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Plasma Fatty Acid-Binding Protein 4 Increases with Renal Dysfunction in Type 2 Diabetic Patients without Microalbuminuria

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BACKGROUND: Fatty acid–binding protein 4 (FABP4) has been linked to metabolic syndrome development, diabetes, and arteriosclerosis, but the role of FABP4 in target organ damage has not been assessed. We evaluated whether plasma FABP4 is associated with renal dysfunction in type 2 diabetic patients.

METHODS: In 263 individuals (161 type 2 diabetic patients and 102 healthy nondiabetic controls), we analyzed the correlation between FABP4 and creatinine or glomerular filtration index (MDRD-GFR) regarding the presence or absence of microalbuminuria. Patients with severe chronic kidney disease (MDRD-GFR <30 mL/min/1.73 m^2) or albuminuria were not included.

RESULTS: FABP4 concentrations were higher in diabetic patients with MDRD-GFR <60 mL/min/1.73 m^2 (P <0.001). We observed a significant, direct correlation between FABP4 and creatinine (r = 0.446, P <0.001) and an inverse correlation between FABP4 and MDRD-GFR (r = −0.511, P <0.001) in type 2 diabetic patients, but not in nondiabetic individuals. These correlations were sustained when only those patients without microalbuminuria were analyzed (r = 0.414, P <0.001 and r = −0.510, P <0.001, respectively). Type 2 diabetic patients with FABP4 in the highest tertile compared with those in the lower tertiles had increased adjusted odds ratios for moderate renal dysfunction [7.5 (95%CI 1.8–30.7), P = 0.005 and 15.3 (3.1–76.4), P = 0.001; respectively], independent of microalbuminuria.

CONCLUSIONS: High FABP4 plasma concentrations are associated with high plasma creatinine and low MDRD-GFR in patients with type 2 diabetes even in the absence of microalbuminuria or clinically relevant alterations of creatinine and MDRD-GFR values. FABP4 concentrations should be taken into consideration as an early marker of kidney damage in patients with type 2 diabetes.

It is becoming increasingly evident that several molecules derived from adipose tissue are not only associated with adiposity and inflammation, but are also involved in the development of insulin resistance. Among them, some members of the lipocalin family—retinol-binding protein 4 (RBP4),[2] lipocalin-2, and fatty acid-binding protein 4 (FABP4)—have been suggested to play important roles in the mechanisms of insulin resistance. They have been proposed as early markers for adiposity associated with metabolic syndrome *(1–5)*. FABP4 is produced by adipocytes and macrophages during their differentiation and intracellular lipid accumulation *(6–10)*. Its main role seems to be intracellular fatty acid transport. Recently, our group and others have communicated that FABP4 plasma concentrations correlate to metabolic syndrome components in diabetic and nondiabetic individuals *(3, 4, 6, 11)*. Furthermore, plasma FABP4 is considered an early marker of metabolic risk for metabolic syndrome development *(11)*. Although FABP4 concentrations seem to be associated with adiposity, other factors such as inflammation status could also influence its concentrations *(6)*. Our group has observed that FABP4 plasma concentrations in type 2 diabetic patients are also associated with high triglycerides, increased lipid peroxidation, and inflammation markers *(6)*; however, the role of FABP4 in target organ damage has not been fully assessed. The pres-

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[2] Nonstandard abbreviations: RBP4, retinol-binding protein 4; FABP4, fatty acid–binding protein 4; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; BMI, body mass index; OR, odds ratio.

ence of a genetic variation (T-87C) at the FABP4 locus results in reduced triglyceride concentrations and significantly reduces the risk for developing either diabetes or cardiovascular disease *(12)*. Furthermore, plasma FABP4 concentrations are independent determinants of carotid IMT in Chinese women *(13)* but are not associated with macrovascular disease in type 2 diabetic patients *(6)*. It has been observed that human liver- and heart-type FABP (FABP1 and FABP3) are expressed in the proximal and distal renal tubular cells, respectively *(14, 15)*, and increased amounts of FABP1 in urine have been postulated as a clinical marker of renal tubulointerstitial damage *(16, 17)*. No data have been published associating FABP4 with renal function, however. The members of the lipocalin family are low-molecular-weight proteins that normally undergo glomerular filtration and tubular reabsorption and could accumulate in plasma during alterations of renal function *(18)*. Lipocalin-2 has been suggested to be a good marker of glomerular dysfunction *(19, 20)*, and we have communicated that high RBP4 plasma concentrations are associated with the early stages of chronic kidney disease in type 2 diabetic patients *(21)*. In this study, we investigated whether FABP4 plasma concentrations are also associated with renal damage in type 2 diabetic patients.

Materials and Methods

CLINICAL STUDY

We studied 263 individuals: 161 type 2 diabetic patients and 102 nondiabetic controls (36–79 years old). The type 2 diabetic patients were diagnosed via criteria from the American Diabetes Association *(22)* and were recruited in the Hospital Universitari Sant Joan de Reus. The control group was randomly selected among individuals with neither diabetes nor metabolic syndrome from a general population sample collection obtained from the same geographic area. Both groups were within the same age interval and matched for sex. Anamnesis and clinical examination, including anthropometrics and blood pressure measurements, were carried out, and we assessed renal dysfunction by estimated glomerular filtration rate (GFR) using the Modification of Diet in Renal Disease (MDRD) equation *(23)*. We also calculated the estimated creatinine clearance by the Cockcroft-Gault equation *(24)*; the data are presented as GFR by the MDRD equation (MDRD-GFR). We defined renal dysfunction according to the recommendations of the National Kidney Foundation *(25)*. Patients with MDRD-GFR $<$60 mL/min/1.73 m^2 were considered to have moderately decreased GFR; type 2 diabetic patients and controls with severely decreased GFR (MDRD-GFR $<$30 mL/min/1.73 m^2) according to chronic kidney disease classification by the National Kidney Foundation were not included, and all control group participants had GFR $>$60 mL/min/1.73 m^2. Carotid and femoral echo-Doppler as well as ankle-brachial index (ABI) were also performed; arteriosclerosis was defined as clinical history of at least one of the following: coronary heart disease, stroke, peripheral vascular disease, $\geq$1 significant arteriosclerotic plaque ($>$40% stenosis), or ABI index $\leq$0.9 or $\geq$1.3. Microalbuminuria was defined as albuminuria $\geq$30 mg/24 h. Patients with albuminuria ($\geq$300 mg/24 h), type 1 diabetes, secondary diabetes, morbid obesity [body mass index (BMI) $>$40 kg/m^2], familial hypercholesterolemia, malignancy, liver disorder, or acute or chronic inflammation were not included. All participants gave written informed consent, and the hospital ethics committee approved the study.

ANALYTICAL METHODS

We measured plasma lipids using enzymatic assays adapted for the Cobas-Mira autoanalyzer (Roche); HbA_{1c} by HPLC on the Hi-auto A1c HA-8140 (Arkray KDR Corporation-Menarini Diagnostics); and glucose, insulin, and creatinine on the automatic autoanalyzer Synchron LXi 725-Synchron Access Clinical Systems (Beckman Coulter) using enzymatic assays, chemiluminescent immunoassays, or colorimetric assays that were adapted to this system. We assessed plasma concentrations of FABP4 by commercial ELISA (BioVendor Laboratory Medicine Inc.) *(4, 11, 13)*. The performance characteristics for this assay were 5.3% CV intraassay and 3.9% CV interassay. The antibodies in human FABP4 ELISA are highly specific for human FABP4, with no detectable cross-reactivity to human FABP1, FABP2, FABP3, or FABP5.

STATISTICAL ANALYSIS

All data are presented as the mean (SD) except where otherwise stated. Statistical analysis used SPSS software (version 13.0, SPSS Inc.). We compared variables between groups using 1-way ANOVA and used univariate linear general models for adjusting results of continuous variables for age and sex. We compared category distributions between groups using the Fisher test and binary logistic regression models for adjusting results of categorical variables for age, sex, and BMI. FABP4 concentrations were categorized into sex-adjusted tertiles. We determined partial Pearson correlation coefficients between FABP4 and other continuous variables using a partial correlation test adjusted for age, sex, and BMI. A binary logistic regression model was used to identify the predictive role of being classified in the highest sex-adjusted FABP4 tertile for the presence of renal dysfunction (MDRD-GFR $<$60 mL/min/1.73 m^2). Adjusted odds ratios (ORs) and their 95% CIs were rep-

Table 1. Clinical and biochemical parameters of type 2 diabetic patients and nondiabetic controls according to MDRD-GFR status.

	MDRD-GFR ≥60		MDRD-GFR <60
	Nondiabetic	Type 2 diabetes	Type 2 diabetes
n (% women)	102 (51)	130 (50)	31 (58)
Age, years	59 (9)	62 (10)	67 (6)[b]
Weight, kg	74.2 (12.0)	77.7 (13.3)[c]	79.8 (10.3)
BMI, kg/m^2	28.8 (4.3)	30.0 (4.3)[c]	31.1 (4.6)
Systolic blood pressure, mmHg[a]	139 (19)	140 (19)	144 (17)
Diastolic blood pressure, mmHg[a]	83 (14)	80 (11)	79 (11)
Hypertension, n (%)	32 (31)	77 (59)[d]	29 (94)[b]
Diabetes duration, years[a]	0	13 (7)[d]	19 (8)[b]
Glucose, mmol/L	5.1 (0.8)	9.5 (3.0)[d]	9.6 (3.3)
Insulin, pmol/L[a]	—	74.0 (94.6)	74.8 (49.7)
HOMA-IR[a]	—	4.2 (4.8)	4.2 (3.1)
HbA_{1c}, %	—	6.9 (1.1)	7.5 (1.2)[b]
Triglycerides, mmol/L[a]	1.3 (0.7)	1.7 (1.0)[d]	1.9 (1.2)
Total cholesterol, mmol/L	5.8 (0.8)	4.7 (0.8)[d]	4.7 (0.8)
LDL cholesterol, mmol/L	3.7 (0.8)	2.8 (0.7)[d]	2.7 (0.7)
HDL cholesterol, mmol/L	1.5 (0.4)	1.1 (0.3)[d]	1.1 (0.3)
FABP4, μg/L[a]	22.7 (10.9)	33.7 (20.0)[d]	53.3 (23.6)[e]
Serum creatinine, μmol/L[a]	71 (12)	78 (11)[d]	116 (24)[e]
MDRD-GFR, mL/min/1.73 m^2	92 (15)	82 (13)[d]	51 (8)[e]
Clinical or subclinical arteriosclerosis, n (%)	—	51 (39)	19 (61)[b]
Nephropathy, n (%)	—	39 (30)	16 (52)
Retinopathy, n (%)	—	26 (20)	19 (61)[b]
Polyneuropathy, n (%)	—	34 (26)	16 (52)[b]
Insulin treatment, n (%)	—	52 (40)	21 (68)[b]
Lipid-lowering treatment, n (%)	—	69 (53)	17 (55)
Oral antidiabetic treatment, n (%)	—	73 (56)	10 (32)

Data are mean (SD) unless otherwise noted. Group comparisons by 1-way ANOVA (continuous variables) or Fisher test (categorical variables) were adjusted for age and sex by a univariate linear general model or by binary logistic regression, respectively. [a] Log transformed before analysis. [c] $P < 0.05$ and [d] $P < 0.001$ for comparisons between type 2 diabetic patients and nondiabetic controls with MDRD-GFR >60; [b] $P < 0.05$ and [e] $P < 0.001$ for comparisons between type 2 diabetic patients with MDRD-GFR<60 and MDRD-GFR ≥60. HOMA-IR, homeostasis model assessment of insulin resistance.

resented as a Forest plot. In all cases, a P value <0.05 was considered statistically significant.

Results

Clinical and biochemical characteristics are presented in Table 1 according to diabetes and renal function. Among type 2 diabetic patients, those with MDRD-GFR <60 had 1.6-fold higher concentrations of FABP4 in plasma than those with MDRD-GFR ≥60 [53.3 (23.6) vs 33.7 (20.0) μg/L, $P < 0.001$], after adjustment for age and sex (Table 1). Both groups had significantly higher FABP4 concentrations than the nondiabetic control group ($P < 0.001$) after adjustment for age and sex (Table 1). FABP4 concentrations in the diabetic group significantly increased ($P < 0.001$) across chronic kidney disease stages as defined by the National Kidney Foundation (17% of participants were in stage 1, 66% in stage 2, and 17% in stage 3) after adjustment for age and sex. This association was not observed in the control group ($P = 0.460$; 53% were in stage 1 and 47% in stage 2) (Fig. 1A).

Serum creatinine concentrations increased ($P < 0.001$) and MDRD-GFR decreased ($P < 0.001$) along with sex-adjusted tertiles of FABP4 in type 2 diabetic patients, but not in nondiabetic controls (Fig. 1B).

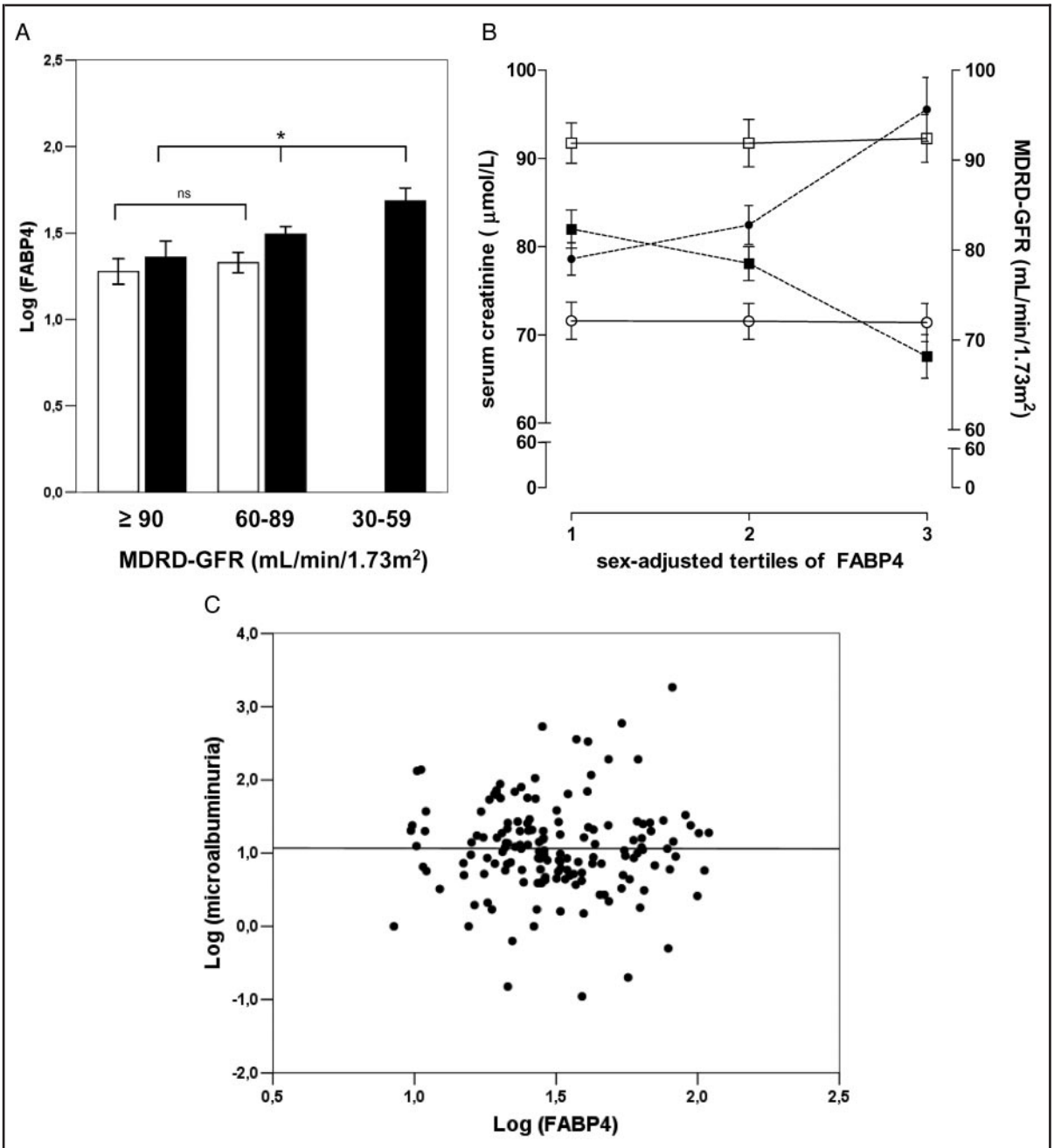

Fig. 1. A. Plasma FABP4 values stratified by stage of chronic kidney disease for nondiabetic controls (white bars) and type 2 diabetic patients (black bars).

Data are means ± SE. Group comparisons by 1-way ANOVA were adjusted for age and sex using a univariate linear general model $*P < 0.001$. NS, non significant. B. Serum creatinine concentrations (circles) and MDRD-GFR values (squares) stratified by sex-adjusted tertiles of plasma FABP4 for nondiabetic controls (solid lines and white symbols) and type 2 diabetic patients (dotted lines and black symbols). Data are means ± SE. Group comparisons by 1-way ANOVA and Bonferroni post hoc analysis. $*P < 0.001$. C. Relation of microalbuminuria and plasma FABP4 in type 2 diabetic patients. The solid line represents the regression line.

Table 2. FABP4 correlations in participants without microalbuminuria.

	All				Type 2 diabetic			
	Nondiabetic		Type 2 diabetic		MDRD-GFR ≥60		MDRD-GFR <60	
	Rho	*P*	*Rho*	*P*	*Rho*	*P*	*Rho*	*P*
Serum creatinine[a]	0.074	0.502	0.414	<0.001	0.151	0.135	0.188	0.427
MDRD-GFR	−0.153	0.159	−0.510	<0.001	−0.336	0.001	−0.204	0.363
Microalbuminuria[a]	—	—	0.060	0.511	0.057	0.576	0.057	0.812

Partial Pearson correlation coefficients were calculated using a partial correlation test adjusted for age, sex, and BMI.
[a] Log transformed before analyses.

Among type 2 diabetic patients, 17% had microalbuminuria. Microalbuminuria was not correlated with FABP4 concentrations in all diabetic patients (Fig. 1C) or according to their renal function state (Table 2). We observed a significant direct correlation between plasma FABP4 and serum creatinine concentrations ($r = 0.446$, $P < 0.001$) and an inverse correlation between plasma FABP4 concentrations and MDRD-GFR values ($r = -0.511$, $P < 0.001$) in type 2 diabetic patients, but not in nondiabetic controls. These correlations remained when only those nonmicroalbuminuric type 2 diabetic patients were taken into consideration, after adjustment for age, sex, and BMI (Table 2). Both correlations remained after adjustment for the presence of hypertension, diabetes control, diabetes duration, plasma concentrations of triglycerides, LDL cholesterol, and HDL cholesterol ($r = -0.444$, $P < 0.001$ for MDRD-GFR and $r = 0.381$, $P < 0.001$ for creatinine). These correlations also remained in the presence of vascular disease and thiazolidinedione treatment in the statistical adjustment ($r = -0.485$, $P < 0.001$ for MDRD-GFR and $r = 0.424$, $P < 0.001$ for creatinine).

A binary logistic regression model—including age, BMI, diabetes duration, diabetes control, hypertension, vascular disease, high triglycerides, high LDL cholesterol, low HDL cholesterol cutoffs, and sex-adjusted tertiles of FABP4 as independent variables—revealed that type 2 diabetic patients in the highest sex-adjusted tertile of FABP4 concentrations had significantly higher adjusted ORs for having abnormal renal function (defined as moderately decreased GFR or stage 3 of chronic kidney disease) than those in the lower 2 tertiles [OR 7.5, (95%CI 1.8–30.7), $P = 0.005$ for highest vs middle tertile and OR 15.3 (3.1–76.4), $P = 0.001$ for highest vs lowest tertile] (Fig. 2).

Discussion

In this study, we report for the 1st time that FABP4 plasma concentrations are inversely associated with GFR in a diabetic population but not in a healthy nondiabetic population. Interestingly, this association was observed even in those participants with MDRD-GFR concentrations >60 and without microalbuminuria. These findings suggest that FABP4 plasma concentrations could be an early clinical marker of renal function derangement in type 2 diabetic patients.

The physiological function of plasma FABP4 is not known. FABP4 plasma concentrations are associated with adiposity and metabolic syndrome and have been shown to be markers for metabolic risk *(3, 4, 6, 11)*. Those individuals with higher FABP4 concentrations have a higher rate of metabolic syndrome development *(11)*. Although there is a lot of recent information about FABP4 concentrations and metabolic syndrome, obesity, and type 2 diabetes, the association between FABP4 plasma concentrations and target organ damage has not been fully investigated. Recent studies show contradictory results about the role of plasma FABP4 on macrovascular disease *(6, 12, 13, 26, 27)*; however, the association between plasma FABP4 and renal function has not been reported.

Because our diabetic group was selected between individuals not suffering from severe kidney disease, we cannot analyze the role of FABP4 as a marker of renal failure. However and more interestingly, we have observed a striking association with glomerular filtration markers. Lipocalins are small proteins that undergo glomerular filtration and subsequent tubular reabsorption *(18)*, although specific data on FABP4 renal metabolism is lacking. Regarding our observations, small functional changes in renal filtration mechanisms could diminish the filtration rate of FABP4 or increase its reabsorption, leading to an increase in plasma concentrations. Microalbuminuria is the most reliable marker of kidney damage risk in diabetic and hypertensive patients *(28–30)*. It has been considered an indicator of renal endothelial function and clearly predicts the development of chronic kidney disease in diabetic patients *(31)*. However, as has

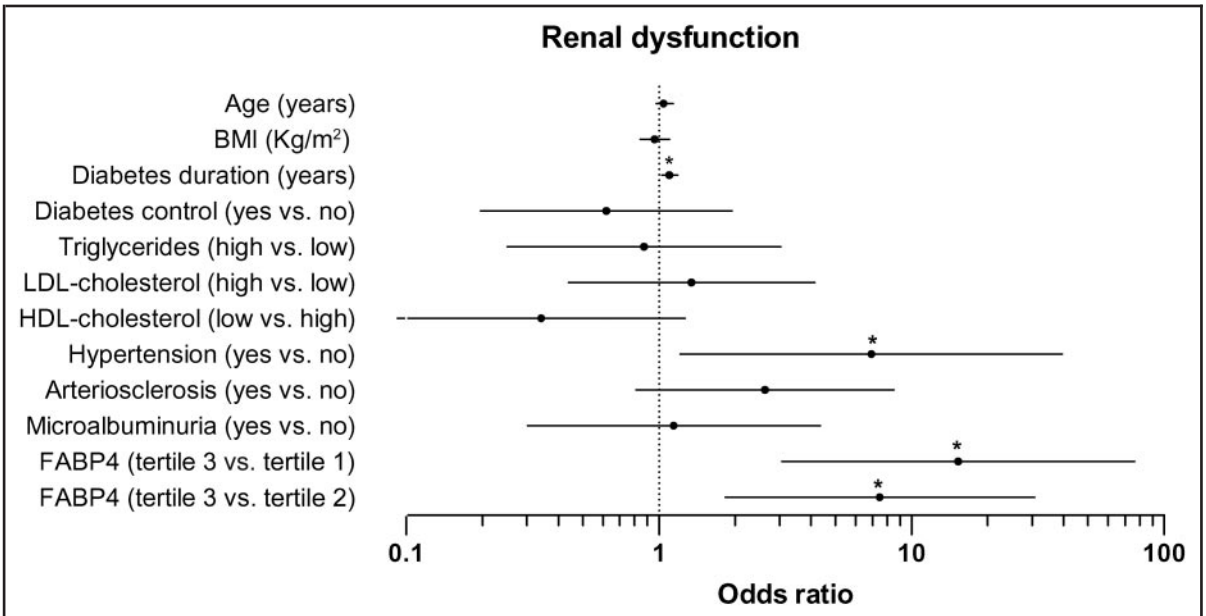

Fig. 2. Forrest plot for renal dysfunction (MDRD-GFR <60 mL/min/1.73 m^2).

Horizontal lines represent adjusted ORs and 95% CIs obtained by binary regression. *P <0.05. Diabetes control (HbA_{1c} <7%); hypertension (systolic blood pressure >130 mm Hg, diastolic blood pressure >85 mm Hg, or pharmacological treatment); high triglycerides (>1.69 mmol/L); low HDL cholesterol [<1.03 mmol/L (men) or <1.29 mmol/L (women) or pharmacological treatment]; high LDL cholesterol (> 2.57 mmol/L). FABP4 tertiles were adjusted for sex.

been observed in our work, microalbuminuria is not related to glomerular function during the early stages of kidney disease. FABP4 concentrations were associated with glomerular filtration parameters and their plasma concentrations were, along with high blood pressure, the main determining factors for a reduced MDRD-GFR value independent of microalbuminuria. Moreover, FABP4 was inversely correlated with MDRD-GFR even in the absence of microalbuminuria in diabetic patients. This finding suggests that FABP4 and microalbuminuria are probably expressed during different forms of kidney dysfunction, as we have recently observed for RBP4 *(21)*, another member of the lipocalin family. Because FABP4 is highly synthesized in obese individuals and those with metabolic syndrome, its biomarker utility could be higher in this group of patients.

We have no evidence about any direct deleterious effects of FABP4 on target organs. As mentioned above, in animal experiments, the deletion of the *FABP4* gene seems to be associated with vascular protection *(26, 27)*; however, no data on effects in other organs are available. Although we have observed that high FABP4 concentrations are associated with increased oxidative stress and inflammatory markers in diabetes *(6)*, the hypothesis that FABP4 could be an etiological agent for renal disease would be rather speculative. FABP1 has been shown to be expressed by NEFA in renal tubular cells *(14, 15)*, and its urine concentrations are considered a marker of renal interstitial damage *(16, 17)*. There is no evidence about FABP4 expression in renal tissue.

High FABP4 plasma concentrations are associated with high plasma creatinine and low glomerular filtration rates (MDRD-GFR) in patients with type 2 diabetes even in the absence of microalbuminuria or clinically relevant alterations in creatinine and MDRD-GFR values. Along with its role as a metabolic derangement marker, plasma FABP4 concentrations should be taken into consideration as an early marker of kidney damage in type 2 diabetes.

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