urinary albumin-to-creatinine ratio

	Independent variable	Men			Independent variable	Women		
		Standardized β	t	P		Standardized β	t	P
Total	A-FABP	0.256	5.830	<0.001	A-FABP	0.155	3.385	0.001
	Age	0.137	2.517	0.012	Age	0.319	5.239	<0.001
	SBP	0.269	6.228	<0.001	SBP	0.092	2.168	0.031
	eGFR	0.259	4.759	<0.001	eGFR	0.297	4.830	<0.001
	HbA1c	0.137	3.111	0.002	HOMA-IR	0.176	3.893	<0.001
Impaired glucose regulation	HDL-c				HDL-c	-0.094	-2.151	0.032
	A-FABP	0.258	5.048	<0.001	A-FABP	0.157	3.024	0.003
	Age	0.225	3.511	0.001	Age	0.351	5.145	<0.001
	SBP	0.228	4.522	<0.001	eGFR	0.319	4.565	<0.001
	eGFR	0.292	4.559	<0.001	HOMA-IR	0.135	2.674	0.008
	TC	0.154	3.061	0.002	HDL-c	-0.101	-2.069	0.039
Type 2 diabetes mellitus	CRP	0.128	2.562	0.011				
	A-FABP	0.278	3.244	0.002	A-FABP	0.302	3.103	0.003
	SBP	0.266	3.093	0.003	SBP	0.295	3.088	0.003
	eGFR	0.303	3.515	0.001	HDL-c	-0.219	-2.253	0.027

Independent variables originally included: adipocyte fatty acid binding protein (A-FABP), age, body mass index (BMI), waist circumference (W), systolic blood pressure (SBP), diastolic blood pressure (DBP), estimated glomerular filtration rate (eGFR), glycated hemoglobin (HbA1c), homeostasis model assessment-insulin resistance (HOMA-IR), total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), C-reactive protein (CRP) and smoking status.

levels. Macrophage accumulation in the kidney is the origin of inflammation in the progression of nephropathy in patients with diabetes mellitus<sup>11</sup>. In macrophages, the expression of A-FABP was mediated by pro-inflammatory stimuli<sup>28</sup>, and in turn, modulates the production of inflammatory cytokine<sup>6</sup>. Thus, it is possible that the ectopic A-FABP expression in macrophages and inflammation are mutually enhanced in the glomerulus, resulting in renal injury and the onset of microalbuminuria. Additionally, animal studies showed that treatment with an A-FABP inhibitor improved whole-body insulin sensitivity of *ob/ob* mice<sup>29</sup>, and targeted disruption of the A-FABP gene alleviated insulin resistance induced by dietary or genetic obesity in mice<sup>6</sup>, which suggested that A-FABP contributed to insulin resistance. Insulin resistance, accompanied by hyperinsulinemia, causes changes in the steady state of renal endothelial functions and hemodynamic harmonization, and eventually leads to the occurrence and progression of microalbuminuria.

The major limitation of the present study was the cross-sectional design, because it was difficult to clarify the cause-effect relationship between the increase in serum A-FABP levels and the presence of microalbuminuria. Additionally, the small sample size of the microalbuminuria groups could affect the statistical significance of the results, even though the prevalence of microalbuminuria in individuals with IGR and newly diagnosed type 2 diabetes mellitus was comparable with previously reported values<sup>12</sup>. Furthermore, given the preserved kidney function in all of the participants, it was difficult to explore the relationship between serum A-FABP levels and chronic kidney disease stages. Further prospective studies are warranted to confirm and generalize the present findings in a larger population with different chronic kidney disease stages.

In conclusion, the present study showed that in a hyperglycemic population, serum A-FABP levels increased in the presence of microalbuminuria. In addition, the serum A-FABP levels were identified as an independent factor positively associated with the UACR.

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## DISCLOSURE

The authors declare no conflict of interest.

## REFERENCES

- García-García PM, Getino-Melián MA, Domínguez-Pimentel V, *et al.* Inflammation in diabetic kidney disease. *World J Diabetes* 2004; 5: 431–443.
- KDOQI. KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease. *Am J Kidney Dis* 2007; 49: S12–S154.
- Hasan MJ, Muqueet A, Sharmeen A, *et al.* Prevalence of microalbuminuria in relation to glycemic control in type-2 diabetic patients in Mymensingh. *Mymensingh Med J* 2015; 24: 18–24.
- Wang Y. Small lipid-binding proteins in regulating endothelial and vascular functions: focusing on adipocyte fatty acid binding protein and lipocalin-2. *Br J Pharmacol* 2012; 165: 603–621.
- Fisher RM, Eriksson P, Hoffstedt J, *et al.* Fatty acid binding protein expression in different adipose tissue depots from lean and obese individuals. *Diabetologia* 2001; 44: 1268–1273.
- Xu A, Wang Y, Xu JY, *et al.* Adipocyte fatty acid-binding protein is a plasma biomarker closely associated with obesity and metabolic syndrome. *Clin Chem* 2006; 52: 405–413.
- Kralisch S, Fasshauer M. Adipocyte fatty acid binding protein: a novel adipokine involved in the pathogenesis of metabolic and vascular disease? *Diabetologia* 2013; 56: 10–21.
- Stejskal D, Karpisek M. Adipocyte fatty acid binding protein in a Caucasian population: a new marker of metabolic syndrome? *Eur J Clin Invest* 2006; 36: 621–625.
- Zhou M, Bao Y, Li H, *et al.* Deficiency of adipocyte fatty-acid-binding protein alleviates myocardial ischaemia/reperfusion injury and diabetes-induced cardiac dysfunction. *Clin Sci (Lond)* 2015; 129: 547–559.
- Toruner F, Altinova AE, Akturk M, *et al.* The relationship between adipocyte fatty acid binding protein-4, retinol binding protein-4 levels and early diabetic nephropathy in patients with type 2 diabetes. *Diabetes Res Clin Pract* 2011; 91: 203–207.
- Yeung DC, Xu A, Tso AW, *et al.* Circulating levels of adipocyte and epidermal fatty acid-binding proteins in relation to nephropathy staging and macrovascular complications in type 2 diabetic patients. *Diabetes Care* 2009; 32: 132–134.
- Wang Z, Wang FF, Zhu XJ, *et al.* Metabolic syndrome and microalbuminuria accompanied with hyperglycemia in community participants. *Zhonghua Yi Xue Za Zhi* 2012; 92: 2526–2529.
- Roshan B, Stanton RC. A story of microalbuminuria and diabetic nephropathy. *J Nephropathol* 2013; 2: 234–240.
- Bao Y, Ma X, Yang R, *et al.* Inverse relationship between serum osteocalcin levels and visceral fat area in Chinese men. *J Clin Endocrinol Metab* 2013; 98: 345–351.
- Hao Y, Ma X, Luo Y, *et al.* Associations of serum adipocyte fatty acid binding protein with body composition and fat distribution in nondiabetic Chinese women. *J Clin Endocrinol Metab* 2015; 100: 2055–2062.
- Levey AS, Stevens LA, Schmid CH, *et al.* A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; 150: 604–612.
- Matthews DR, Hosker JP, Rudenski AS, *et al.* Homeostasis model assessment: insulin resistance and beta-cell function

- from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985; 28: 412–419.
18. Department of Noncommunicable Disease Surveillance. Report of a WHO Consultation: definition, diagnosis and classification of diabetes mellitus and its complication. Part1: Diagnosis and classification of diabetes mellitus. Geneva: World Health Organization, 1999.
  19. Yang G, Fan L, Tan J, *et al.* Smoking in China: findings of the 1996 National Prevalence Survey. *JAMA* 1999; 282: 1247–1253.
  20. Zhang Z. Univariate description and bivariate statistical inference: the first step delving into data. *Ann Transl Med* 2016; 4: 91.
  21. Zhang Z. Variable selection with stepwise and best subset approaches. *Ann Transl Med* 2016; 4: 136.
  22. Hillege HL, Fidler V, Diercks GF, *et al.* Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in general population. *Circulation* 2002; 106: 1777–1782.
  23. Okazaki Y, Furuhashi M, Tanaka M, *et al.* Urinary excretion of fatty acid-binding protein 4 is associated with albuminuria and renal dysfunction. *PLoS One* 2014; 9: e115429.
  24. Cabré A, Lázaro I, Girona J, *et al.* Plasma fatty acid-binding protein 4 increases with renal dysfunction in type 2 diabetic patients without microalbuminuria. *Clin Chem* 2008; 54: 181–187.
  25. Hsu CC, Chang HY, Huang MC, *et al.* Association between insulin resistance and development of microalbuminuria in type 2 diabetes: a prospective cohort study. *Diabetes Care* 2011; 34: 982–987.
  26. Hao Y, Ma X, Luo Y, *et al.* Serum adipocyte fatty acid binding protein levels are positively associated with subclinical atherosclerosis in Chinese pre- and postmenopausal women with normal glucose tolerance. *J Clin Endocrinol Metab* 2014; 99: 4321–4327.
  27. Tanaka M, Furuhashi M, Okazaki Y, *et al.* Ectopic expression of fatty acid-binding protein 4 in the glomerulus is associated with proteinuria and renal dysfunction. *Nephron Clin Pract* 2014; 128: 345–351.
  28. Kazemi MR, McDonald CM, Shigenaga JK, *et al.* Adipocyte fatty acid-binding protein expression and lipid accumulation are increased during activation of murine macrophages by tolllike receptor agonists. *Arterioscler Thromb Vasc Biol* 2015; 25: 1220–1224.
  29. Furuhashi M, Tuncman G, Görgün CZ, *et al.* Treatment of diabetes and atherosclerosis by inhibiting fatty-acid-binding protein aP2. *Nature* 2007; 447: 959–965.