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Retinol binding protein 4 concentrations are influenced by renal function in patients with type 2 diabetes mellitus

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Abstract

Retinol binding protein 4 (RBP-4), a newly discovered adipocytokine, has been involved in glucose and lipid metabolism. We assess the impacts of renal function on plasma RBP-4 levels in patients with type 2 diabetes mellitus with a wide range of nephropathy. Plasma RBP-4 levels were measured using the enzyme immunoassay method in 38 type 2 diabetes mellitus patients with nephropathy and were compared with those in 20 patients with normoalbuminuria. The levels of plasma RBP-4 were increased by 1.4- and 3.3-fold in patients with renal disease with macroalbuminuria ($P = .04$) and end-stage renal disease (plasma creatinine level >2.0 mg/dL) ($P < .0001$) compared with those in patients with normal renal function. In addition, RBP-4 levels were correlated with the creatinine level and 24-hour creatinine clearance (Ccr) on simple and multiple regression analyses in all patients. Furthermore, in patients having Ccr of more than 60 mL/min, RBP-4 levels were correlated with the homeostasis model assessment (HOMA)-r index and triglyceride (TGL) both on simple and multiple regression analyses. Interestingly, in patients having Ccr of less than 60 mL/min, RBP-4 levels were not correlated with the HOMA-r index and TGL on simple regression analysis. The RBP-4 concentrations are influenced by renal function in type 2 diabetes mellitus patients. In addition, RBP-4 levels were correlated with HOMA-r and TGL in diabetic subjects without end-stage renal disease.

1. Introduction

Retinol binding protein 4 (RBP 4), a newly discovered adipocytokine, has been involved in insulin resistance and obesity [1]. Retinol binding protein 4 is produced by peripheral tissues including liver and adipose tissues [2]. Injection of RBP-4 into mice decreases insulin signaling in muscle and induces the expression of the gluconeogenic enzyme phosphoenolpyruvate carboxykinase in the liver [2]. Retinol binding protein 4 has been involved in glucose and lipid metabolism in several clinical studies [3-8]. A recent study described that concentrations of the RBP-4 were elevated in plasma of diabetic patients and were higher in those with microalbuminuria [9]. The result suggests that plasma RBP-4 levels in patients with type 2 diabetes mellitus are affected by nephropathy.

However, little is known about the relationship between circulating RBP-4 levels and systemic insulin resistance in diabetic patients with nephropathy and what the clinical implication is. Especially, it has not been clarified whether end-stage renal disease in type 2 diabetes mellitus is associated with plasma RBP-4 levels that influence glucose and lipid metabolism.

To address the issue, the purpose of the present study was to investigate the association between a wide range of diabetic nephropathy and plasma RBP-4 levels that influence glucose and lipid metabolism in type 2 diabetes mellitus.

2. Methods

2.1. Subjects

We screened 68 consecutive Japanese patients with type 2 diabetes mellitus who were admitted to our department. Among these, 58 who did not have symptomatic organic heart disease as determined by physical examination, chest

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Table 1
Clinical characteristics of studied patients

	A. Normoalbuminemia	B. Microalbuminemia	C. Macroalbuminemia	D. Renal failure	*P*
n	20	14	14	10	
Age (y)	59 ± 14	58 ± 14	63 ± 12	63 ± 9	NS
Sex (male/female)	11/9	7/7	6/8	6/4	
Duration of diabetes (y)	8.1 ± 5.3	14.3 ± 6.2	15.4 ± 5.2	18.7 ± 6.7	A-B, A-C, A-D: $P < .01$
Height (cm)	159 ± 12	155 ± 13	157 ± 10	162 ± 11	NS
Body weight (kg)	67 ± 15	64 ± 13	63 ± 9.9	62 ± 13	NS
BMI (kg/m^2)	26.7 ± 5.3	26.3 ± 3.8	25.6 ± 3.6	23.5 ± 3.3	NS
SBP (mm Hg)	126 ± 17	135 ± 13	139 ± 29	151 ± 16	A-D: $P < .01$
DBP (mm Hg)	75 ± 15	74 ± 12	79 ± 13	80 ± 17	NS
AST (IU/L)	21 ± 8	25 ± 6	19 ± 3	22 ± 11	NS
ALT (IU/L)	22 ± 11	26 ± 12	21 ± 14	16 ± 3	NS
T-cho (mg/dL)	191 ± 36	198 ± 49	212 ± 31	182 ± 38	NS
TGL (mg/dL)	122 ± 55	132 ± 82	141 ± 78	130 ± 65	NS
FPG (mg/dL)	148 ± 37	135 ± 29	154 ± 26	139 ± 29	NS
F-IRI (μU/mL)	10.1 ± 4.4	9.5 ± 5.1	7.8 ± 3.0	8.2 ± 3.6	NS
HOMA index	3.5 ± 1.5	2.9 ± 1.3	2.9 ± 1.1	2.7 ± 1.7	NS
HbA_{1c} (%)	7.8 ± 1.2	7.5 ± 0.6	7.7 ± 0.8	7.1 ± 1.3	NS
BUN (mg/dL)	16 ± 4	15 ± 5	15 ± 4	40 ± 12	A-D, B-D, C-D: $P < .0001$
Cr (mg/dL)	0.6 ± 0.1	0.6 ± 0.1	0.7 ± 0.2	4.2 ± 3.1	A-D, B-D, C-D: $P < .0001$
U-micro TP (mg/Cr)	15 ± 6	63 ± 59	893 ± 884	NA	A-C, B-C: $P < .01$
U-macro TP (g/d)	0.15 ± 0.07	0.21 ± 0.11	1.1 ± 0.9	1.5 ± 2.0	A-D, B-D: $P < .01$, A-C, B-C: $P < .05$
Ccr (mL/min)	109 ± 27	121 ± 27	109 ± 61	21 ± 18	A-D, B-D, C-D: $P < .0001$
RBP-4 (μg/mL)	23.3 ± 2.5	25.7 ± 3.4	35.8 ± 3.8	84.4 ± 7.3	A-C: $P < .05$, A-D, B-D, C-D: $P < .0001$

Data are mean ± SD. DBP indicates diastolic blood pressure; AST, aspartate aminotransferase; ALT, alanine aminotransferase; FPG, fasting plasma glucose; F-IRI, fasting immunoreactive insulin; HbA_{1c}, hemoglobin A_{1c}; T-cho, total cholesterol; Cr, creatinine; U-micro TP, urine microalbuminemia; U-macro TP, urine macroalbuminemia; NA, not assessed; NS, not significant.

x-ray, 12-lead electrocardiography, and echocardiography were enrolled. We used 58 consecutive Japanese patients with type 2 diabetes mellitus who were admitted to our department. There were no significant differences between the numbers of patients treated with or without an α-glucosidase inhibitor, pioglitazone, statin, and calcium channel antagonist. The study was approved by the ethics review board of our institution, and prior informed consent was obtained from patients. All patients have no history of diabetic ketoacidosis.

2.2. Experimental protocol

Twenty-four–hour urine specimens were collected for 2 consecutive days to measure urinary albumin and creatinine excretions in all patients with diabetes; mean values of these parameters were adopted for data analyses. In the present study, the 58 patients with type 2 diabetes mellitus were divided into 4 subgroups of diabetic nephropathy, determined according to urinary albumin excretion (UAE) and plasma creatinine level (Cr) for data analyses as follows. The grouping was based on previous studies [10]: stage 1, 20 patients with normal UAE <30 mg per 24 hours; stage 2, 14 patients with microalbuminuria (30 < UAE < 300 mg per 24 hours); stage 3, 14 patients with overt proteinuria (UAE >300 mg per 24 hours; 10 patient had 24-hour creatinine clearance [Ccr] >60 mL/min, and 4 patients had Ccr <60 mL/min); and stage 4, 10 subjects with plasma Cr >2 mg/dL. A total of 58 patients with diabetes (20 in stage 1, 14 in stage 2, and 3 in stage 3) had Ccr >60 mL/min, and 14 subjects (4 in stage 3 and 10 in stage 4) had Ccr <60 mL/min.

2.3. Biochemical measurement

Plasma glucose levels were measured by the glucose oxidase method, hemoglobin A_{1c} levels were measured by high-performance liquid chromatography, plasma insulin levels were measured by enzyme-linked immunosorbent assay (Insulin EIA kit; Morinaga, Tokyo, Japan), and urinary albumin levels were measured by immunoturbidometry (TIA MicoAlb kit; Nittobo, Tokyo, Japan). Insulin resistance was evaluated by the homeostasis model assessment (HOMA) index ([fasting plasma insulin {in microunits per milliliter} × fasting plasma glucose {in millimoles per liter}]/22.5).

The methods used to generate polyclonal anti-human RBP-4 antibody and to validate the enzyme-linked immunosorbent assay system are commercially available (Adipogen, Seoul, Korea). Recombinant RBP-4 was added to each well of microtiter plate to a concentration of 100 ng/mL. The coated plate was then washed 3 times with phosphate-buffered saline (PBS) containing 1% bovine serum albumin and 0.05% Tween 20, blocked with 200 μL stabilizer (ABI, Columbia, MD) at 37°C for 1 hour, and washed 3 times with PBS containing 1% bovine serum albumin and 0.05% Tween 20. Along with RBP-4 with standards of concentration of 0.1 to 250 μg/mL, 50 μL of human plasma at a dilution of 1:100, which was collected from subjects who had fasted overnight, was applied to

Table 2
Simple regression analyses between RBP-4 and various parameters

Parameters	AII (N = 58)		Ccr >60 (L/d) (n = 44)		Ccr <60(L/d) (n = 14)	
	r	*P* value	*r*	*P* value	*r*	*P*
Height (cm)	0.227	.0868	0.291	.0557	−0.077	.7934
Body weight (kg)	0.003	.9833	0.218	.1554	0.110	.7092
BMI (kg/m^2)	−0.212	.1109	0.02	.8991	0.232	.4297
SBP (mm Hg)	0.279	.0338	0.158	.3067	−0.042	.8853
DBP (mm Hg)	0.256	.0521	0.124	.4213	0.451	.1056
AST (IU/L)	−0.231	.0808	−0.115	.4581	0.387	.1713
ALT (IU/L)	−0.246	.0631	0.035	.8213	0.076	.7975
T-cho (mg/dL)	−0.086	.5205	0.172	.2639	−0.092	.7540
TGL (mg/dL)	0.137	.3065	0.514	.0004	−0.207	.4777
FPG (nmol/mL)	−0.024	.8601	−0.032	.8349	0.286	.3221
F-IRI (μU/mL)	0.024	.8589	0.403	.0067	0.042	.8863
HOMA index	0.098	.4637	0.500	.0006	0.231	.4278
HbA_{1c} (%)	−0.161	.2282	−0.009	.9531	0.095	.7461
BUN (mg/dL)	0.814	<.0001	0.024	.8749	0.831	.0002
Cr (mg/dL)	0.783	<.0001	0.28	.0661	0.762	.0015
U-micro TP (mg/Cr)	NA	NA	0.119	.4429	NA	NA
U-macro TP (g/d)	0.38	.0033	0.123	.4281	0.002	.9942
Ccr (mL/min)	−0.457	<.0001	−0.2	.1927	−0.875	<.0001

See Table 1 for other abbreviations.

each test well. Afterward, 50 μL anti–RBP-4 was added to each well and incubated at 37°C for 1 hour. The secondary antibody reaction was performed at 37°C for 1 hour, and then each well was washed 3 times. Colorimetric reaction was performed for 20 minutes with the use of horseradish peroxidase–conjugated streptavidin diluted 1:1000 in PBS and 2,2′-azino-bis(2-ethylbenzothiazoline-6-sulfonic acid) as substrate. Optical densities were measured at 450 nm. Assay linearity was performed by diluting a serum having a known serum RBP-4 concentration of up to 1:8 and measuring the remaining RBP-4.

2.4. Statistical analysis

The data are presented as means ± SD and were analyzed by commercial software (StatView; SAS Institute, Cary, NC). Differences between the groups were analyzed by the Kruskal-Wallis test and/or Bonferroni multiple comparison test as appropriate. A *P* value of less than .05 was considered statistically significant. Simple (Spearman rank) correlation coefficients were calculated, and a stepwise multiple regression analysis was then used to evaluate the independent associations of these variables. For the multivariate analysis, F values of 4 or greater were considered significant.

3. Results

3.1. Clinical characteristics of patients with type 2 diabetes mellitus with or without diabetic nephropathy

The clinical characteristics of all patients with type 2 diabetes mellitus with or without diabetic nephropathy are shown in Table 1. There were no significant differences in age, sex, height, body weight, body mass index (BMI), fasting plasma glucose, insulin, total cholesterol, or triglyceride (TGL) levels between the patients with type 2 diabetes mellitus, respectively (Table 1). Systolic blood pressures (SBPs) in patients in stage 4 were significantly higher than those in patients in stage 1 ($P = .0002$).

Plasma blood urea nitrogen (BUN) and Cr in patients in stage 4 were significantly higher than those in patients in stages 1, 2, and 3 ($P < .0001$) (Table 1). In addition, urine microalbuminemia and macroalbuminemia in patients in stages 3 and 4 were significantly higher than those in patients in stages 1 and 2 ($P < .05$ or $P < .01$) (Table 1). Creatinine clearance was significantly increased in patients in stage 4 compared with those in stages 1, 2, and 3, respectively ($P < .0001$) (Table 1).

3.2. Levels of RBP-4 in patients with type 2 diabetes mellitus with or without diabetic nephropathy

Plasma RBP-4 levels in patients with diabetes were significantly increased according to degree of nephropathy (Table 1). The RBP-4 level was not changed in patients in stage 1 compared with patients in stage 2 ($P = .93$) (Table 1). The RBP-4 values in patients in both stage 3 and stage 4 were significantly higher than those in patients in stage 1 ($P = .04$ and $P < .0001$ for patients in stages 3 and 4, respectively). The levels of plasma RBP-4 were increased by 1.4- and 3.3-fold in patients with renal disease with macroalbuminemia and end-stage renal disease (Cr >2.0 mg/dL) compared with those in patients with normal renal function ($P = .04$ and $P < .0001$ for each) (Table 1).

3.3. Relationship between RBP-4 and clinical factors

Simple regression analyses showed that RBP-4 was correlated with various clinical factors (Table 2). Among these factors, SBP ($r = 0.28$, $P = .0338$), BUN ($r = 0.81$, $P < .0001$), macroalbuminuria ($r = 0.38$, $P < .0001$), Cr ($r = 0.78$, $P < .0001$), and Ccr ($r = −0.46$, $P < .0001$) exhibited strong associations with RBP-4 in all patients in stages 1 to 4 (Table 2). Next, SBP, BUN, macroalbuminuria, Cr, and Ccr were selected as the valuables of multiple regression analysis. On multiple regression analysis, RBP-4 levels were associated with Cr and Ccr (F = 14.5 for each) in patients in stages 1 to 4.

In patients in stages 1, 2, and 3 having Ccr >60 mL/min, RBP-4 levels were significantly correlated with fasting plasma insulin ($r = 0.40$, $P = .0067$), HOMA-r index ($r = 0.50$, $P = .0006$), and TGL ($r = 0.51$, $P = .0004$) on simple regression analysis (Table 2). In addition, plasma RBP-4 levels were associated with HOMA-r and TGL in diabetic subjects with Ccr with more than 60 mL/min on multiple regression analysis (F = 14.5 and 15.6 for each) (Table 3). Interestingly, in patients in stages 3 and 4 having Ccr of less than 60 mL/min, RBP-4 levels were not correlated with the HOMA-r index ($r = 0.23$, $P = .42$) and TGL ($r = −0.21$, $P = .48$) on simple regression analysis (Table 2).

Table 3
Stepwise regression analyses between RBP-4 and various parameters

Independent variables	Regression coefficient	Standard error	Standard regression coefficient	F
Ccr >60 mL/min				
HOMA-r	3.643	0.955	0.442	14.483
TGL	0.074	0.019	0.459	15.614
Ccr <60 mL/min				
24-h Ccr	−0.718	0.2	−0.627	12.867
Cr	3.092	1.529	0.353	4.089

See Table 1 for other abbreviations.

In patients in stages 3 and 4 having Ccr of less than 60 mL/min, RBP-4 levels were correlated with the BUN (r = 0.83, P = .0002), Cr (r = 0.76, P = .0015), and Ccr (r = −0.88, P < .0001) on simple regression analysis. Next, BUN, Cr, and Ccr were selected as the valuables of multiple regression analysis. On multiple regression analysis, plasma RBP-4 levels were associated with Cr (F = 4.1) and Ccr (F = 12.9) in diabetic subjects with Ccr of less than 60 mL/min on multiple regression analysis (Table 3).

4. Discussion

The present study has demonstrated the clinical implication of renal dysfunction on plasma RBP-4 levels in patients with type 2 diabetes mellitus with nephropathy. Previous studies reported that adipocytokines such as leptin and adiponectin have been elevated in renal dysfunction [11-14]. Similar to the adipocytokines, plasma RBP-4 levels in patients with type 2 diabetes mellitus with advanced nephropathy were higher than those in patients without nephropathy.

In general, retinol, the precursor of the retinoic acid hormone, is transported in the serum by a specific carrier, the RBP [15]. Some types of RBP have been identified and analyzed in renal dysfunction [15-19]. The levels of serum retinol were increased in experimental acute renal failure [16], and the serum of patients with chronic renal failure contains increased levels of the RBP form truncated at the C terminal [17]. In the present study, multiple regression analyses revealed a strong association of high RBP-4 with decrease in renal function. The results indicated that plasma RBP-4 was associated with renal function, represented by Ccr and Cr in patients with diabetic nephropathy. An explanation is that elevated RBP-4 levels are a consequence of impaired kidney function in patients with renal failure. Impaired clearance/catabolism of RBP-4 in the kidney may lead to the accumulation of RBP-4 in plasma. This implies that macroalbuminuria contributes to elevated plasma RBP-4 levels.

A previous study found that renal dysfunction, assessed by urinary RBP, correlates with a worsening of glomerular filtration and can be a useful tool for detection of renal dysfunction [20]. The higher plasma levels of RBP-4 in subjects with microalbuminuria were accompanied by increased urinary levels of RBP-4 [9]. Our unpublished observation demonstrated that the RBP-4 levels in the urine were also increased in type 2 diabetes mellitus subjects with macroalbuminemia and end-stage renal disease (TM, FA, and HY, unpublished observation). The data indicate that urinary RBP-4 is also associated with renal dysfunction as well as plasma RBP-4. In addition, the disturbance of production and/or catabolism of RBP-4 may be characterized in patients with macroalbuminemia and end-stage renal disease.

Several studies suggest that RBP-4 might have clinical implications for glucose and/or lipid metabolism [3-8]. Furthermore, RBP-4 has recently been reported to be associated with markers of inflammation in obesity [21,22]. In contrast, other studies have found that plasma RBP-4 gene expression was associated with glucose transporter 4 messenger RNA expression in adipose tissue but not with insulin resistance [6,21]. The current study demonstrated that the RBP-4 level was related to HOMA-r and TGL in diabetic subjects with Ccr of more than 60 mL/min.

Recently, Cabre et al [23] have found a relationship between renal dysfunction and circulating RBP-4. Plasma RBP-4 concentrations were positively correlated with serum Crs and inversely correlated with glomerular filtration rate [23]. The results indicated that plasma RBP-4 concentration might be associated with renal dysfunction. Similar to the report, we found a relationship between renal dysfunction and circulating RBP-4 in Japanese type 2 diabetes mellitus patients. Of note, we have added the results that circulating RBP-4 levels were not correlated with the HOMA-r index and hypertriglyceмia in Japanese type 2 diabetes mellitus patients with end-stage renal disease. Thus, it seems unlikely that RBP-4 will be useful for assessing insulin resistance and hypertriglycemia of type 2 diabetes mellitus in end-stage renal disease. The biologic action of RBP-4 and insulin in end-stage renal disease will need to be clarified.

The present study has some limitations. First, the study included a relatively small number of patients. Second, there is a limitation associated with the interpretation of data in a cross-sectional study. A prospective longitudinal study would be necessary to address these issues as well as to identify factors determining the plasma RBP-4 levels in response to the development of diabetic nephropathy. Finally, we cannot exclude the possibility that factors other than those examined in the present study have influence on the plasma levels of RBP-4.

In summary, the present study demonstrated the independent impacts of diabetic nephropathy on plasma RBP-4 levels in type 2 diabetes mellitus. In addition, RBP-4 levels were correlated with HOMA-r and TGL in diabetic subjects without end-stage renal disease.

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