

# **Relationship between uric acid levels and impaired glucose tolerance in subjects with metabolic syndrome**

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## **Body**

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### ABSTRACT

**Objective:** Metabolic syndrome (MetS) is a clustering of cardio-metabolic risk factors. Elevated serum uric acid levels are frequent in cases with cardiovascular disease carrying many attributes of MetS. The role of uric acid in the MetS pathogenesis and the development of Type 2 Diabetes Mellitus (DM) was not fully understood. In this study, the relationship between serum uric acid levels and MetS criteria and oral glucose tolerance test (OGTT) results was studied.

**Methodology:** This study was carried out in 83 patients having at least three MetS diagnosis criteria recommended by National Cholesterol Education Program Adult Treatment Panel III. After collecting 12-hour fasting venous blood samples of subjects, 2-hour OGTT was performed with 75 g oral glucose. A glucose level between 140 and 199 mg/dl at hour 2 was defined as impaired glucose tolerance.

**Results:** The 2-hour glucose value of 25 cases (31%) out of 83 cases was determined to be 140 mg/dl and over. In the multiple linear regression analysis, it was found that uric acid level and waist circumference, and body mass index and 2-hour OGTT levels were significantly related. **Conclusion:** In this study, in cases having high risk for type 2 DM, it was found that uric acid levels were related by some MetS components. Uric acid concentrations did not effect basal glycemia and insulin sensitivity.

**KEY WORDS:** Metabolic syndrome, Uric acid, Glucose intolerance.

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### INTRODUCTION

Metabolic syndrome (MetS) is a cluster of metabolic abnormalities defined as the clustering of several cardiovascular risk factors in an individual including visceral obesity, hypertension, hypertriglyceridemia, low high density lipoprotein-cholesterol (HDL-C) level, and impaired glucose tolerance (IGT).<sup>1</sup> IGT is an important intermediate step in the natural course of type 2 diabetes mellitus (DM).<sup>2</sup> Patients with IGT have higher risk for type 2 DM and development of cardiovascular disease (CVD), therefore; they constitute an important target group in primary prevention.<sup>3</sup> It is known that there is a relation between serum uric acid levels and cardiovascular

## Relationship between uric acid levels and impaired glucose tolerance in subjects with metabolic syndrome

conditions, including hypertension, MetS, coronary artery disease, cerebrovascular disease, vascular dementia, preeclampsia, and kidney disease.

Increasing evidence suggests that uric acid may play a role in the MetS and therefore some authors have provided evidence for including elevated serum uric acid with impaired renal clearance as a component of MetS.<sup>5</sup>

In this study, the relationship between biochemical indices and uric acid levels were studied in a group of cases having high risk of developing type 2 DM.

### METHODOLOGY

Eighty-three patients with MetS admitted to the Diabetes Outpatient Clinic of Istanbul Goztepe Training and Research Hospital were enrolled in the study. The presence of at least three of the following criteria proposed by National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) definition was required for the diagnosis of MetS: Blood pressure  $\geq$  130/85 mmHg [or use of antihypertensive agents]; fasting plasma glucose (FPG) greater than 110 mg/dL [or use of antidiabetic medications]; fasting triglyceride  $\geq$  150 mg/dL; HDL-C less than 40 mg/dL (male) or less than 50 mg/dL (female); and waist circumference greater than 102 cm for males or greater than 88 cm for females.

Exclusion criteria were known DM or FPG greater than 126 mg/dl, use of antihypertensives, lipid lowering drugs or drugs that are known to effect uric acid levels; steroid or hormone replacement treatment; hypothyroidism; pregnancy; hepatic, renal and cardiac failure, and presence of gout.

Local ethical committee approval and patient consent were obtained for the study. Detailed patient history were collected and physical examination were performed on all patients. Anthropometric measurements (height, weight, waist circumference) were carried out by same person using standard measurement instruments on patients with hospital clothing, while standing. Body mass index (BMI) was calculated by dividing the patient's weight by the square of his or her height (mass/height<sup>2</sup>, kg/m<sup>2</sup>). Waist circumference was measured while standing at the narrowest place of waist midway between the anterior superior iliac spine and the lower rib margin in light expiration.

After resting for 10 minutes, blood pressures of patients were measured in a sitting position from both arms, using mercury blood pressure device with appropriate cuff by same person taking Korotkoff Phase I and Phase V sounds as base. Second measurement was performed minimum three minutes after the first one. Average systolic and diastolic blood pressures from both measurements were recorded.  $\geq$  130 mmHg and over systolic blood pressure (SBP) and  $\geq$  85 mmHg and over diastolic blood pressure (DBP) were accepted as hypertension.

After collecting fasting venous blood samples of subjects, 2-hour oral glucose tolerance test (OGTT) was performed with 75 g oral glucose. A glucose level between 140 and 199 mg/dl at hour 2 was defined as IGT.<sup>6</sup> After 12 hours of night fasting, venous blood samples were taken, centrifuged (2500 cycle/min) and separated into serums for the biochemical indices. Glucose, total cholesterol, low-density lipoprotein cholesterol (LDL-C), HDL-C, triglyceride and uric acid levels were determined by enzymatic method and insulin level was determined by electrochemiluminescence immunoassay (ECLIA) method with a Roche E170 device. Insulin sensitivity was assessed by Homeostasis Model Assessment of Insulin Resistance (HOMA-IR). Accordingly, insulin resistance was calculated through the following formula: Fasting insulin level ( $\mu$ U/ml)  $\times$  FPG (mmol/L) / 22.5.<sup>7</sup>

In this study, statistical analysis were carried out by GraphPad Prism V.3 software. In the evaluation of data, descriptive statistical methods (mean, standard deviation) along with the independent t test to compare two groups were used. The relationship between uric acid level and variables was determined by multiple linear regression analysis. Results were evaluated on a significance level of p less than 0.05.

### RESULTS

A total of 83 patients who were followed due to MetS diagnosis aged 18 years and older (64 female, mean age: 51.1 $\pm$ 9.5; 19 male, mean age: 50.1 $\pm$ 14.2) were enrolled in the study. According to OGTT results, of the subjects 58 (69%) were found to have normal glucose tolerance, and 25 (31%) to have IGT. OGTT value greater than 140 and

## Relationship between uric acid levels and impaired glucose tolerance in subjects with metabolic syndrome

less than 140 between the groups, SBP, DBP, waist circumference, BMI, FPG, Uric acid, HDL-C, triglyceride, insulin and HOMA-IR levels were observed no significant relationship ( $p$  greater than 0.05), OGTT 1 hour value greater than 140 was significantly higher in the IGT group ( $p$  less than 0.001) (Table-I). Linear multiple regression analysis was performed to determine the relationship of uric acid levels with MetS components and IGT.

Uric acid levels were observed to be significantly associated with waist circumference ( $r=0.180$ ,  $p=0.0001$ ), BMI ( $r=0.248$ ,  $p=0.009$ ) and 2-hour OGTT value ( $r=0.288$ ,  $p=0.038$ ) (Figure-1).

## DISCUSSION

MetS is associated with increased cardiovascular morbidity and mortality, which constitutes the basis of clinical importance of the syndrome.<sup>8</sup> Although many epidemiological studies indicate that elevated uric acid levels were a risk factor for cardiovascular mortality, this case was not clarified yet.<sup>9,10</sup> In subjects with high MetS risk, uric acid is thought to be the determinative variable for the development of Type 2 DM.<sup>11</sup> As a risk factor for MetS and CVD, glucose increase after OGTT found to be superior than fasting plasma glucose for determining insulin resistance. However, it is not practical to perform OGTT on every patient therefore it is recommended to apply the test in patients with 110-126 mg/dl fasting blood glucose. Consequently, high risk group for MetS should be defined and then insulin resistance components should be studied.

IGT represents a prediabetic state positioned somewhere between normal glucose tolerance and diabetes, which is also assumed to make individuals in this state high y susceptible to atherosclerotic disease.<sup>6,12,13</sup>

Table-I: Distribution of subjects with MetS by OGTT results.

	greater than 140 (n=25)	less than 140 (n=58)	t	p
Age ( year)	52.2±10.84	50.26±10.44	0.77	0.444
SBP (mmHg)	148.8±16.91	148.53±16.86	0.07	0.948
DBP (mmHg)	95.6±4.86	95.43±8.29	0.10	0.925
BMI (kg/m <sup>2</sup> )	33.28±3.41	33.19±4.66	0.09	0.927
WC (cm)	98.12±7.82	98.21±6.83	-0.05	0.96
FPG (mg/dl)	113±5.89	110.41±9.18	1.30	0.199
Uric acid (mg/dl)	4.55±1.27	4.84±1.25	-0.98	0.331
HDL-C (mg/dl)	47.84±8.75	46.57±12.44	0.46	0.644
Triglyceride (mg/dl)	144.76±74.74	180.45±115.38	-1.42	0.159
Insulin (μU/ml)	11.44±5.03	12.1±5.21	-0.54	0.594
OGTT 1-hour	106.56±10.22	96.84±12.86	3.35	0.001
HOMA-IR	3.19±1.45	3.26±1.3	-0.20	0.844
Triglyceride/ HDL-C	3.14±1.71	4.36±3.34	-1.73	0.087

SBP: systolic blood pressure, DBP: diastolic blood pressure, BMI: body mass index, WC: waist circumference, FPG: fasting plasma glucose, C: cholesterol, OGTT: oral glucose tolerance test, HOMA-IR: Homeostasis Model Assessment of Insulin Resistance.

In large epidemiological studies, hyperuricemia has been shown to cause increased incidence of CVD, and increased mortality in those with CVD.<sup>10,14</sup> In NHANES 1 epidemiological follow-up study, 5926 subjects were followed up for a mean of 16.4 years. Increased serum uric acid levels measured at baseline were found to be independently associated with increase in mortality. In addition, when corrected for other risk factors, every increase of 1 mg/dl was found to increase death rate due to cardiovascular and ischemic heart disease both in men and women.<sup>10</sup>

In the 8-year prospective study by Kekalainen et al<sup>15</sup> it was found that while dyslipidemia, hypertension and uric acid levels were associated with insulin resistance, hypertension and very-low-density lipoprotein cholesterol were associated with impaired first phase insulin secretion. In insulin resistant patients, plasma uric acid concentrations are higher due to the decrease of uric acid renal clearance. Nonetheless, plasma uric acid level is not a very sensitive indicator of the insulin resistance. Normal uric acid levels do not necessarily mean insulin sensitivity.<sup>16</sup>

## Relationship between uric acid levels and impaired glucose tolerance in subjects with metabolic syndrome

In our study, while a significant association was observed between uric acid level and 2-hour OGTT value, basal glycemia and insulin sensitivity were seen not to have effected. In ***CARDIA study***, 10 year change in serum uric acid and its relation to changes in other metabolic risk factors were evaluated in young adults.

In that study, although change in all of the metabolic factors was associated with change in uric acid, in multivariable analyses only BMI and triglyceride had a significant independent association with uric acid levels.

Obesity is one of the most important factors associated with MetS and Type 2 DM rising in recent years.<sup>18,19</sup> In studies conducted with adults, it was found that increased BMI is associated with hyperuricemia.<sup>19,20</sup> Leptin is produced at adipocytes and it is one of the hormones that plays a key role in controlling body mass. Increased leptin levels are associated with insulin resistance in early Type 2 DM and MetS. Bedir A et al. demonstrated that leptin has a role in the relationship between obesity and hyperuricemia.<sup>21</sup>

In addition, hypertriglyceridemia and free fat acids were found to be associated with hyperuricemia independent from central body fat deposition and obesity.<sup>19,22</sup> In this study, significant relationship between uric acid levels and waist circumference and BMI was observed while there was no relationship with triglyceride level.

The fact that uric acid was found to be associated with waist circumference and BMI in our study supports the information that uric acid is strongly associated with obesity, especially with abdominal obesity.

In conclusion, in MetS subjects with obesity and IGT, evaluation and treatment of uric acid levels seems to be an approach that should be considered in preventing atherosclerotic cardiac diseases.

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