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Relationship between serum retinol-binding protein 4 and visfatin and the metabolic syndrome

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ABSTRACT

Background: This study investigates the relationship between serum concentration of RBP4 and visfatin and the metabolic syndrome.

Methods: Patients with metabolic syndrome were studied between October, 2004 and September, 2005. All study subjects were aged 40 and over and lived in Taichung city, Taiwan. The Third Report of the National Cholesterol Education Program's Adult Treatment Panel (ATP III, 2001) was used to define the metabolic syndrome. Serum RBP4 and visfatin levels were measured by enzyme-linked immunosorbent assay.

Results: Serum mean RBP4 levels in subjects who had all five abnormal components of metabolic syndrome (mean ± SD = 40.8 ± 18.6) and those who had all components except hyperglycemia (43.5 ± 23.5) were significantly higher than those in healthy controls (30.3 ± 14.0 μg/ml) ($p < 0.05$). Similar results were not found in serum visfatin levels. Using log-transformed serum RBP4 or visfatin levels as a dependent variable, we found that subjects with all five and four abnormal components of metabolic syndrome had significantly higher mean serum RBP4 levels ($p = 0.043$ and 0.034, respectively), compared to healthy controls, after adjusting for other covariates. In contrast, similar results were not found in serum visfatin levels.

Conclusion: Metabolic syndrome is significantly associated with serum RBP4, but not serum visfatin.

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1. Introduction

The metabolic syndrome has been associated with atherosclerosis and cardiovascular risk [1]. The predominant underlying risk factors for metabolic syndrome appear to be abdominal obesity [1–4] and insulin resistance [5,6]. Recently, a few studies have found the association of increased serum several biomarkers, such as retinol-binding protein 4 (RBP4) and visfatin, with the risk of insulin resistance [7–10].

RBP4 is an adipocyte-secreted protein. One study demonstrated that mice without glucose transporter 4 (GLUT4) in adipocytes (adipose-Glut4^{-}/$^{-}$ mice) had insulin resistance in muscle and the liver, suggesting that insulin-resistant fat tissue secretes a factor that may induce insulin resistance in other tissues [11]. While adipose-Glut4^{-}/$^{-}$ mice have normal serum levels of most adipocyte-secreted molecules known to influence insulin action [12], serum RBP4 in adipose-Glut4^{-}/$^{-}$ mice was elevated 2.5-fold, compared with control mice [11]. Besides, transgenic overexpression of human RBP4 or injection of recombinant RBP4 causes insulin resistance in normal mice and genetic deletion of RBP4 enhances insulin sensitivity [11]. Together, the results of these animal studies suggest the possible existence of an inter-tissue mechanism capable of causing insulin resistance.

Visfatin (pre-B-cell colony-enhancing factor, PBEF), a newly discovered adipokine, appears to be preferentially produced by visceral adipose tissue and has insulin-mimetic actions. Fukuhara et al. [13] have found that it increases glucose uptake in 3T3-L1 adipocytes and L6 myocytes and suppresses it in H4IIEC3 hepatocytes. Its binding site is different from that of insulin; it directly binds to insulin receptors, activating the phosphorylation of the insulin-signaling cascade. Other studies have found elevated levels of visfatin in the plasma of patients with insulin resistance [8–10].

Because insulin resistance is the key component of metabolic syndrome, this preliminary study investigates the relationship between RBP4 and visfatin and metabolic syndrome by measuring serum levels of RBP4 and visfatin in patients with five abnormal components of metabolic syndrome, those with all except hyperglycemia, and normal controls.

2. Materials and methods

2.1. Experimental subjects

According to the definition of the Third Report of the National Cholesterol Education Program's Adult Treatment Panel (NECP ATP III, 2001), there are 5 components of metabolic syndrome. The most important of these underlying risk factors of metabolic syndrome are abdominal obesity and insulin resistance. Therefore, elevated fasting glucose and elevated waist circumference may be important components. However, presence of defined abnormalities in any 3 of these 5 measures constitutes a diagnosis of the metabolic syndrome. In order to pursue the significant findings in this preliminary study, we chose subjects with extreme conditions: all five abnormal components of metabolic syndrome vs all normal components. Besides, the constellation of metabolic risk factors is strongly associated with type 2 diabetes mellitus or the risk for this condition. Elevated fasting glucose may be the most important component. To understand whether hyperglycemia affects the levels of RBP4 and visfatin, we have also chosen subjects with all components except hyperglycemia in this preliminary study.

Thirty-seven (37) patients with all five abnormal components of metabolic syndrome, 36 with the same abnormal components excluding hyperglycemia, and 45 with none of these abnormal components were randomly recruited from Taichung City, Taiwan, between October, 2004 and September, 2005. All study subjects, aged 40 years and over, participated in the routine healthy check-up in the outpatient clinic of the Department of Family Medicine of China Medical University & Hospital (CMUH) in that period. The modified criteria outlined in the NECP ATP III was used to define metabolic syndrome based on five abnormal components: (1) fasting plasma glucose $\geq$110 mg/dl (6.1 mmol/L); (2) serum triglycerides $\geq$150 mg/dl (1.7 mmol/L); (3) serum HDL-cholesterol (HDL-C) $<$40 mg/dl (1.0 mmol/L) in men and $<$50 mg/dl (1.3 mmol/L) in women; (4) blood pressure (BP) $\geq$130/85 mmHg; or (5) waist circumference $>$90 cm in men and $>$80 cm in women (Asia-Pacific cutoff limits). Subjects were considered with any of the above abnormal components, or if they regularly took pills for the treatment of hypertension, hyperlipidemia, or hyperglycemia.

2.2. Anthropometric measurement and laboratory examination

All participants provided their personal information and were weighed in light clothing, and their heights, waist, and hip-circumference were measured in our outpatient clinic. Body mass index (BMI) was calculated (kg/m^2) as an index of the overall adiposity. With patients standing, waist circumference was measured midway between the iliac and the costal margin. BP was measured from the right arm by an electronic device (COLIN, VP-1000, Japan) twice after the subjects had rested for 20 min. The mean of two BP recordings was used for statistical analysis.

After the physical examination, blood was drawn from an antecubital vein in the morning after 12-h overnight fasting and sent for analysis within 4 h of collection. The separated serum was stored at $-70\,^{\circ}$C until the measurement of RBP4 and visfatin levels. Biochemical markers such as serum HDL-C, triglycerides, and fasting glucose were analyzed using a biochemical autoanalyzer (Beckman Coluter, Lx-20, USA) at the Clinical Laboratory of CMUH. This study complied with the Declaration of Helsinki. The institutional ethics review boards of CMUH approved this research and informed consent was obtained from each participant.

2.3. Serum RBP4 and visfatin levels

RBP4 levels were measured using an enzyme-linked immunosorbent assay kit (ELISA) (Immundiagnostik AG, Bensheim, Germany). The interassay and intraassay coefficients of variation (CVs) were 9.8% and 5% respectively, and the lower detection limit of the assay was 0.9 μg/l. Visfatin levels were measured using an ELISA kit (Phoenix Pharmaceuticals, Inc., California, USA). The interassay and intraassay CVs were $<$5% and $<$14% respectively, and the lower detection limit of the assay was 0.1 ng/ml. The laboratory technician who measured

serum concentrations of RBP4 and visfatin did not have access to study subject information.

2.4. Statistical analysis

Demographic characteristics and laboratory data were categorized into three groups (subjects with all five abnormal components, subjects with all abnormal components except hyperglycemia, and healthy controls) and reported by mean (±standard deviation (SD)) for continuous variables and number (percentage) for categorical variables. Differences in the levels of RBP4 and visfatin among the three groups and serum RBP4 and visfatin levels in each component of the metabolic syndrome were determined by one-way ANOVA followed by Scheffe's multiple-comparison post hoc test. Multiple linear regression models were used to examine the relationship between serum RBP4 or visfatin levels and the metabolic syndrome after adjusting for other covariates, including gender, age, BMI, and smoking status. Since serum RBP4 and visfatin levels were positively skewed, logarithmic transformations were used to normalize their distributions before analysis. All analyses were conducted using SPSS statistical software. A two-sided p-value of <0.05 was considered statistically significant.

3. Results

The demographic characteristics and laboratory information were compared among the three groups (Table 1). The three groups had similar percent of gender as well as mean ages and smoking statuses. Compared to healthy controls, subjects with five or four abnormal components of metabolic syndrome had higher values of BMI, waist circumference, serum triglycerides, HDL-C, and systolic and diastolic BP. Fasting glucose concentrations was higher in subjects who had all five components than those who had four components of metabolic syndrome except hyperglycemia and healthy controls. Serum mean RBP4 levels in subjects who had all five abnormal components (40.8 ± 18.6) and those who had four abnormal components of metabolic syndrome except hyperglycemia (43.5 ± 23.5) were significantly higher than those in healthy controls (30.3 ± 14.0 μg/ml) ($p < 0.05$). Similar results were not found in serum visfatin levels (Table 1).

Table 2 shows mean serum RBP4 and visfatin levels in different components of metabolic syndrome with/without medication treatment. We found that mean serum RBP4 levels were significantly higher in subjects with hypertension with or without treatment than those with normal BP. Similar results were also noted in hypertriglyceridemia or hypo-HDL-C, but not hyperglycemia. Mean serum RBP4 levels between the hypertensive, hypertriglyceridemic, or hypo-HDL-C subjects with or without medication treatment were not significantly different. Mean serum RBP4 levels were also significantly higher in subjects with central obesity than those without. However, mean serum RBP4 levels were not significantly different among the subjects with hyperglycemia with or without treatment and those with normal glucose levels. Subjects with BMI ≥ 27 kg/m^2 and <27 kg/m^2 had also similar mean serum RBP4 levels (39.8 vs 36.3 μg/ml). For serum visfatin, we did not find any significant difference in different components of metabolic syndrome with/without medication treatment.

Table 1 – Demographic and laboratory characteristics of the patient groups.

	Healthy controls	Subjects with 5 abnormal components except hyperglycemia	Subjects with 5 abnormal components
N	45	36	37
Male (%)	25 (56%)	22 (61%)	20 (54%)
Age (year)	59.2 ± 11.1	56.4 ± 10.0	61.8 ± 10.5
Cigarette smoking			
Non-	33 (73.3%)	19 (52.8%)	23 (62.2%)
Former	3 (6.7%)	6 (16.7%)	8 (21.6%)
Current	9 (20.0%)	11 (30.6%)	6 (16.2%)
BMI (kg/m^2)	22.0 ± 2.3	$28.0 \pm 2.3^*$	$28.0 \pm 3.0^*$
Waist circumference (cm)	74.4 ± 7.2	$92.5 \pm 6.3^*$	$93.9 \pm 7.1^*$
Fasting glucose (mmol/L[a])	5.05 ± 0.33	5.38 ± 0.39	$8.99 \pm 3.11^{*,\dagger}$
Triglycerides (mmol/L[b])	0.85 ± 0.34	$2.34 \pm 0.64^*$	$2.63 \pm 1.45^*$
HDL-C (mmol/L[c])	1.45 ± 0.34	$0.85 \pm 0.13^*$	$0.93 \pm 0.16^*$
Systolic BP (mmHg)	118 ± 7	$149 \pm 17^*$	$158 \pm 23^*$
Diastolic BP (mmHg)	70 ± 7	$89 \pm 9^*$	$90 \pm 13^*$
RBP4 (μg/ml)	30.3 ± 14.0	$43.5 \pm 23.5^*$	$40.8 \pm 18.6^*$
Visfatin (ng/ml)	30.6 ± 27.5	27.0 ± 14.1	27.5 ± 13.2

BMI, body mass index; HDL-C, HDL-cholesterol; BP, blood pressure; RBP4, retinol-binding protein 4. One-way ANOVA followed by Scheffe' multiple-comparison post hoc test.

[a] To convert glucose to mg/dL, divide values by 0.0555.

[b] To convert triglycerides to mg/dL, divide values by 0.0113.

[c] To convert HDL-C to mg/dL, divide values by 0.0259.

* $p < 0.05$ vs healthy controls.

† $p < 0.05$ vs subjects with all components of metabolic syndrome except hyperglycemia.

Table 2 – Serum RBP4 and visfatin levels in each component of the metabolic syndrome.

	n	RBP4, mean ± SD (min, med, max)[a]	p	Visfatin, mean ± SD (min, med, max)[a]	p
Fasting glucose (mmol/L)			0.524		0.620
Normal	81	36.2 ± 19.8 (6.6, 31.5, 99.3)		29.0 ± 22.5 (5.5, 24.8, 184.9)	
6.1–6.9	8	38.7 ± 28.3 (11.3, 33.9, 100.7)		35.5 ± 14.3 (11.7, 36.6, 56.3)	
≥7.0	10	37.1 ± 12.5 (20.2, 34.8, 61.7)		25.5 ± 10.2 (8.6, 23.7, 44.5)	
With medication	19	43.6 ± 16.8 (22.3, 37.8, 74.8)		25.0 ± 13.3 (6.1, 26.1, 51.4)	
BP (mmHg)			0.005		0.487
Normal	45	30.3 ± 14.0 (6.6, 29.5, 66.3)		30.6 ± 27.5 (5.5, 24.1, 184.9)	
≥130/85	35	41.4 ± 21.4 (11.3, 36.7, 100.7)*		25.2 ± 13.9 (6.1, 22.4, 57.6)	
With medication	38	42.8 ± 21.0 (7.2, 35.5, 95.3)*		29.1 ± 13.2 (7.6, 26.3, 71.8)	
Triglycerides (mmol/L)			0.005		0.505
Normal	45	30.3 ± 14.0 (6.6, 29.5, 66.3)		30.6 ± 27.5 (5.5, 24.1, 184.9)	
≥1.7	59	41.8 ± 20.9 (7.2, 36.7, 100.7)*		26.3 ± 13.0 (6.1, 25.4, 57.6)	
With medication	14	43.4 ± 22.5 (19.5, 34.4, 95.3)		30.9 ± 15.8 (12.0, 28.3, 71.8)	
HDL-C (mmol/L)			0.002		0.448
Normal	45	30.3 ± 14.0 (6.6, 29.5, 66.3)		30.6 ± 27.5 (5.5, 24.1, 184.9)	
F < 1.3, M < 1.0	60	40.7 ± 20.1 (7.2, 35.9, 100.7)*		26.2 ± 12.9 (6.1, 25.6, 57.6)	
With medication	13	48.5 ± 24.9 (19.5, 43.2, 95.3)*		31.8 ± 16.0 (12.0, 28.6, 71.8)	
Waist circumference (cm)			<0.001		0.373
Normal	45	30.3 ± 14.0 (6.6, 29.5, 66.3)		30.6 ± 27.5 (5.5, 24.1, 184.9)	
F > 80, M > 90	73	42.1 ± 21.1 (7.2, 36.7, 100.7)*		27.2 ± 13.6 (6.1, 25.9, 71.8)	

Abbreviations as in Table 1; F, female; M, male.
One-way ANOVA followed by Scheffe' multiple-comparison post hoc test.
[a] Mean ± standard deviation (minimum, median, maximum).
* $p < 0.05$; compared with normal group.

In multiple linear regression models, using log-transformed serum RBP4 or visfatin levels as a dependent variable, we found that subjects with all five and four abnormal components of metabolic syndrome had significantly higher mean serum RBP4 levels ($p = 0.043$ and 0.034 respectively) compared to healthy controls, after adjusting for gender, age, BMI, and smoking status (Table 3). In the same multivariable models, mean serum RBP4 levels in men (42.2 ± 21.6 μg/ml) were significantly higher than those in women (31.5 ± 14.3 μg/ml). Although mean serum RBP4 levels were higher in subjects with central obesity than those without in the univariate analysis, BMI was not significantly associated with serum RBP4 levels in the multivariate analyses (Table 3). Since, compared to healthy controls, the higher mean serum RBP4 levels were very similar between subjects with all five and four components of metabolic syndrome, we combined these two. We found subjects with metabolic syndrome (4 or 5 abnormal components) had significantly higher mean RBP4 levels than the healthy controls ($\beta = 0.151$, standard error = 0.066, $p = 0.024$) after adjusting for other covariates. Even after further adjusting for the history of using medication for diabetes mellitus, we found that subjects with all five or four

Table 3 – Relationship between serum logRBP4 and logVisfatin levels and the metabolic syndrome in multiple linear regression models.*.

	β	SE (β)	p	95% CI	
RBP4					
Healthy controls (as reference)					
All abnormal except hyperglycemia	.153	.071	.034	.012	.293
All abnormal	.149	.073	.043	.005	.293
Sex Male (as reference)	−.093	.047	.049	−.187	.000
Age	.001	.002	.470	−.003	.006
BMI	−.003	.009	.707	−.020	.014
Cigarette smoking (never smoked as reference)	.044	.049	.370	−.053	.142
Visfatin					
Healthy controls (as reference)					
All abnormal except hyperglycemia	−.011	.082	.889	−.173	.150
All abnormal	−.004	.083	.966	−.168	.161
Sex Male (as reference)	−.063	.054	.241	−.170	.043
Age	.002	.002	.359	−.002	.007
BMI	−.003	.010	.741	−.023	.016
Cigarette smoking (never smoked as reference)	.072	.056	.205	−0.40	.183

abnormal components of metabolic syndrome had marginal significantly higher mean serum RBP4 levels ($\beta = 0.133$, standard error = 0.070, $p = 0.060$), compared to healthy controls. In contrast, anti-diabetic agents were not negatively and significantly associated with serum RBP4 levels ($p = 0.452$). Similar results for the relationship between mean RBP4 levels and metabolic syndrome were also found, after adjusting for the history of using medication for hypertension, diabetes mellitus or hypertriglyceridemia and other covariates ($\beta = 0.140$, standard error = 0.074, $p = 0.062$). Still, history of using medication for hypertension, diabetes mellitus or hyperlipidemia was not significantly associated with serum RBP4 levels ($p = 0.740$) in the same model. For serum visfatin levels, we did not find any significant association with metabolic syndrome (Table 3).

4. Discussion

In this study, serum RBP4 levels were significantly higher in patients with hypertriglyceridemia, hypertension, central obesity and low HDL-C than in normal groups. After adjusting for other covariates, metabolic syndrome with 5 or 4 abnormal components was also positively associated with RBP4 levels.

In the past, RBP4 was considered to be one specific transport protein for retinol (vitamin A) in the circulation and its only known function was to deliver retinol to tissues [14]. However, recently, Yang et al. [11] found that RBP4 is also associated with insulin resistance. Injection of recombinant RBP4 in normal mice causes insulin resistance; conversely, genetic deletion of *RBP4* increases insulin sensitivity. Another study showed RBP4 levels negatively correlated with insulin sensitivity in non-obese subjects without type 2 diabetes [15]. These findings, in combination with ours, suggest increased RBP4 is associated with insulin resistance in subjects with metabolic syndrome, even though they did not have hyperglycemic condition.

Worthy of mention is that subjects with all five components of metabolic syndrome and subjects with four components except hyperglycemia had similar serum RBP4 levels. Even though the constellation of metabolic risk factors is strongly associated with type 2 diabetes mellitus or the risk for this condition, we found that mean serum RBP4 levels between subjects with all five components of metabolic syndrome and subjects with four components except hyperglycemia were not significantly different. Except for hyperglycemia, abdominal obesity is another most important one of these underlying risk factors of metabolic syndrome. At least two studies have shown that non-diabetic obesity is associated with elevated serum RBP4 levels in humans [7,16]. Graham et al. [7] found that people with obese non-diabetes (39.4 ± 5.0 μg/ml) and obese diabetes (40.8 ± 10.8 μg/ml) had 1.9 times higher serum RBP4 than lean controls (23.8 ± 1.0 μg/ml). Another study done by Haider et al. [16] showed that RBP4 was reduced after weight loss in morbidly obese subjects. These findings raise the question whether serum RBP4 level is more strongly correlated with central obesity than with fasting glucose. Future studies can investigate the association between the fasting glucose and serum RBP4 in lean subjects with hyperglycemia.

One previous study showed serum RBP4 levels to be normalized by rosiglitazone, an insulin-sensitizing drug [11]. In this study, we did not find a negative and significant association between use of anti-diabetic agents and serum RBP4 levels. The different findings between ours and Yang et al. [11] are probably due to: (1) Different kinds of anti-diabetic agents prescribed in our study subjects, including sulfonylurea and delay glucose absorption, not only the insulin-sensitizing drugs; and (2) the small sample size in our study.

This study did not find serum visfatin levels to be significantly correlated with any component of metabolic syndrome. Visfatin appears to be preferentially produced by the visceral adipose tissue and to have insulin mimetic actions [13]. However, inconsistent observations from various studies of visfatin have been noted [17], emphasizing that the pathophysiologic role of visfatin in humans is largely unknown and deserves further examination.

There are some limitations of the study. First, the study lacks data on insulin levels and the homeostasis model assessment of insulin resistance (HOMA-IR). However, metabolic syndrome may also serve as a surrogate measure of the insulin resistance phenotype because it identifies a proportion of subjects with insulin resistance without directly measuring insulin action [18,19]. Second, the sample size of this study was relatively small. Third, this is a cross-sectional study, thus the causality of cause–effect relationship cannot be elucidated. Fourth, a lack of the group with 3, instead of 4 and 5, abnormal components of the metabolic syndrome was present in this study. Thus, we cannot address the effect of RBP4 and visfatin on subjects with three abnormal components of metabolic syndrome.

In summary, this study found metabolic syndrome with all five or four abnormal components except hyperglycemia to be positively associated with serum RBP4, but not visfatin levels. A longitudinal and larger study is needed to confirm our findings.

Conflict of interest

The authors state that they have no conflict of interest.

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