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Association of Serum Retinol-Binding Protein 4 and Visceral Adiposity in Chinese Subjects with and without Type 2 Diabetes

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Objective: Previous studies have shown that adipose-derived serum retinol-binding protein 4 (RBP4) levels are increased in insulin-resistant mouse models and in subjects with insulin resistance or type 2 diabetes. However, the association of visceral fat and serum RBP4 has not been studied. The purpose of this study was to investigate the relationship between serum RBP4 and regional fat distribution in Chinese subjects with and without type 2 diabetes.

Design: We measured serum RBP4 concentrations from 1033 Chinese subjects with various degrees of obesity and tested the association between visceral adiposity and serum RBP4. In a subgroup of this study, euglycemic-hyperinsulinemic clamp was performed to measure insulin sensitivity. The association between visceral adiposity and serum RBP4 was also determined in response to rosiglitazone treatment in a subgroup of patients with diabetes.

Results: Serum RBP4 level was positively correlated with visceral adipose area in male ($r = 0.171$; $P < 0.001$) and female ($r = 0.215$; $P < 0.001$) subjects. However, there was no correlation between serum RBP4 and body mass index. Subjects with visceral obesity had higher serum RBP4 concentrations than those without visceral obesity in both men and women. Rosiglitazone treatment in patients with diabetes resulted in a lower serum RBP4 level (35.2 ± 10.2 *vs.* 24.9 ± 5.6 μg/ml, before *vs.* after treatment). These changes were accompanied by improved insulin sensitivity and reductions in visceral fat area. The latter was found to be highly correlated with the decline of serum RBP4 levels ($r = 0.471$; $P = 0.027$).

Conclusions: Serum RBP4 level is positively associated with visceral adiposity in both men and women. Our data suggest that RBP4 may contribute to the development of insulin resistance along with other adipokines. **(*J Clin Endocrinol Metab* 92: 3224–3229, 2007)**

ADIPOSE TISSUE MAY function as an endocrine organ by secreting several adipocytokines (also called adipokines) (1), which may be involved in the development of insulin resistance and type 2 diabetes (2–5). The mRNA level of retinol-binding protein 4 (RBP4), a newly discovered adipokine (6), has been reported to be up-regulated in adipose tissue of adipose-Glut4$^{-/-}$ mice. Treating adipose-Glut4$^{-/-}$ mice with rosiglitazone, an insulin-sensitizing drug, reduced the RBP4 mRNA expression in adipose tissue and RBP4 levels in serum (6). Moreover, serum RBP4 concentrations correlated well with insulin resistance and associated cardiovascular risk factors in men (7). However, a recent human study showed that RBP4 mRNA was down-regulated in sc adipose tissue of obese women, and circulating RBP4 concentrations were similar in normal-weight, overweight, and obese women despite increased insulin resistance (8).

Visceral adipose tissue was reported to be more closely associated with the risk of insulin resistance, hypertension, and hyperlipidemia than total body fat or body mass index (BMI) (9). Visceral and sc adipose tissues exhibit important metabolic differences (10–14), such that visceral fat area (VFA) greater than 100–130 cm^2 represents a strong risk for cardiovascular and metabolic abnormalities (15). This may be due to an increased production of adipokines from visceral fat than that from sc fat (16, 17). However, the potential association of visceral adiposity and serum RBP4 levels has not been investigated. The objective of this study was to determine the association of visceral adiposity and circulating RBP4 levels in Chinese subjects with and without type 2 diabetes.

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Abbreviations: BMI, Body mass index; GDR, glucose disposal rate; $HOMA_{IR}$, homeostasis model assessment of insulin resistance; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; RBP4, retinol-binding protein 4; SFA, sc fat area; VFA, visceral fat area.

Subjects and Methods

Study groups

All subjects were of Chinese origin (Han Chinese) and lived in the same region at the time of the study. All subjects underwent complete physical examinations and routine biochemical analyses of blood. Oral glucose tolerance test (OGTT) and magnetic resonance imaging were also performed. Seated systolic and diastolic blood pressures were measured by manual sphygmomanometer after the subjects had rested for 5 min. The study was approved by the human research ethics committee of the hospital, and informed consent was obtained from all subjects.

A total of 1033 Chinese subjects (475 men and 558 women) from Shanghai Diabetes Studies (18) were recruited into this study. Among all subjects, 542 had normal glucose tolerance (NGT), 151 were diagnosed as impaired glucose tolerance (IGT), and 340 had type 2 diabetes. All concomitant medications were withdrawn 2 wk before the study.

Subgroup 1. A total of 51 subjects (age, 38 ± 12 yr; 25 men and 26 women) with normal glucose tolerance underwent euglycemic-hyperinsulinemic clamp. None of the subjects took any lipid-lowering or antihypertensive medications. Each subject was asked to abstain from alcohol and excessive physical exercise for 2 d before the clamp study.

Subgroup 2. A total of 22 newly diagnosed diabetes patients (14 men and 8 women) were treated with rosiglitazone. Patients with type 1 diabetes, ketonuria (3+), glutamic acid decarboxylase antibody (+), or protein tyrosine phosphatase-like protein insulinoma-associated protein 2 antibody (+) were excluded. Patients who were diagnosed with urinary tract infection, urolithiasis, liver cirrhosis, congestive heart failure, macrovascular disease, overt proteinuria, or other known major diseases were also excluded. Rosiglitazone was taken 4 mg daily for 6 months.

Anthropometric index and fat distribution

BMI was calculated as the weight in kilograms divided by the square of the height in meters. Waist and hip circumferences were measured, and waist-to-hip ratio was calculated. Abdominal VFA and sc fat area (SFA) were measured by magnetic resonance imaging (Signa 1.5T; General Electric Co.) at the level of L4–L5. Each fat area was calculated as previously described (19). For determining abdominal visceral obesity, a value of 100 cm^2 was selected as the cutoff point. This was based on a recent publication suggesting that this cutoff point was more appropriate for an Asian population (20). The World Health Organization criteria were used to characterize subjects as overweight or obese *vs.* nonobese (21).

OGTT and homeostasis model assessment (HOMA)

Subjects were fasted overnight before the OGTT. After a blood sample was taken for fasting plasma glucose measurement, a 2-h OGTT was performed with a standard glucose load (75 g glucose) (22). HOMA of insulin resistance ($HOMA_{IR}$) was calculated based on fasting insulin and glucose according to the equation: $HOMA_{IR}$ = fasting serum insulin (μU/ml) × fasting plasma glucose (mmol/liter)/22.5 (23). Insulin resistance was determined by $HOMA_{IR,}$ in which the 75th percentile value was used as the cutoff point to define insulin resistance, which corresponds to a $HOMA_{IR}$ value of 2.31 as per Shanghai Diabetes Studies background population study results.

Hyperinsulinemic-euglycemic clamp

Hyperinsulinemic-euglycemic clamp was performed as previously described (24). Briefly, iv catheters were inserted into antecubital veins of both arms, and baseline samples were taken. A 10-min priming infusion of insulin (40 U/ml; Novo Nordisk, Bagsvaerd, Denmark) was initiated to raise the circulating insulin level before a constant infusion rate (40 mU/m^2·min) was given to maintain the steady-state insulin during the next 140 min. Glucose infusion (20% glucose infusate) was started to maintain plasma glucose concentration to the baseline level. Blood samples were taken every 5 min for glucose measurement. Blood samples were drawn every 10 min for insulin measurement. The glucose disposal rate (GDR) was used as a measure of insulin sensitivity (24).

RBP4, adiponectin, and insulin measurement

Serum samples were kept at −70 C for subsequent assays. Serum RBP4, adiponectin, and insulin concentrations were measured in duplicates by RIA (RBP4: Phoenix, Belmont, CA; adiponectin/insulin: Linco Research, St. Charles, MO). The intraassay coefficients of variation were 8% for RBP4, 10% for adiponectin, and 10% for insulin, respectively.

Statistical analysis

We used SPSS version 11.5 (SPSS Inc., Chicago, IL) for our statistical analyses. Each variable was examined for normal distribution and significantly skewed variables were log transformed. Results were expressed as means ± SD. Characteristics of subjects among or between groups were compared by one-way ANOVA or covariance. Comparisons between groups before and after treatment were calculated by Wilcoxon signed rank test. Spearman correlation was used. All reported P values were two-tailed, and P values < 0.05 were considered statistically significant.

Results

As shown in Table 1, subjects with type 2 diabetes had higher $HOMA_{IR}$ index and cholesterol and triglyceride levels

TABLE 1. Comparison of metabolic components, regional fat distribution, and adipokines among subjects with type 2 diabetes, IGT, and NGT

Parameters	Men				Women			
	NGT (n = 228)	IGT (n = 75)	DM (n = 172)	R	NGT (n = 314)	IGT (n = 76)	DM (n = 168)	R
Age (yr)	47 ± 14	57 ± 13[a]	55 ± 10[a]	−0.104[f]	48 ± 13	54 ± 10[a]	56 ± 10[a]	0.201[e]
BMI (kg/m^2)	25 ± 4	26 ± 5[b]	26 ± 3	0.068	25 ± 4	27 ± 4[a]	26 ± 4[b,d]	0.012
WHR	0.90 ± 0.07	0.93 ± 0.07[a]	0.94 ± 0.05[a]	−0.006	0.88 ± 0.08	0.93 ± 0.08[a]	0.93 ± 0.09[a]	0.086[f]
SP (mm Hg)	125 ± 16	138 ± 17[a]	132 ± 19[a,d]	−0.190	121 ± 19	135 ± 18[a]	136 ± 19[a]	0.102[f]
DP (mm Hg)	81 ± 11	87 ± 10[a]	85 ± 11[a]	0.097[f]	80 ± 10	84 ± 10[a]	84 ± 11[a]	0.125[e]
FPG (mmol/liter)	5 ± 1	6 ± 1[a]	8 ± 2.0[a,c]	0.255[e]	5 ± 1	6 ± 1[a]	7 ± 2[a,c]	0.229[e]
PG2H (mmol/liter)	5 ± 1	9 ± 2[a]	15 ± 7[a,c]	0.126[e]	6 ± 1	9 ± 1[a]	14 ± 6[a,c]	0.076
FINS (μU/ml)	10 ± 7	12 ± 8[a]	14 ± 9[a]	0.152[e]	11 ± 8	14 ± 7[a]	14 ± 10[a]	0.098[f]
$HOMA_{IR}$	2 ± 1	3 ± 2[a]	5 ± 4[a,c]	0.213[e]	2 ± 2	3 ± 2[a]	5 ± 4[a,c]	0.162[e]
TC (mmol/liter)	5.0 ± 1.1	5.2 ± 1.3[a]	5.4 ± 1.3[a]	0.088	5.1 ± 1.1	5.5 ± 1.0[a]	5.6 ± 1.2[a]	0.219[e]
TG (mmol/liter)	1.6 ± 1.1	1.5 ± 0.8	2.0 ± 1.3[a,c]	0.248[e]	1.5 ± 0.9	1.6 ± 0.8	2.2 ± 1.5[a,d]	0.302[e]
HDL-C (mmol/liter)	1.2 ± 0.3	1.1 ± 0.3	1.1 ± 0.3[b]	−0.880	1.3 ± 0.4	1.3 ± 0.5	1.2 ± 0.3[a,d]	0.100[f]
LDL-C (mmol/liter)	3 ± 1	3 ± 1	3 ± 1	0.840	3 ± 1	4 ± 1	4 ± 3[a]	0.210[e]
Adiponectin (μg/ml)	16 ± 11	15 ± 13[b]	14 ± 8[a]	−0.138[e]	18.9 ± 10.5	21.3 ± 13.1	18.9 ± 10.8	−0.100[f]
RBP4 (μg/ml)	26 ± 8	24 ± 7	30 ± 11[a,c]		22 ± 7	21 ± 7	24 ± 9[a,c]	
SFA (cm^2)	135 ± 84	149 ± 66[a]	147 ± 50[a]	0.075	210 ± 86	229 ± 87	217 ± 72[b]	−0.034
VFA (cm^2)	89 ± 58	101 ± 53[a]	119 ± 41[a,d]	0.171[e]	83 ± 51	100 ± 47[a]	103 ± 45[a]	0.215[e]

Data represent means ± SD. Data were analyzed with one-way ANOVA. Spearman correlation analyses were used to determine the association between RBP4 and other parameters. R values refer to the Spearman correlation coefficient. DP, Diastolic blood pressure; FINS, fasting insulin; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; PG2H, 2-h plasma glucose; SP, systolic blood pressure; TC, total cholesterol; T2DM, type 2 diabetes; TG, triglyceride; WHR, waist-to-hip ratio.

[a] $P < 0.01$ *vs.* NGT.
[b] $P < 0.05$ *vs.* NGT.
[c] $P < 0.01$ *vs.* IGT.
[d] $P < 0.05$ *vs.* IGT.
[e] $P < 0.01$.
[f] $P < 0.05$.

and lower high-density lipoprotein cholesterol levels than those with NGT in both men and women (Table 1). Serum RBP4 level was elevated in subjects with diabetes (Table 1). However, serum RBP4 level was normal in IGT and NGT subjects (Table 1).

Serum RBP4 concentrations were significantly higher in men (26.8 ± 9.4 μg/ml) than in women (22.5 ± 7.8 μg/ml, $P < 0.0001$; Table 1). Spearman correlation analysis showed that serum RBP4 was correlated positively with $HOMA_{IR}$ index (r = 0.213), fasting plasma glucose (r = 0.255), triglyceride (r = 0.248), and VFA (r = 0.171) in men (Table 1). Similar correlations were found in women (Table 1). The relationship between serum RBP4 concentrations and VFA in both men and women was independent of $HOMA_{IR}$ index (Fig. 1). Furthermore, there was an inverse correlation between serum RBP4 and serum adiponectin and between serum adiponectin and VFA (Table 1) in both men and women. No correlation was found between serum RBP4 and BMI or serum RBP4 and SFA.

Subjects with visceral obesity had higher serum RBP4 levels than those with nonvisceral obesity (28.3 ± 9.8 *vs.* 25.6 ± 9.0 μg/ml, $P < 0.01$) in men (24.0 ± 8.3 *vs.* 21.4 ± 7.1 μg/ml, $P < 0.01$) and in women, after age had been controlled. However, there was no difference in serum RBP4 levels between lean (BMI < 25 kg/m^2), overweight (30 kg/m^2 > BMI ≥ 25 kg/m^2), and obese subjects (BMI ≥ 30 kg/m^2).

As shown in Fig. 2, serum RBP4 was inversely correlated with GDR (r = −0.314; $P < 0.05$) and positively correlated with VFA (r = 0.474; $P < 0.001$) in subjects with NGT. These correlations hold true for both men (RBP4 with GDR, r = −0.374 and $P = 0.066$; RBP4 with VFA, r = 0.464 and $P = 0.020$) and women (RBP4 with GDR, r = −0.357 and $P = 0.073$; RBP4 with VFA, r = 0.433 and $P = 0.027$).

Administration of rosiglitazone greatly ameliorated hyperinsulinemia in diabetic patients and improved fasting and postprandial glucose levels (Fig. 3). In addition, rosiglitazone treatment also decreased low-density lipoprotein cholesterol, blood pressure, and $HOMA_{IR}$ index (data not shown). Furthermore, administration of rosiglitazone resulted in a decrease in serum RBP4 level (35.2 ± 10.2 *vs.* 24.9 ± 5.6 μg/ml, before *vs.* after treatment, $P < 0.001$), an increase in serum adiponectin level (15.7 ± 6.3 *vs.* 32.5 ± 16.0 μg/ml, before *vs.* after treatment, $P < 0.001$), and a decrease in VFA (137.0 ± 35.0 *vs.* 102.2 ± 27.2 cm^2, before *vs.* after treatment, $P < 0.001$) (Fig. 3). There was a positive correlation between changes of serum RBP4 level and that of VFA both in men and women (r = 0.471; $P = 0.027$) (Fig. 4).

Discussion

RBP4, a recently discovered adipokine, was reported to cause insulin resistance and diabetes (6, 7). It has been suggested that RBP4 interferes with insulin signaling in skeletal muscle and liver and thus results in hyperglycemia (6, 25). In the present study, we showed that the serum RBP4 level was higher in patients with diabetes than those without diabetes. Furthermore, serum RBP4 was correlated with $HOMA_{IR}$, the index of insulin resistance. Because $HOMA_{IR}$ represents both hepatic and peripheral (skeletal muscle and adipose tissue) insulin resistance, we performed a euglycemic-hyperinsulinemic clamp study to determine the correlation between serum RBP4 and whole-body insulin sensitivity (measured by GDR). Indeed, there is a strong correlation between serum RBP4 level and whole-body GDR. It is conceivable that elevated RBP4 may alter insulin signaling in skeletal muscle and liver. Consequently, insulin-mediated glucose transporter (GLUT4) translocation in muscle and gluconeogenic enzymes such as phosphoenolpyruvate carboxykinase (PEPCK) in the liver may be impaired in obese diabetic patients (6). Future studies are needed to elucidate the molecular mechanisms by which RBP4 may interfere with insulin action in insulin-sensitive tissues.

It is well known that obesity is strongly associated with insulin resistance. Recent advances in adipose biology have revealed that several adipokines may contribute to insulin resistance. Studies have shown that serum RBP4 levels are associated with waist circumference (26) and correlated to the percent trunk fat rather than to the percent body fat (27). In the present study, we reported that visceral obesity, not abdominal sc obesity, was linked to increased serum RBP4 levels (because subjects with visceral obesity had higher serum RBP4 levels than those with nonvisceral obesity). Furthermore, we found that the serum adiponectin level was inversely correlated with the serum RBP4 level. This is consistent with previous studies that showed that the serum adiponectin level was reduced in obese subjects (10). A lower serum adiponectin level may contribute to impaired glucose

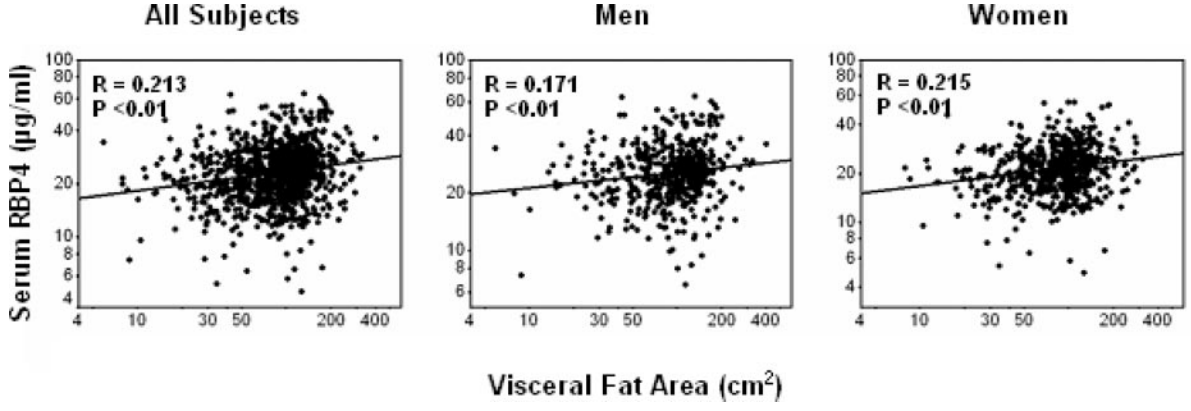

FIG. 1. Relationship between serum RBP4 level and VFA in subjects with NGT, IGT, or type 2 diabetes. Data were plotted on log −log (base-10) scales. Spearman correlation analysis was conducted in all subjects (*left*), men (*center*), or women (*right*).

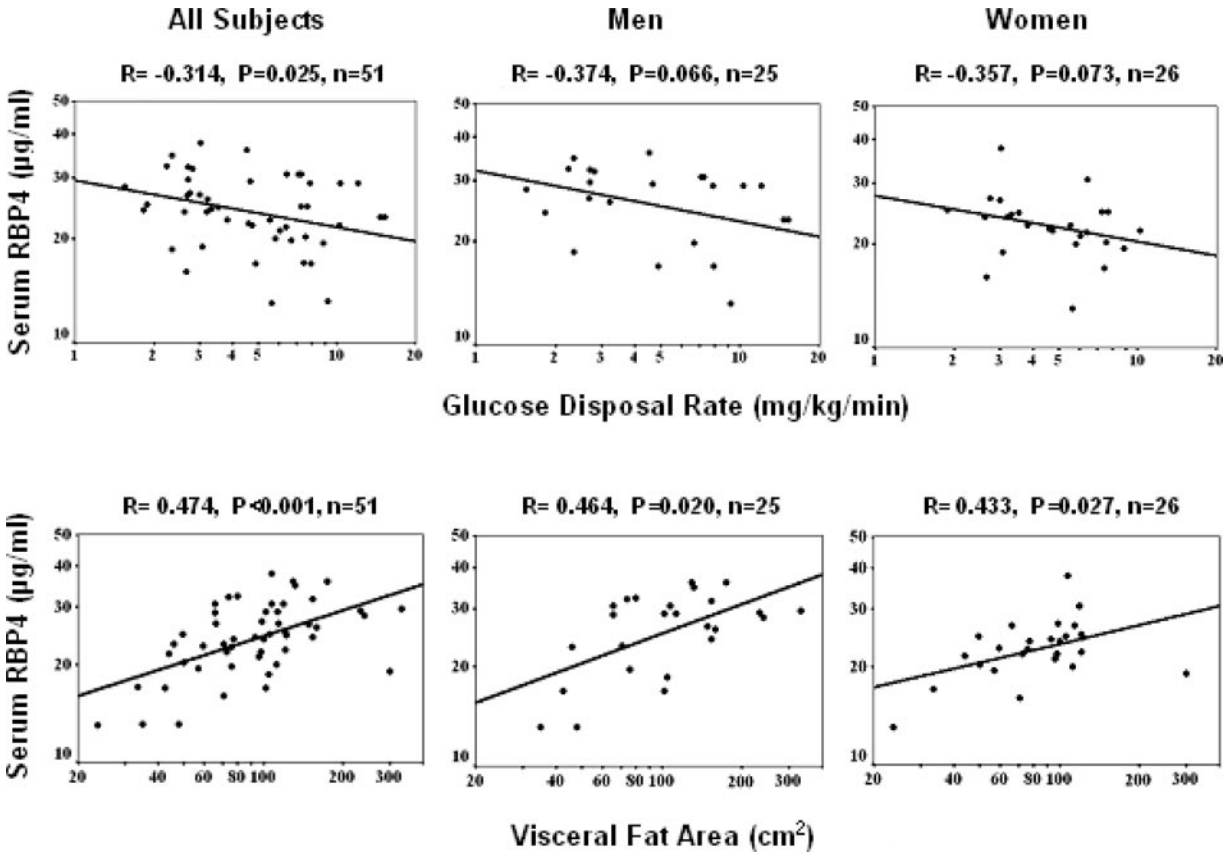

FIG. 2. Relationship between serum RBP4 level and GDR (*upper panel*) and VFA (*lower panel*) in subjects with NGT. Data were plotted on log −log (base-10) scales. Spearman correlation analysis was conducted in all subjects (*left*), men (*center*), or women (*right*).

transport in skeletal muscle and excessive hepatic glucose production (28, 29). It appears that RBP4 and adiponectin are tightly regulated in response to weight gain, especially in the visceral adipose area.

Thiazolidinediones are established insulin sensitizers (30), which have been widely prescribed to improve insulin sensitivity in patients with diabetes. We set out to test the hypothesis that thiazolidinedione treatment will result in a

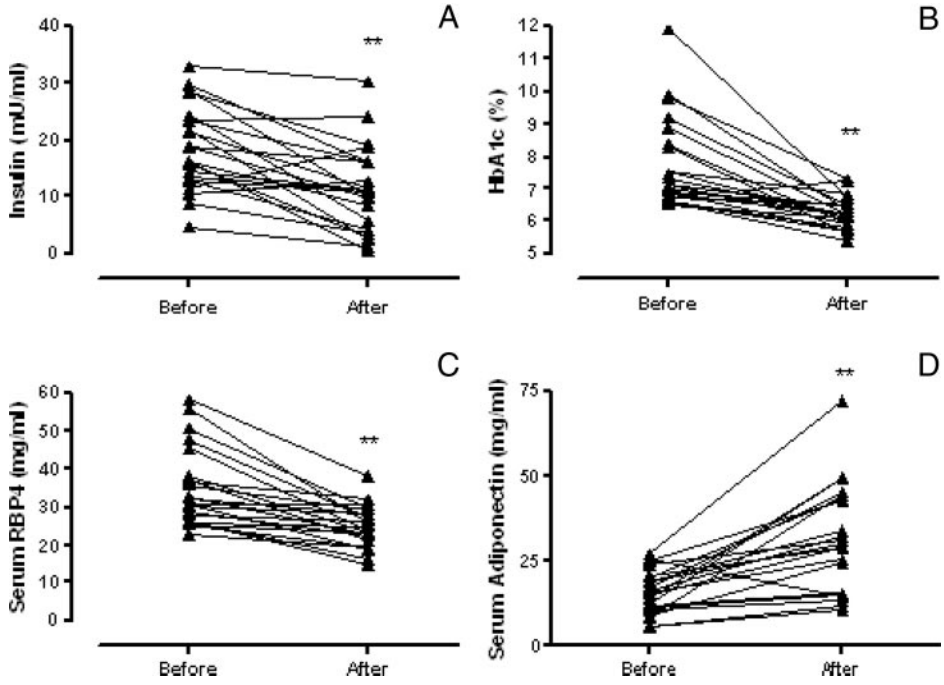

FIG. 3. Serum insulin (A), glycosylated hemoglobin (HbA1c) (B), serum RBP4 (C), and adiponectin (D) levels before and after treatment with rosiglitazone (4 mg daily for 6 months) in newly diagnosed type 2 diabetic patients. Statistical significance of differences is calculated by Wilcoxon signed rank test. **, $P < 0.001$, after *vs.* before treatment.

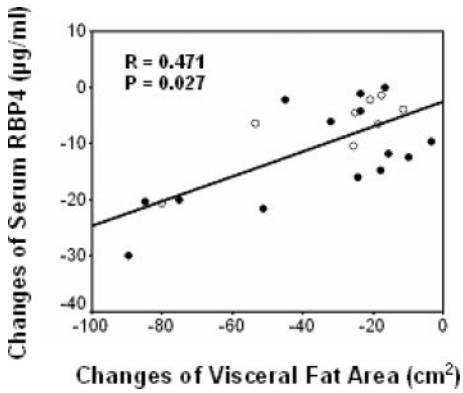

FIG. 4. Changes of serum RBP4 levels and VFA in subjects with type 2 diabetes (n = 22) in men (●) and women (○) after treatment of rosiglitazone 4 mg daily for 6 months. Spearman correlation analysis was conducted in all subjects.

decrease in serum RBP4 level in patients with diabetes. Indeed, patients treated with rosiglitazone for 6 months showed a significant decrease in serum RBP4 levels and an increase in adiponectin levels, which were accompanied by improved insulin sensitivity. Furthermore, we also observed rearrangement of body fat distribution with decreases of VFA and increases of SFA in response to rosiglitazone treatment.

Consistent with a previous study (26), our data showed that men had higher serum RBP4 concentration than that of women. This may be because women had significantly higher SFA and lower VFA than men. The gender difference in RBP4 level, however, does not affect the relationship between serum RBP4 and most metabolic parameters measured in this study. The gender difference in adiponectin has also been reported previously (31).

In conclusion, serum RBP4 level is positively correlated with visceral adiposity in Chinese subjects with and without type 2 diabetes. Subjects treated with rosiglitazone showed reduced visceral fat mass, decreased serum RBP4 levels, and improved insulin sensitivity. However, additional work is warranted to determine whether increased serum RBP4 is the cause or the consequence of insulin resistance.

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