J. Shanghai Jiaotong Univ. (Sci.), 2016, 21(6): 757-762
DOI: 10.1007/s12204-016-1791-3

Serum Levels of RBP4 Might Not Be Determined by Diabetes Mellitus but by Kidney Function and Renal Replacement Therapy

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Abstract: It has been reported that retinol-binding protein 4 (RBP4) is associated to adiposity, insulin resistance, and type 2 diabetes. Meanwhile, circulating RBP4 levels are also affected by renal function. The aim of the present study is to investigate whether serum levels of RBP4 are primarily associated with different stages of chronic kidney disease (CKD) or type 2 diabetes, if there is more potential relevance between RBP4 and renal replacement therapy. The serum levels of RBP4 were assessed by commercial competitive enzyme-linked immunosorbent assay (ELISA) kit in 212 patients with the CKD stages 1—5 and in 24 healthy controls, while its correlation with clinical and metabolic parameters was analyzed. The serum level of RBP4 had a strong correlation with estimated glomerular filtration rate (eGFR) ($P < 0.001$). Stratified by eGFR and treatment, no more differences in RBP4 serum concentration were detected between type 2 diabetic and non-diabetic subjects [CKD stages 1—5, non-dialysis (ND), hemodialysis (HD) and peritoneal dialysis (PD); $P > 0.05$ for all]. The elevation of RBP4 become higher in HD than in PD and ND in CKD5 patients ($P = 0.008$ and $P = 0.04$, respectively), while there was no significant difference between PD and ND groups. Multivariate linear regression analysis demonstrated three independent predictors of eGFR ($\beta = -0.676$, $P < 0.001$), C-reactive protein (CRP) ($\beta = -0.573$, $P < 0.001$) and creatine ($\beta = 0.509$, $P = 0.024$) in the study population. The study results demonstrated that the serum level of RBP4 was negatively related to the eGFR, whether diabetes mellitus (DM) affected the blood concentration of RBP4 or not. And the serum level of RBP4 exhibited significant difference in different renal replacement therapies.
Key words: chronic kidney disease (CKD), retinol binding protein 4 (RBP4), renal replacement therapy, diabetes mellitus (DM)
CLC number: R 692.5 **Document code:** A

0 Introduction

The retinol-binding protein 4 (RBP4) mainly influenced by kidney function[1-3] has been suggested recently as novel adipokine, maybe contributing to the type 2 diabetes mellitus (DM) and the onset of insulin resistance in obese subjects[4-5].

RBP4 is a 21 kDa plasma protein which is mainly synthesized in the liver and catabolized in the kidneys after glomerular filtration. The binding of retinol (ROH) to RBP4 plays a key role in the retinol metabolism which takes an important part in a variety of physiological processes[6-7]. In healthy individuals, RBP4 is secreted into the circulation in a 1∶1∶1 complex with ROH and transthyretin (TTR)[8]. The molecular weight of RBP4 (76 kDa) increases after it binds with TTR and thus its glomerular filtration and catabolism are reduced [9-10]. After ROH is delivered to its target tissues, the affinity of RBP4 to TTR decreases and RBP4 is subjected to degradation in kidney[6,11].

Kidney injury has become an urgent important problem for public health[12-14]. Biological markers are required in the context for the diagnosis and treatment of a renal disorder. Since the kidney is the main site of RBP4 catabolism, RBP4 serum concentration is associated with renal function and has been supposed as surrogate marker of kidney function[15-18]. Increased serum RBP4 levels are also associated with body mass

Received date: 2015-01-26
Foundation item: the National Natural Science Foundation of China (Nos. 81570603, 81270824 and 81670632), the New-100 Talent Plan of Shanghai Jiao Tong University School of Medicine, the Shanghai Talents Development Fund (No. 201350) and the Shanghai Pujiang Talent Projects (No. 15PJ1406700)
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index (BMI), waist-to-hip ratio (WHR), serum triglyceride (TG) levels, and systolic blood pressure (BP)[4,19]. A recent study also finds that serum RBP4 correlates with subclinical inflammation[20].

However, it is not completely understood whether the serum level of RBP4 is affected by other parameters. So the aim of the present study is to investigate the interactions among plasma RBP4, renal function, systemic inflammation and lipid disorder, and to investigate the relation between RBP4 and kidney function in patients undergoing renal replacement therapy.

1 Materials and Methods

1.1 Subjects

All subjects were of Chinese origin (Han Chinese) and lived in the same region at the time of the study. All subjects underwent physical examinations and routine biochemical analyses of blood. Exclusion criteria were less than 18 years old and pregnancy. The study was approved by the human research ethics committee of Shanghai Jiao Tong University Affiliated Sixth People's Hospital. Serum samples of 24 subjects (15 male/ 9 female) served as controls and were obtained from the Physical Examination Center. The inclusion criteria for healthy subjects were no known diagnosis of any kidney, liver or metabolic disease. Additionally, serum samples of 212 patients (131 male/81 female) with diagnosis of chronic kidney disease (CKD) were obtained from the department of nephrology.

Renal function was quantified by estimated glomerular filtration rate (eGFR) which was calculated according to modification of diet in renal disease (MDRD) formula including serum creatinine concentration, age and gender[21]. The stages of CKD were used as grouping characteristic and were assigned in accordance with the K/DOQI guidelines[21].

Lack of diabetes was defined based on medical history and fasting glucose in the absence of anti-diabetic medications. BMI was calculated as weight (in kilogram) divided by height (in meter) squared (kg/m^2). The subjects' waist was measured with a soft tape midway between the lowest rib and the iliac crest. The hip circumference was measured at the widest part of the gluteus region. The WHR was then calculated.

1.2 Laboratory Analysis

Blood samples were collected from antecubital veins after an overnight fast and centrifuged, and serum was immediately frozen at $-80\,^{\circ}C$ until measurement. In hemodialysis (HD) patients, blood samples were taken before the start of a dialysis session to minimize the potential effect of previous dialysis on the studied parameters. All anthropometric, clinical and biochemical parameters of the participants were collected by trained personnel.

Alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyltransferase (GGT), albumin, serum albumin and glucose levels were measured by routine laboratory methods. Serum hsCRP concentrations were determined by nephelometric analysis/chemiluminescent immunoassay (Immulite 2000). HbA1c was measured by cation-exchange high performance liquid chromatography (Tosoh HLC-723 G7, Tosoh Co). Serum cholesterol, triglyceride, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), creatinine and uric acid levels were determined by enzymatic colorimetry method (Hitachi 7600-110, Hitachi Ltd). Plasma glucose concentrations were measured using an automatic biochemistry analyzer (Hitachi 7170, Hitachi Ltd).

1.3 Measurements of RBP4

Plasma RBP4 concentration was measured using a commercially available kit (R&D Systems Inc) following the manufacturer's recommendations (intra-assay coefficient of variation is 5.7%; inter-assay coefficient of variation is 5.8%). The minimum detectable dose is 0.224 mg/L.

1.4 Statistical Analysis

Results are expressed as mean and standard deviation (normally distributed variables) or median and range for data with a non-normal distribution, unless otherwise indicated, with $P < 0.05$ indicating significance. Comparisons of continuous variables between groups were then made using ANOVA (normally distributed variables) or Kruskal-Wallis (non-normally distributed variables) tests.

Relationships between variables were assessed by Spearman's correlation analysis. Multiple linear regression analysis was used to identify the independent contributions of each parameter on serum RBP4 level. A value of P less than 0.05 represented statistical significance in all analyses. All statistical analyses were performed on a personal computer with SPSS version 18.0.

2 Results

Anthropometric and clinical data were demonstrated in Table 1. There was a steady decline of eGFR from control to CKD 5 with $P < 0.001$ between all groups. Fasting glucose was higher in CKD 5 than in CKD4 ($P < 0.05$) and CKD3 ($P < 0.01$). Haemoglobin was reduced in CKD 3—5 ($P < 0.001$ for all) in comparison to control subjects. C-reactive protein (CRP) was higher both in CKD4 and CKD5 than in CKD1—3 ($P < 0.001$ for all). The subjects of all five groups did not differ in BMI, WHR, and C peptide. Additionally, approximately 44% of the CKD patients were positively diagnosed as DM.

The serum RBP4 was elevated with the CKD stage, and correlated with eGFR. The RBP4 serum concentration varied with progression of CKD (Table 1). RBP4 serum concentrations were gradually elevated with the

Table 1 Anthropometric and biochemical data

Parameter	Control	CKD1	CKD2	CKD3	CKD4	CKD5
Number (male/female)	24(15/9)	10(6/4)	19(9/10)	20(9/11)	30(17/13)	133(90/43)
Age/(years old)	50.17 ± 9.52	43.45 ± 13.90	64.58 ± 16.74	59.21 ± 17.58	67.07 ± 11.84	59.44 ± 14.21
BMI/($\mathrm{kg \cdot m^{-2}}$)	—	24.07 ± 2.80	25.49 ± 3.35	24.08 ± 3.62	25.11 ± 3.62	23.13 ± 3.90
WHR	—	0.89 ± 0.03	0.93 ± 0.05	0.89 ± 0.05	0.92 ± 0.01	0.93 ± 0.05
CRP/($\mathrm{mg \cdot L^{-1}}$)	—	0.32 (0.2—4.7)	0.57 (0.2—4.2)	0.875 (0.2—93.4)	8.42 (0.2—190)	4.93 (0.2—144)
BUN/($\mathrm{mmol \cdot L^{-1}}$)	4.5(3.6—7.6)	4.5(3.0—6.4)	6(3.9—15.4)	9.7(4.3—19.5)	10.2(3.8—33)	18.9(2.8—60.3)
Scr/($\mu\mathrm{mol \cdot L^{-1}}$)	74(45—96)	61(43—82)	84(60—107)	126(90—192)	263(170—374)	797(319—2085)
CysC/($\mathrm{mg \cdot L^{-1}}$)	—	0.61 (0.48—0.91)	1.03 (0.5—1.62)	1.27 (0.86—2.63)	2.39 (1.66—3.27)	4.12 (1.69—7.67)
AST/($\mathrm{U \cdot L^{-1}}$)	19(12—36)	18(15—123)	21(11—912)	20(12—89)	17(8—40)	16(5—85)
ALT/($\mathrm{U \cdot L^{-1}}$)	15.5(7—55)	20.5(10—200)	18(8—267)	16(4—164)	13.5(4—72)	12(1—175)
Alb/($\mathrm{g \cdot L^{-1}}$)	49(48—54)	40(20—48)	37(18—47)	39(30—57)	39.5(20—48)	39(15—49)
CHOL/($\mathrm{mmol \cdot L^{-1}}$)	4.6 (3.29—6.66)	5.03 (3.42—9.43)	5.23 (2.98—10.68)	5.7 (3.08—8.42)	5.07 (1.31—7.6)	4.42 (1.82—10.81)
HDL/($\mathrm{mmol \cdot L^{-1}}$)	1.35 (0.76—1.88)	0.99 (0.84—1.95)	1.23 (0.81—2.53)	1.24 (0.75—2.18)	1.11 (0.68—2.47)	1.01 (0.22—2.02)
LDL/($\mathrm{mmol \cdot L^{-1}}$)	3.07 (1.84—5.02)	3.12 (1.46—5.89)	3.32 (0.92—6.54)	2.85 (1.46—4.88)	2.67 (1.31—4.58)	2.37 (0.63—5.71)
TG/($\mathrm{mmol \cdot L^{-1}}$)	1.11 (0.53—3.76)	1.99 (0.51—2.54)	1.52 (0.79—3.34)	2.2 (0.82—4.29)	1.3 (0.23—3.97)	1.32 (0.28—12.66)
Diabetic patients (n/N)	24(0/24)	10(3/7)	19(10/9)	20(9/11)	30(18/12)	133(54/79)
FPG/($\mathrm{mmol \cdot L^{-1}}$)	5.29 (4.34—5.9)	5.39 (4.49—15.42)	5.4 (4.48—13.1)	6.41 (2.76—19.26)	5.76 (4.68—11.02)	4.975 (2.04—16)
C Peptide/($\mu\mathrm{g \cdot L^{-1}}$)	—	2.91 ± 0.03	2.42 ± 1.09	2.47 ± 0.72	6.16 ± 3.15	8.62 ± 6.02
$q_{\mathrm{eGFR1.73}}$/ ($\mathrm{mL \cdot min^{-1}}$)	98.3 (74.4—143.7)	104.8 (92.5—163.3)	76.7 (60.24—89.3)	46.6 (31.2—57.3)	19.11 (1.51—2.86)	5.73 (1.59—1.47)
Hemoglobin/($\mathrm{g \cdot L^{-1}}$)	151.89 ± 10.40	141.29 ± 30.34	133.32 ± 23.15	112.47 ± 20.10	105.27 ± 24.32	97.67 ± 22.53
c_{RBP4}/($\mathrm{mg \cdot L^{-1}}$)	34.04 ± 9.46	48.09 ± 18.12	51.20 ± 9.86	73.78 ± 22.62	113.89 ± 34.51	115.45 ± 28.95
TTR/($\mathrm{mg \cdot L^{-1}}$)	155.9 (144—988)	160 (138.9—294.7)	145.9 (134.5—237.5)	156.7 (138.7—307.9)	154.8 (138.2—305.5)	152.2 (132.3—355.3)

Note: Data are demonstrated as mean ±SD or median according to the parametric or nonparametric data; CKD1—CKD5 represent the CKD stages 1—5; BUN represents blood urea nitrogen; Scr is serum creatinine; CysC is cystatin C; FPG is fasting glucose; CHOL is total cholesterol; TG is triglyceride; HDL is high density lipoprotein; LDL is low density lipoprotein; Alb is albumin; $q_{\mathrm{eGFR1.73}}$ is eGFR per $1.73\,\mathrm{m^2}$; c_{RBP4} is RBP4 level; TTR is transthyretin; n is the number of subjects; N is the number of total subjects.

CKD stages, while the control group was the lowest (Fig. 1(a)). One-way ANOVA analysis showed that the RBP4 levels were significantly elevated in CKD4 and CKD5 in comparison to CKD1, CKD2 and CKD3 ($P < 0.001$ for all) (Table 1 and Fig. 1(a)). The correlation analysis showed that the concentration of RBP4 was reversely correlated with eGFR (correlation coefficient $r = -0.739$, $P < 0.000\,1$; Fig. 1(b)).

The serum RBP4 was not determined by DM. As shown in Fig. 2(a), the eGFR exhibited no statistical difference between diabetes and non-diabetes in the subjects we studied (median eGFR per $1.73\,\mathrm{m^2}$ of $12.7\,\mathrm{mL/min}$ (range 1.59—113.3) versus $12.2\,\mathrm{mL/min}$ (range 2.27—163.4); $P > 0.05$). Meanwhile, there was also no significant difference of RBP4 serum levels between diabetic and non-diabetic subjects [$(95.92 \pm 33.60)\,\mathrm{mg/L}$ versus $(94.90 \pm 44.65)\,\mathrm{mg/L}$; $n = 142$, $P > 0.05$ Fig. 2(b)]. Moreover, the assessment of the RBP4 serum concentration in each CKD stage showed no significant difference between diabetic and non-diabetic

subjects, and the RBP4 serum level was elevated with the progression of CKD (Fig. 2(c)).

Different renal replacement therapy might affect the serum level of RBP4 in the CKD 5 subjects. As indicated in Fig. 3(a), plasma concentrations of RBP4 were much higher in HD than in peritoneal dialysis (PD) and non-dialysis (ND) ($P = 0.008$ and $P = 0.04$, respectively). However, there was no significant difference between PD and ND ($P = 0.81$) (Fig. 3(a)). In addition, RBP4 was higher in HD group than in PD group, but there was no significant difference between diabetes and non-diabetes (Fig. 3(b)).

There were still other parameters correlated with the serum level of RBP4. In this study, RBP4 concentrations were only correlated with eGFR levels ($\beta = -0.676$, $P < 0.001$), CRP levels ($\beta = -0.573$, $P < 0.001$) and serum creatine levels ($\beta = 0.509$, $P = 0.024$). Other parameters (presence of type 2 diabetes and lipids metabolism) were not associated with RBP4 serum levels ($P > 0.05$) (Table 2).

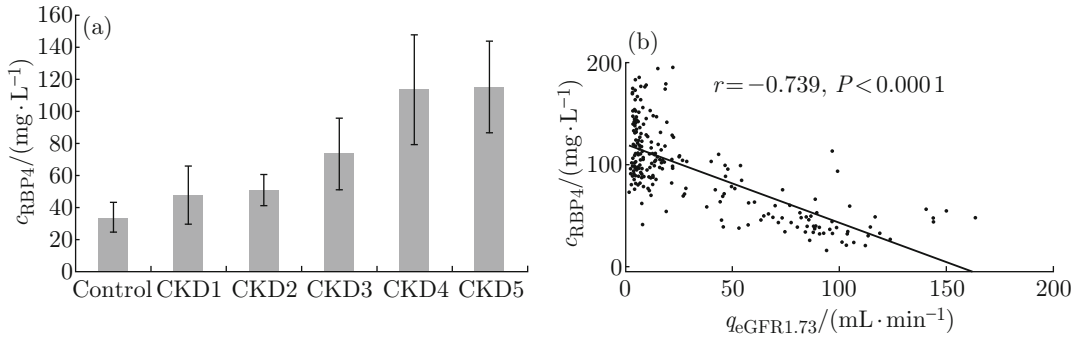


Fig. 1 Serum levels of RBP4 in different CKD stages versus eGFR

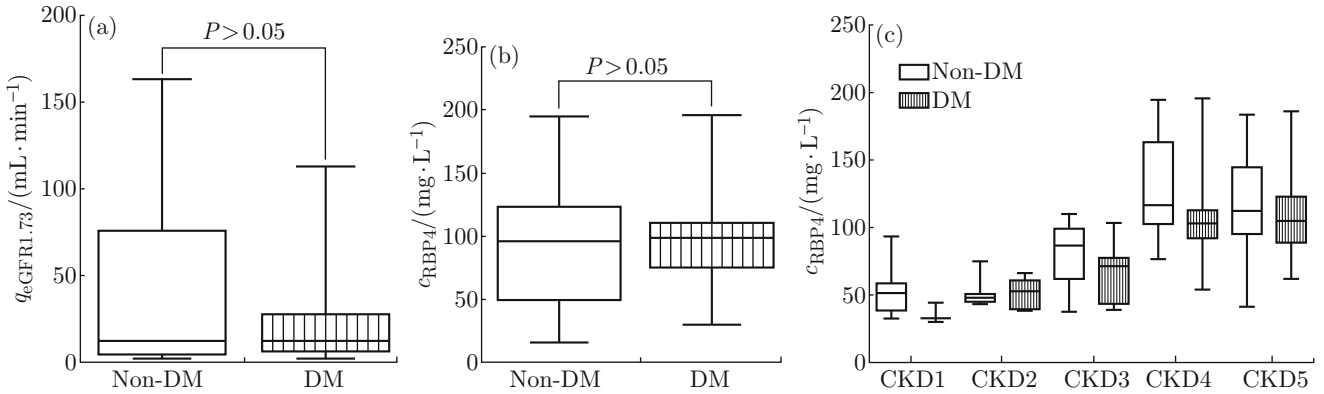
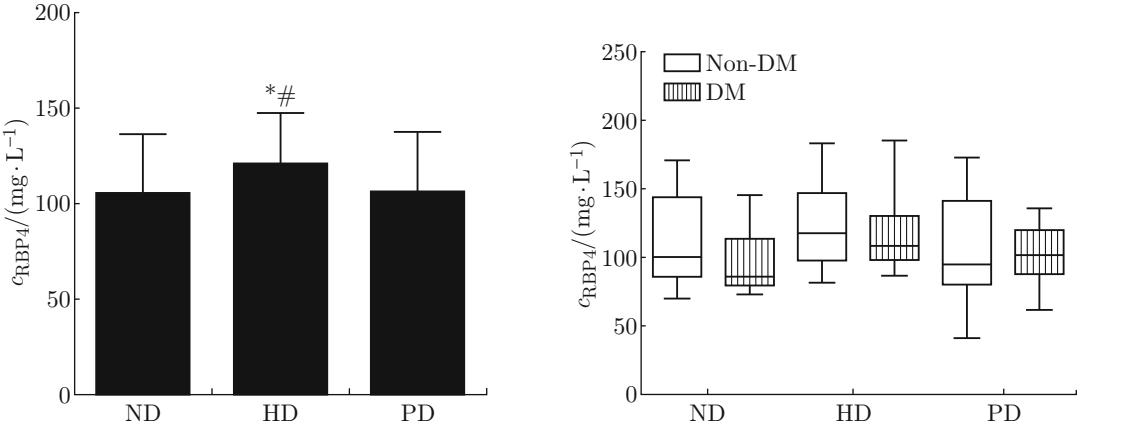


Fig. 2 The eGFR and RBP4 levels in diabetic and non-diabetic patients



(a) Serum RBP4 levels in patients with different renal replacements

(b) Diabetes did not affect serum RBP4 in CKD5

Fig. 3 Serum RBP4 in CKD5 stage patients

Table 2 RBP4 concentrations correlated with eGFR, CRP and serum creatine

Parameter	r	P
eGFR	−0.647	0.001
CRP	−1.233	0.001
Creatine	0.042	0.024
Hemoglobin	0.172	0.444
C peptide	0.062	0.784
Total cholesterol	0.153	0.496
HDL-cholesterol	−0.134	0.552
LDL-cholesterol	0.107	0.636
TTR	0.164	0.466
ALT	−0.044	0.848
AST	−0.082	0.718
BUN	0.019	0.935
CysC	−0.208	0.353

3 Discussion

Kidney injury, including acute and chronic kidney disease, is a common disease and has become an urgent problem for public health. Therefore, there is an urgent need for biomarkers that can detect kidney diseases[22-24]. The serum RBP4 in patients is elevated with CKD[25-26]. This is probably caused by a decreased ability of the kidneys to filter and degrade low-molecular weight proteins in proximal tubular cells[27-28], in turn leads to an abnormal retention of small serum proteins, and results in increased serum levels of these proteins[17,29]. The acute renal failure in rats demonstrates that this increase of RBP4 seems to be a positive feedback signal for the hepatic release of ROH and RBP4, which further increases the RBP4 serum concentration[30]. Therefore, a loss of kidney function is associated with the disturbed RBP4 metabolism. In this study, serum RBP4 levels increased in parallel with CKD progression, which might display the importance of kidney in the metabolism of the RBP4. The multivariate linear regression analysis showed a closest association of RBP4 with eGFR.

Furthermore, both of RBP4 and eGFR exhibited no difference between diabetic and non-diabetic subjects. After stratification, no further differences in the RBP4 serum concentration were detectable between diabetic and non-diabetic subjects for each eGFR group. The finding in the present study was also in line with previous reports[1].

Moreover, in the present study we also observed that plasma concentrations of RBP4 were higher in HD group than in ND and PD subjects of CKD5 ($P = 0.008$ and $P = 0.04$, respectively). Compared to controls ($P = 0.81$), RBP4 levels in patients who were under ND therapy did not increase. Ziegelmeler et al.[2] reported increased RBP4 level in patients on long-term HD, which is in accordance with our findings. Besides, we also found that no significant difference existed between ND and PD. We inferred that the remnant renal function might influence the RBP4 level between different therapy groups, but the parameter was not assessed in the present study. As we demonstrated that other factors were also correlated with the serum level of RBP4, we believed that the potential reason was complex and should be further explored.

There were still some limitations in the present study. It is a cross-sectional design and the sample amount is small, which makes our results less robust than ideal. Therefore, large and longitudinal studies are needed to better explain the relationship with RBP4 in CKD. Because the subjects of our study are only Han Chinese, the generalizability to other ethnicities is unknown. The potential pathophysiological mechanism needs to be further explored. More studies are needed to evaluate clinical implications of our findings.

4 Conclusion

The reduced catabolism of RBP4 in CKD patients resulted in an elevation in serum RBP4. The RBP4 level might not be determined by diabetes. Furthermore, this study provided a new finding of different serum RBP4 levels in patients undergoing different renal replacements.

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