Retinol-Binding Protein 4 as a Novel Risk Factor for Cardiovascular Disease in Patients With Coronary Artery Disease and Hyperinsulinemia

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Abstract: *Background:* Retinol-binding protein 4 (RBP4) is an adipokine associated with insulin resistance (IR) and obesity-related metabolic disorders. To evaluate its association with cardiovascular disease, we compared serum RBP4 concentrations in patients with coronary artery disease (CAD) and in controls. *Methods:* Sixty patients with coronary angiography-confirmed CAD, including 30 with CAD and 30 with CAD and hyperinsulinemia (CAD/HIns group), and 29 healthy subjects were enrolled. Serum RBP4, IR indexes and cardiovascular risk factors were assessed in these subjects. *Results:* Serum RBP4 concentrations were significantly higher in the CAD/HIns than in the CAD and control groups ($P < 0.01$ each). RBP4 concentration was significantly associated with cardiovascular risk factors, including body mass index and concentrations of triglycerides, high-density lipoprotein cholesterol, uric acid, high-sensitivity C reactive protein and adiponectin ($P < 0.01$ each). Two-hour postprandial insulin ($\beta = 0.224$), homeostatic model assessment of IR score ($\beta = 0.456$) and adiponectin concentration ($\beta = 0.294$) were independent factors associated with RBP4 ($P < 0.01$ each). *Conclusions:* RBP4 concentration is associated with cardiovascular risk factors related to IR and CAD. Circulating RBP4 could be a marker of metabolic complications and atherosclerosis and could be used to assess CAD.

Key Indexing Terms Coronary artery disease; Retinol-binding protein 4; Hyperinsulinemia. **[Am J Med Sci 2014;348(6):474–479.]**

Adipose tissue is now viewed as an active endocrine organ, secreting many types of adipokines such as adiponectin (APN), resistin, leptin and tumor necrosis factor α.[1–3] Retinol-binding protein 4 (RBP4), first identified in 2005 using gene chips and shown to be a retinol carrier protein in blood,[4] is an adipokine primarily secreted by the liver and adipose tissue found to be associated with the development of insulin resistance (IR).[5–9] Elevated serum RBP4 concentrations increase IR by inhibiting insulin receptor substrate-1 phosphorylation and phosphatidylinositol 3-kinase activation.[4] According to the "common soil" hypothesis,[10–13] IR may be the fundamental link connecting many metabolic abnormalities and[14] atherosclerotic diseases, including ischemic heart disease, coronary artery disease (CAD) and arteriosclerosis obliterans. However, the relationship of RBP4 to atherosclerosis has not yet been determined.

Sun et al[15] did a study among 468 women who developed coronary heart disease and 472 matched controls during 16 years of follow-up, then found that in this cohort of women, higher circulating full-length and total RBP4 levels were associated with increased risk of coronary heart disease in a time-dependent fashion. Intima-media thickness (IMT) was shown to be directly associated with CAD risk factors.[5,16] Assessments of flow-mediated dilatation, IMT and other clinical parameters in 50 subjects with T2DM found that serum RBP4 levels reflect endothelial dysfunction in adults newly diagnosed with T2DM.[17] Moreover, several other studies showed that circulating RBP4 levels correlate with IMT,[18–22] suggesting that measuring serum RBP4 may be a more useful marker of endothelial dysfunction than IMT. Moreover, RBP4 was found to be independent associated with small, dense, low-density lipoprotein (LDL) and with oxidized LDL,[23,24] suggesting that RBP4 plays an important role in atherosclerotic disorders. In elderly individuals, RBP4 concentrations were associated with metabolic syndrome (MetS) and its components in both genders and with prior cerebrovascular disease (CVD) in men,[25] suggesting that circulating RBP4 may be a marker of metabolic complications and possibly of atherosclerosis and CAD. In contrast, some other studies suggested that serum RBP4 is not predictive of CAD risk and is not a marker for MetS or IR in patients with CAD. Circulating RBP4 levels were reported to be higher in type 2 diabetic (T2DM) subjects with than without previous clinical atherosclerosis, suggesting that RBP4 may be a biomarker of CAD in T2DM subjects.[26] In contrast, a study assessing whether circulating RBP4 was predictive of CVD in 1036 patients who developed CAD over a 6-year period found that CVD risk increased as RBP4 levels increased but that this association was lost after adjustment for other CVD risk factors.[14] Moreover, no differences in RBP4 concentrations and RBP4-to-transthyrethin ratio were observed between nondiabetic patients with CAD and controls or between individuals with and without the MetS.[27]

The role of RBP4 in IR and CAD remains unclear. Classic CVD risk factors, including body mass index (BMI), waist-to-hip ratio, blood pressure (BP) and blood lipid and high sensitivity C-reactive protein (hsCRP) concentrations, represent only part of the risk of CVD. Associations between RBP4 and these classic CVD risk factors in patients with CAD and hyperinsulinemia have not yet been evaluated. To investigate the associations between RBP4 and CVD risk factors, serum RBP4 concentrations were compared in groups of patients with CAD and CAD plus hyperinsulinemia (CAD/HIns) and in healthy controls.

SUBJECTS AND METHODS

Subjects

Subjects were recruited while undergoing routine clinical procedures between August 2009 and May 2010 at the

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XiangYa Hospital in Hunan Province in China. Three groups were studied: (1) 30 patients with CAD; (2) 30 CAD/HIns patients and (3) 29 healthy subjects (control group). CAD was defined as remote myocardial infarction or luminal diameter stenosis >50% in at least 1 coronary artery or major branch. Hyperinsulinemia was defined according to the criteria of the Chinese Diabetes Society as fasting insulin concentration ≥15 mU/L and insulin concentration after glucose load ≥80 mU/L. Subjects previously diagnosed with or treated for diabetes; those with malignant tumors, acute or chronic infection, or who experienced recent trauma or surgery; those classified as New York Heart Association level III or IV and subjects with liver or kidney dysfunction were excluded. The study protocol was approved by our local ethics committee, and all subjects provided written informed consent.

Methods

Anthropometric measurements were performed while subjects were lightly clothed and without shoes. Height was measured to the nearest 0.1 cm and weight was measured to the nearest 0.1 kg using an automatic height-weight scale. BMI was calculated as the weight (in kilograms) divided by the square of height (in meters).

Blood samples were collected into chilled tubes containing EDTA-Na2 and centrifuged at 3000 rpm at 4°C for 15 minutes. Fasting plasma glucose (FPG), serum triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), LDL cholesterol, uric acid (UA), hsCRP and free fatty acid concentrations were measured using an autoanalyzer (Beckman CX-7 Biochemical Autoanalyzer; Beckman Coulter, Inc, Fullerton, CA). Serum concentrations of fasting insulin (FIns) and 2-hour postprandial insulin (2hPInS) were measured using a chemiluminescence method.

Serum samples were stored frozen at −80°C until assayed. RBP4 and APN were measured by enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, MN). The intra- and inter-assay coefficients of variation of these tests were <9% and <11%, respectively.

IR was estimated using homeostatic model assessment of IR (HOMA-IR), calculated as [fasting insulin × fasting glucose]/22.5.[28] Beta cell function was estimated using HOMA-B, calculated as 20 × FIns/(FPG − 3.5)[29]; and insulin sensitivity was estimated using insulin sensitivity index (ISI), calculated as LN [1/(FPG × FIns)].[30]

Statistical Analysis

Data are expressed as mean ± standard deviations (SDs) or as medians and interquartile ranges. Non-normally distributed variables were analyzed using log-transformed values. Differences between pairs of groups were assessed using Student's *t*-tests. Spearman's rank coefficient analysis were performed to determine relationships between RBP4, APN and other variables. Partial correlations analyses were performed to determine associations between RBP4 levels and other factors when controlling some factors such as gender, age or BMI. The Stepwise multiple linear regression analyses was used to select statistically significant variables. *P*-values <0.05 were considered significant. Data were analyzed using SPSS 13.0 for Windows (SPSS Inc, Chicago, IL).

RESULTS

Participants' Characteristics

There were no significant differences among the CAD, CAD/HIns, and control groups in gender distribution, systolic BP, diastolic BP (DBP) or waist-to-hip ratio. Controls were significantly younger ($P < 0.01$). BMI, FIns, 2hPIns, HOMA-IR, HOMA-B and ISI ($P < 0.01$ each), as well as UA and APN ($P < 0.05$ each) were significantly higher in the CAD/HIns group than in the other 2 groups (Table 1).

Serum RBP4 Concentrations

Serum RBP4 concentrations were higher in the combined CAD/HIns and CAD groups than in the control group ($P < 0.01$; Figure 1, Table 1). RBP4 concentrations were similar in the CAD and control groups but were significantly higher in the CAD/HIns than in either of the other 2 groups ($P < 0.01$).

Associations Between Serum RBP4 Levels and Subjects' Gender and Age

Serum RBP4 concentrations were similar in men and women (22.71 ± 11.44 μg/mL versus 22.53 ± 8.75 μg/mL, P = nonsignificant). Age was positively associated with serum RBP4 ($r = 0.361$, $P = 0.001$), even after adjustment for gender and BMI ($r = 0.339$, $P = 0.002$).

Relationship Between RBP4 and Cardiovascular Risk Factors

Serum RBP4 concentrations were positively correlated with BMI, TG, UA and hsCRP concentrations and negatively correlated with HDL-C and APN concentrations (Table 2). HDL-C showed the strongest correlation with RBP4 ($r = -0.290$; $P < 0.01$).

Determinants of Serum RBP4

After adjustment for age and gender, serum RBP4 concentrations were modestly correlated with FPG ($r = 0.239$), FIns ($r = 0.560$), 2hPIns ($r = 0.422$) and APN ($r = -0.296$) concentrations and with HOMA-IR ($r = -0.567$), HOMA-B ($r = 0.393$) and ISI ($r = -0.567$) scores ($P < 0.05$ each). Stepwise multiple linear regression analyses showed that 2hPIns ($\beta = 0.224$) and APN ($\beta = 0.294$) concentrations and HOMA-IR score ($\beta = 0.456$) were independent determinants of serum RBP4 concentrations ($P < 0.01$ each).

Clinical Characteristics Relative to Serum RBP4 Quartiles

To assess the associations between serum RBP4 concentrations and other CAD risk factors, subjects were divided into serum RBP4 quartiles (Table 3). The proportion of patients with combined CAD/HIns increased as RBP4 levels increased, as did FPG, HDL-C, UA, hsCRP, FIns, 2hPIns, HOMA-IR and ISI.

DISCUSSION

Previous studies have suggested that RBP4 concentration is significantly associated with IR,[4] T2DM,[4] atherosclerosis[14,21,22,25,27] and renal dysfunction.[26,31,32] The present study examined serum RBP4 levels in patients with CAD and CAD/HIns patients, who have not yet developed glucose metabolism disorders. We confirmed that serum RBP4 levels were elevated in CAD/HIns patients and that the proportion of patients with combined CAD/HIns increased as RBP4 levels increased. In addition, we found that serum RBP4 concentrations were significantly associated with IR, measured as HOMA-IR scores; with beta cell function, measured as HOMA-B score and with insulin sensitivity, measured using ISI score. We also found that HOMA-IR score was an independent determinant of serum RBP4, and that plasma insulin, not

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