Original Article

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

Elif Yorulmaz[1], Mehmet Uzunlulu[2], Hatice Yorulmaz[3], Aytekin Oguz[4]

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).[1] IGT is an important intermediate step in the natural course of type 2 diabetes mellitus (DM).[2] 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.[3] It is known that there is a relation between serum uric acid levels and cardiovascular conditions, including hypertension, MetS, coronary artery disease, cerebrovascular disease, vascular dementia, preeclampsia, and kidney disease.[4] 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.[5]

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 e" 130/85 mmHg [or use of antihypertensive agents]; fasting plasma glucose (FPG) >110 mg/dL [or use of antidiabetic medications]; fasting triglyceride e" 150 mg/dL; HDL-C < 40 mg/dL (male) or < 50 mg/dL (female); and waist circumference > 102 cm for males or > 88 cm for females.

Exclusion criteria were known DM or FPG >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^2, kg/m^2). 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 expirium. 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 muff 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. 130 mmHg and over systolic blood pressure (SBP) and 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.[6] 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 (µIU/ml) x FPG (mmol/L) / 22.5.[7]

In this study, statistical analysis were carried out by GraphPad Prisma 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 $p<0.05$.

RESULTS

A total of 83 patients who were followed due to MetS diagnosis aged 18 years and older (64 female, mean age: 51.1±9.5; 19 male, mean age: 50.1±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 >140 and <140 between the groups, SBP, DBP, waist circumference, BMI, FPG, Uric acid, HDL-C, triglyceride, insulin and HOMA-IR levels were observed no

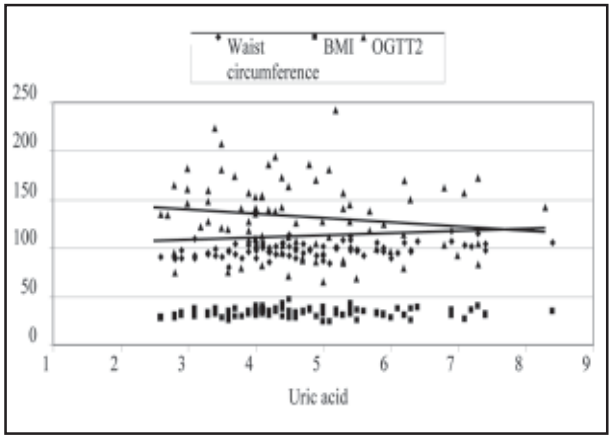

Fig-1: Uric acid level was observed to be significantly associated with waist circumference (r= 0.180 p=0.0001), BMI (r=0.248 p=0.009) and OGTT 2. hour (r=0.288 p=0.038) in multiple linear regression analysis.

significant relationship (p> 0.05), OGTT 1 hour value >140 was significantly higher in the IGT group (p<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.[8] Although many epidemiological studies indicate that elevated uric acid levels were a risk factor for cardiovascular mortality, this case was not clarified yet.[9,10] In subjects with high MetS risk, uric acid is thought to be the determinative variable for the development of Type 2 DM.[11] 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 highly susceptible to atherosclerotic disease.[6,12,13]

In large epidemiological studies, hyperuricemia has been shown to cause increased incidence of CVD, and increased mortality in those with CVD.[10,14] 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.[10]

In the 8-year prospective study by Kekalainen et al[15] 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.[16] 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.[17] In that study, although change in all of the metabolic factors was associated with change in uric acid, in multivariable analyses only BMI and

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

	>140 (n=25)	*<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/m²)	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
Trigyceride/ 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

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.[18,19] In studies conducted with adults, it was found that increased BMI is associated with hyperuricemia.[19,20] 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.[21] In addition, hypertriglyceridemia and free fat acids were found to be associated with hyperuricemia independent from central body fat deposition and obesity.[19,22] 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.

REFERENCES

1. National Cholesterol Education Program. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA. 2001;285:2486-97.
2. Sinha R, Fisch G, Teague B, Tamborlene W, Banyas B, Allen K, et al. Prevalence of impaired glucose tolerance among children and adolescents with marked obesity. N Engl J Med. 2002;346:802-10.
3. Rao SS, Disraeli P, McGregor T. Impaired glucose tolerance and impaired fasting glucose. Am Fam Physician. 2004;69:1961-1968.
4. Feig DI, Kang DH, Johnson RJ. Uric acid and cardiovascular risk. N Engl J Med. 2008;359(17):1811-1821.
5. Shelmadine B, Bowden RG, Wilson RL, Beavers D, Hartman J. The effects of lowering uric acid levels using allopurinol on markers of metabolic syndrome in end-stage renal disease patients: A pilot study. Anadolu Kardiyol Derg. 2009;9(5):385-389.
6. American Diabetes Association. Screening for type 2 diabetes. Diabetes Care. 2004;27:11-14.
7. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985;28:412–9.
8. Isomaa B, Henricsson M, Almgren O, Tuomi T, Taskinen M-R, Groop L. Cardiovascular morbidity and mortality associated with the metabolic syndrome. Diabetes Care. 2001;24:683-9.
9. Culleton BF, Larson MG, Kannel WB, Levy D. Serum uric acid and risk for cardiovascular disease and death: The Framingham Heart Study. Ann Intern Med. 1999;131:7-13.
10. Fang J, Alderman MH. Serum uric acid in cardiovascular mortality: The NHANES I epidemiologic follow-up study, 1971-1992. National Health and Nutrition Examination Survey. JAMA. 2000;283:2404-2410.
11. Chou P, Li CL, Wu GS, Tsai ST. Progression to type 2 diabetes among high risk groups in Kin-Chen, Kinmen. Diabetes Care. 1998;21:1183-87.
12. DECODE Study Group, on behalf of the European Diabetes Epidemiology Group. Glucose Tolerance and cardiovascular mortality: Comparison of fasting and 2 hour diagnostic criteria. Arch Intern Med. 2001;161:397-404.
13. Mori Y, Hoshino K, Yokota K, Itoh Y, Tajima N. Japanese IGT subjects with high insulin response are far more frequently associated with the metabolic syndrome than those with low insulin response. Endocrine. 2006;29(2):351-355.
14. Niskanen LK, Laaksonen DE, Nyyssonen K, Alfthan G, Lakka HM, Lakka TA, et al. Uric acid level as a risk factor for cardiovascular and all-cause mortality in middle-aged men: A prospective cohort study. Arch Intern Med. 2004;164:1546-1551.
15. Kekalainen P, Sarlund H, Laakso M. Long-term association of cardiovascular risk factors with impaired insulin secretion and insulin resistance. Metabolism 2000;49:1247-1254.
16. Facchini F, Chen YD, Hollenbeck CB, Reaven GM. Relationship between resistance to insulin-mediated glucose uptake, urinary uric acid clearance, and plasma uric acid concentration. JAMA 1991;266:3008-3011.
17. Rathmann W, Haastert B, Icks A, Giani G, Roseman JM. Ten-year change in serum uric acid and its relation to changes in other metabolic risk factors in young black and white adults: the CARDIA study. Eur J Epidemiol 2007;22(7):439-445.
18. Hayden MR, Tyagi SC. Intimal redox stres: Accelerated atherosclerosis in metabolic syndrome and type 2 diabetes mellitus. Atheroscleropathy. Cardiovasc Diabetol. 2002;1:3.
19. Conen D, Wietlisbach V, Bovet P, Shamlaye C, Riesen W, Paccaud F, et al. Prevalence of hyperuricemia and relation of serum uric acid with cardiovascular risk factors in a developing country. BMC Public Health. 2004;4:9.
20. Bonora E, Targher G, Zenere MB, Saggiani F, Cacciatori V, Tosi F, et al. Relationship of uric acid concentration to cardiovascular risk factors in young men. The role of obesity and central fat distribution, The Verona Young Men Atherosclerosis Risk Factors Study. Int J Obes Relat Metab Disord. 1996;20:975-980.
21. Bedir A, Topbaº M, Tanyeri F, Alvur M, Arik N. Leptin might be a regulator of serum uric acid concentrations in humans. Jpn Heart J. 2003;44:527-536.
22. Williamson JR, Kilo C, Ido Y. The role of cytosolic reductive stress in oxidant formation and diabetic complications. Diabetes Res Clin Pract. 1999;45:81-82.