Relationship Between Plasma Adiponectin, Retinol-Binding Protein 4 and Uric Acid in Hypertensive Patients With Metabolic Syndrome

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ABSTRACT

Background and Objectives: Adipokines have been suggested for their potential use in tracking the clinical progress in the subjects with metabolic syndrome (MS). To investigate the relationship between the serum levels of adipokines (adiponectin and retinol-binding protein 4 (RBP4)) and the serum level of uric acid in hypertensive (HTN) patients with MS.

Methods: In this study, 38 totally untreated HTN patients were enrolled. Anthropometric measurements, blood pressure (BP) were taken in the 12 HTN patients without MS and the 26 HTN patients with MS. Fasting blood samples were collected for measurement of adiponectin, RBP4, nitric oxide (NO), glucose, creatinine, uric acid, lipid profile and insulin.

Results: The HTN with MS group had significant higher values of body mass index, waist length, serum uric acid and triglyceride levels than the HTN without MS group. Compared to the HTN without MS group, the HTN with MS group showed significantly lower adiponectin (p=0.030), NO (p=0.003) and high density lipoprotein levels (p<0.001). Serum adiponectin levels negatively correlated with insulin level (R=-0.453, p=0.026) and uric acid level (R=-0.413, p=0.036), and serum RBP4 levels positively correlated with uric acid level (R=0.527, p=0.006) in the HTN with MS group. Multiple linear regression analysis using RBP4 and adiponectin levels as the dependent variables showed that uric acid level correlated with serum RBP4 level (p=0.046) and adiponectin level (p=0.044).

Conclusion: The HTN with MS group showed a correlation with two types of adipokines (adiponectin, RBP4) and uric acid. Adiponectin, RBP4 and uric acid may be important components associated with MS, especially when associated with hypertension.

KEY WORDS: Adiponectin; Retinol-binding protein 4; Uric acid; Hypertension; Metabolic syndrome.

Introduction

Metabolic syndrome (MS), that is the clustering of abnormalities in glucose metabolism, lipid metabolism, and blood pressure (BP), and is associated with an increased prevalence of subclinical damage in a variety of organs. MS increases the risk for the target organ damage in hypertensive (HTN) patients and the development of type 2 diabetes mellitus.

Hyperuricemia mediates the development of end-organ damage such as increased carotid intima-media thickness, and it is regarded as a cardiovascular risk factor and a determinant of MS, although the other studies have concluded that an association between serum uric acid and cardiovascular disease merely reflects the link between serum uric acid and other risk factors.

Adiponectin is known to have anti-inflammatory and anti-atherogenic activities and adiponectin levels significantly correlated with various indices (including serum uric acid) of MS. Circulating levels of retinol-binding protein-4 (RBP4) are elevated in humans with insulin resistance, which is a hallmark of MS. It can also predict early stages in the development of insulin resistance, a major cause of type 2 diabetes as well
as cardiovascular disease. Impairment of nitric oxide (NO) release is associated with endothelial dysfunction.

In this study, we screened the metabolic parameters, renal involvement, uric acid, adiponectin, RBP4, NO and insulin in HTN patients with or without MS. We investigated the relationship between the plasma levels of adiponectin and RBP4 with the other variables of MS in the HTN with MS group. Finally, we also clarified the association between the two types of adipokines (adiponectin, RBP4) and uric acid, which are the known markers of endothelial dysfunction and cardiovascular damage in MS, in the HTN with MS group.

Subjects and Methods

Patients
In total, seventy consecutive patients diagnosed with essential hypertension were enrolled from the outpatient clinic at Bucheon St. Mary’s Hospital, Bucheon, South Korea. Hypertension was defined as official systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg. These patients had no history of anti-hypertensive and anti-diabetic treatment and they had not taken lipid lowering agents within the last 6 months. The main exclusion criteria were: the presence of clinical or laboratory evidence of congestive heart failure, atrial fibrillation, previous stroke, significant valvular heart disease, previous myocardial infarction, history of coronary bypass, secondary cause of hypertension, and neoplastic disease. The patients informed consent had been obtained during the initial visit.

The patients were categorized into two groups: HTN without MS group and HTN with MS group. The study protocol was approved by the Ethics Committee of Bucheon St. Mary’s Hospital.

Definition of metabolic syndrome
MS was diagnosed when two or more of the following criteria were present in the HTN patients: abdominal obesity (waist circumference >90 cm and >80 cm in women), hypertriglyceridemia (>150 mg/dL), reduced high density lipoprotein-cholesterol (HDL-C) (<40 mg/dL in men and <50 mg/dL in women), high fasting blood glucose (≥100 mg/dL), and sex, 12 patients were selected from the remaining 44 patients and they were categorized into HTN with MS group. Considering for age, body mass index (BMI), creatinine, total cholesterol, triglyceride, HDL-C levels were reduced in the HTN with MS group. Serum levels of uric acid were higher in both the patient groups (HTN without MS : HTN with MS=1.26 ± 5.03, p=0.106). Triglyceride levels were elevated in the HTN with MS group. Serum adiponectin (HTN with MS : HTN without MS =8.57 ± 6.58 : 4.53 ± 4.31, p=0.030) and NO (HTN without MS : HTN with MS=61.2±28.0 : 27.5±22.5, p=0.003) concentrations were lower in the HTN with MS group. Serum levels of RBP4 were elevated in the HTN with MS group, although this was not statistically significant (HTN without MS : HTN with MS=21.3±12.6 : 38.4±29.7, p=0.106). Serum levels of uric acid were higher in both the patient groups (HTN without MS : HTN with MS=0.13±1.26 : 5.03±1.19, p=0.040). Triglyceride levels were elevated and HDL-C levels were reduced in the HTN with MS group (Table 1).

Statistics
The results are expressed as means ± standard deviation. Comparisons of the serum markers between the HTN with MS and the HTN without MS groups were analyzed by using the independent t-test. Nonparametric test was also performed using Mann-Whitney test. Correlations between the levels of adiponectin, RBP4, NO and uric acid were also analyzed using the Pearson correlation test. Several multiple linear regression models were also performed by using plasma adiponectin, RBP4 or NO as the dependent variable and using age, body mass index (BMI), creatinine, total cholesterol, triglyceride, HDL-C, and uric acid level as independent variables in the HTN with MS group. All statistical calculations were performed using a commercially available statistical package (SAS, version 8.0, NC). A value of p<0.05 was considered statistically significant.

Results
Of the seventy consecutive HTN patients, 26 patients were categorized into HTN with MS group. Considering for age and sex, 12 patients were selected from the remaining 44 patients and they were categorized into HTN without MS group. Only BMI and waist circumference were significantly higher in the HTN with MS group. Serum adiponectin (HTN without MS : HTN with MS=19.6±12.3 : 21.3±12.6, p=0.106) and NO (HTN without MS : HTN with MS=1.19±0.70 : 2.19±1.6, p=0.007) concentrations were lower in the HTN with MS group. Serum levels of RBP4 were elevated in the HTN with MS group, although this was not statistically significant (HTN without MS : HTN with MS=21.3±12.6 : 38.4±29.7, p=0.003). Serum levels of uric acid were higher in both the patient groups (HTN without MS : HTN with MS=1.13±1.26 : 5.03±1.19, p=0.040). Triglyceride levels were elevated and HDL-C levels were reduced in the HTN with MS group (Table 1).
Relationship between classical and novel biomarkers in hypertensive patients with or without metabolic syndrome

Correlation between two adipokines, uric acid and NO are summarized in Table 2. In the HTN with MS group, serum adiponectin levels were negatively correlated with uric acid ($r=-0.413$, $p=0.036$) (Fig. 1) and insulin levels ($r=-0.453$, $p=0.026$) and positively with QUICKI ($r=0.442$, $p=0.031$). RBP4 levels showed positive correlation with uric acid ($r=0.527$, $p=0.006$) (Fig. 2), but serum NO levels did not correlate positively with uric acid, insulin or QUICKI. These correlations were not observed in the HTN without MS group. Multiple linear regression analysis with serum adiponectin and RBP4 levels as the dependent variables revealed that only uric acid

Table 1. Clinical characteristics and metabolic variables of hypertensive patients with or without metabolic syndrome

|                      | MS (-) n=12 | MS (+) n=26 | p   |
|----------------------|-------------|-------------|-----|
| Age (years)          | 49±9        | 48±8        | 0.947|
| Sex (M/F)            | 5/7         | 12/14       | 0.800|
| BMI (kg/m$^2$)       | 23.2±1.8    | 25.9±3.2    | 0.012|
| Waist (cm)           | 84.9±4.9    | 89.9±6.0    | 0.012|
| Sys. BP (mmHg)       | 150±13      | 147±14      | 0.539|
| Dia. BP (mmHg)       | 98±10       | 100±10      | 0.558|
| Heart rate (/minutes)| 68±68       | 72±15       | 0.106|
| Fasting glucose (mg/dL) | 93±9    | 96±9       | 0.306|
| HbA1C (%)            | 5.5±0.4     | 5.5±0.4     | 0.755|
| Creatinine (mg/dL)   | 0.8±0.2     | 0.8±0.2     | 0.850|
| Total cholesterol (mg/dL) | 209±38     | 207±41     | 0.878|
| Triglyceride (mg/dL) | 103±43      | 165±76      | 0.012|
| HDL-C (mg/dL)        | 53±10       | 43±8        | <0.001|
| Spot urine MCR (mg/g)| 43±40       | 71±220      | 0.094|
| hs-CRP (mg/dL)       | 1.79±2.71   | 2.21±6.85   | 0.848|
| Fibrinogen (mg/dL)   | 282±77      | 324±54      | 0.111|
| Uric acid (mg/dL)    | 4.13±1.26   | 5.03±1.19   | 0.040|
| Insulin (µU/mL)      | 4.6±2.5     | 6.8±3.5     | 0.129|
| QUICKI               | 0.39±0.04   | 0.37±0.04   | 0.099|
| RBP4 (µg/mL)         | 21.3±12.6   | 38.4±29.7   | 0.106|
| Adiponectin (µg/mL)  | 8.57±6.58   | 4.53±4.31   | 0.030|
| Nitric oxide (µmol/mL) | 61.2±36.0   | 27.5±22.5   | 0.003|

BMI: body mass index, BP: blood pressure, HDL-C: high density-lipoprotein-cholesterol, MCR: microalbumin to creatinine ratio, hs-CRP: high sensitivity C-reactive protein, QUICKI: quantitative insulin sensitivity check index, RBP4: retinol-binding protein 4

Table 2. Correlation between classical and novel biomarkers in hypertensive patients with or without metabolic syndrome

|          | UA       | Adiponectin | RBP4 | NO       |
|----------|----------|-------------|------|----------|
| MS (-)   |          | Pearson     |      |          |
|          | product-moment | correlation coefficient |      |          |
| UA       | 1        | -0.482      |      | 1        |
| Adiponectin | 0.247    | -0.339      |      | 1        |
| RBP4     | 0.088    | 0.370       |      | -0.438   |
| NO       |          |             |      |          |
| MS (+)   |          | Pearson     |      |          |
|          | product-moment | correlation coefficient |      |          |
| UA       | 1        |             |      |          |
| Adiponectin | -0.413*  |             |      |          |
| RBP4     | 0.527†   | 0.113       |      | 1        |
| NO       | -0.243   | -0.149      |      | -0.286   |

*Correlation is significant at the 0.05 level. †Correlation is significant at the 0.01 level. MS: metabolic syndrome, UA: uric acid, RBP4: retinol binding protein 4, NO: nitric oxide
correlated independently with serum RBP4 and adiponectin level (Table 3 and 4).

**Discussion**

We have presented a correlation between the two types of adipokines (adiponectin and RBP4) and uric acid in the HTN with MS group. RBP4 had a positive correlation with uric acid, while adiponectin had an inverse correlation with uric acid. In addition, we also demonstrated that the HTN with MS group had significantly higher values of serum uric acid and lower serum adiponectin and NO levels than the HTN without MS group. The strength of this study was that the subjects were initially diagnosed as HTN had not taken any medication; thus there were no confounding factors such as anti-hypertensive, anti-diabetic and lipid-lowering agents which are known to affect cytokine levels. Secondly, we used multiple linear regression analysis to confirm the association between the two adipokines (adiponectin or RBP4), NO and uric acid, which are the known risk factors of MS and cardiovascular events in HTN accompanying MS.

Our study also showed that the levels of serum uric acid were elevated in the HTN with MS group. Hyperuricemia is related to an increased incidence of high BMI, high BP, high triglycerides and a 10-year probability of coronary heart disease. It is also associated with insulin resistance and its mechanism is a decreased renal excretion of uric acid.

Increased serum RBP4 levels were known to contribute to impaired insulin-stimulated glucose uptake in muscle and elevated hepatic glucose production, both of which are characteristic of type 2 diabetes. RBP4 level is currently known to be independently associated with uric acid level in patients with type 2 diabetes mellitus. Our data showed that serum RBP4 levels were elevated in the HTN with MS group, but was not significantly different than in the HTN without MS group (p=0.106). However, RBP4 was strongly correlated with uric acid which was a cardiovascular risk factor and a determinant of MS. The levels of two types of adipokines (adiponectin and RBP4) showed a significant relationship with uric acid in the HTN with MS group and it was stronger between RBP4 and uric acid. Only RBP4 levels showed an independent relationship with uric acid after multivariate regression analysis when considering for age, BMI, creatinine, total cholesterol and QUICKI. Elevated plasma levels of RBP4 are known to be related with cerebrovascular disease and metabolic complication.

In conclusion, plasma levels of the two types of adipokines (adiponectin and RBP4) or uric acid by pharmacological treatment might lead to a reduced risk for cardiovascular event.

In our study, serum adiponectin levels were decreased in the HTN with MS group as compared to the HTN without MS group. Adiponectin levels also correlated with uric acid, but this relationship was weaker than the relationship between RBP4 and uric acid. In contrast to the other adipocyte-derived proteins, adiponectin has anti-inflammatory and anti-atherogenic activities. Low levels of adiponectin are considered as a hallmark of MS and increases the risk of insulin resistance, visceral adiposity and related MS. The plasma levels of NO were significantly different between the two groups. But NO failed to exhibit a relationship with the other clinical or biochemical markers of hypertension with MS. It may be due to its labile character and a relatively small number of patients in this study.

The limitations of our study are a cross-sectional design and small sample size. Large, prospective, placebo-controlled intervention trials are needed to document whether changing the levels of the two types of adipokines (adiponectin and RBP4) or uric acid by pharmacological treatment might lead to a reduced risk for cardiovascular event.

In conclusion, plasma levels of the two types of adipokines (adiponectin and RBP4) or uric acid showed a correlation in the HTN with a complication of MS group. This result can add further evidence of RBP4 as a marker of metabolic complication in addition to adiponectin, especially in the HTN patients.

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