Uric Acid Concentration in Subjects at Risk of Type 2 Diabetes Mellitus: Relationship to Components of the Metabolic Syndrome

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High uric acid concentration is a common finding in subjects with risk factors for cardiovascular disease (CVD), including some characteristics of the metabolic syndrome. However, its exact role in this setting and in the progression to type 2 diabetes mellitus (DM) is not well understood and could be affected by confounding factors such as hypertriglyceridemia. Our study aimed to establish the relationship between uric acid (avoiding the interference of high triglyceride levels), insulin sensitivity, and components of the metabolic syndrome in a group of subjects at high risk of developing DM. Among 201 subjects included in the study, 111 (55.2%) showed an abnormal oral glucose tolerance and uric acid levels higher than those measured in subjects with normal glucose tolerance. Body mass index (BMI), triglycerides, diastolic blood pressure (DBP), and 2-hour glycemia in the oral glucose tolerance test (OGTT) contributed independently to uric acid concentration (R^2 = .59). However, uric acid did not affect either insulin sensitivity or glucose tolerance. The recovery tests revealed that a triglyceride concentration ≥ 3 mmol/L interfered with the measurement of uric acid level when a colorimetric method was used, but not when a dry-chemistry method was used. In conclusion, uric acid concentration is higher in subjects at high risk of DM with abnormal glucose tolerance and is independently determined by various components of the metabolic syndrome.

THE METABOLIC SYNDROME is a cluster of metabolic abnormalities associated with an increased risk of cardiovascular diseases (CVDs) consisting of obesity, glucose tolerance abnormalities, hypertension, hypertriglyceridemia, and low high-density lipoprotein (HDL)-cholesterol levels.[1] Higher serum uric acid levels are common in subjects with CVD who show many features of the metabolic syndrome.[2,3] In addition, it has been suggested that uric acid is a predictor variable in the development of type 2 diabetes mellitus (DM) in high-risk subjects.[4] Many epidemiological studies have suggested that increased uric acid levels are a risk factor for cardiovascular mortality, but this is still unclear. Large community-based prospective studies have not been able to ascertain the role of uric acid in the development of CVD; some studies reported a direct association between higher uric acid levels and both coronary heart disease and death from CVD, but this association disappeared when careful adjustment for other CVD risk factors was applied.[5,6]

Hypertriglyceridemia usually coexists with other metabolic abnormalities in the insulin-resistance syndrome. This may lead to triglyceride-related turbidity and interference when uric acid levels are measured using colorimetric (mostly uricase-based) techniques,[7] and thus to an artificially high measurement of uric acid levels and an overestimation of their relevance.

Our study aimed to clarify the relationship between uric acid (without the interference of high triglyceride levels), insulin sensitivity, and components of the metabolic syndrome in a group of subjects at high risk of developing DM.

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SUBJECTS AND METHODS

After approval by the local medical ethics committee, 201 subjects (123 men, 78 women) at a higher risk of DM were included in our study. A higher risk of DM was defined as: (1) first-degree relative with DM or (2) previous fasting plasma glucose ≥ 5.4 mmol/L.[8] Subjects were consecutively included from the outpatient clinic of the Diabetes Unit of the Hospital Clínic, who attended a diabetes prevention program. None had known their oral glucose tolerance state before inclusion in this study, and none was receiving a diuretic treatment.

After a 12-hour overnight fast, 3 baseline blood samples (-10, -5, and 0 minutes) were collected in order to measure insulin and glucose levels. Then, a 75-g oral glucose tolerance test (OGTT) was performed. The test was preceded by at least 3 days of unrestricted diet and usual physical activity. Baseline samples were used to calculate insulin sensitivity (%S) and β-cell function (%β) using the computerized homeostasis model assessment (HOMA) method. The model assumes that the principal differences between individuals can be expressed in terms of differences in relative β-cell responsiveness to glucose and in peripheral and hepatic sensitivity to insulin and glucose. Beta-cell function and insulin sensitivity are expressed as percentages of those in a reference young lean population, set at 100%.[9] Two hours glycemia in the OGTT was used to classify subjects as normal glucose tolerance (NGT), impaired glucose tolerance (IGT), and diabetes, according to World Health Organization (WHO) criteria.[10] Total cholesterol, triglycerides, uric acid, and creatinine levels were also measured in baseline samples. Creatinine was used as a parameter for renal function. Physical examination included height, weight, body mass index (BMI), and systolic/diastolic blood pressure (SBP/DBP); the values measured were recorded in triplicate for all included subjects and by the same trained person. Obesity was defined as a BMI ≥ 27 kg/m^2.

Glucose levels were measured using the hexokinase method. Enzymatic methods were used to measure cholesterol and triglyceride levels (cholesterol esterase and cholesterol oxidase for the former, and glycerol kinase and glycerol phosphate oxidase for the latter). The levels of these 3 constituents were measured in a DAX 72 analyzer (Bayer Diagnostics, Tarrytown, NY) using the reagents supplied by the manufacturer. Insulin levels were determined by immunoradiometric assay (IRMA; Medgenix Diagnostics, Fleurus, Belgium) with a coefficient of variation within and between assays of 5.2% and 6.9%, respectively. No cross-reaction with proinsulin was detected.

The subjects' uric acid concentrations were measured in a Vitros 250

analyzer (Ortho-Clinica Diagnostics, Rochester, NY) using a dry chemistry method. To rule out the possible interference of triglyceride concentration in uric acid mesurements, serum samples with a high triglyceride concentration were mixed with normal triglyceride concentration samples. Sixty different samples with increasing lipid concentrations were obtained and they were studied using a recovery test, measuring uric acid levels with a enzymatic colorimetric method and a dry-chemistry method.

Statistical Methods

The results are presented as means ± SD and proportions. Variables not normally distributed were log-transformed (triglycerides, insulin, %β, %S). Different groups were compared using the Student's *t* test or analysis of variance and Scheffé test. A stepwise multiple linear regression analysis was performed to evaluate which of the insulin resistance syndrome variables determined the degree of insulin sensitivity. The same statistical analysis was used after sex normalization to identify the insulin resistance variables directly related to uric acid levels. All cases located beyond the Cook distance were excluded from analysis. Significance was defined as $P < .05$ for all statistical tests, and these were performed using version 6.1.3 for Windows of the SPSS (SPSS Inc, Chicago, IL) computer program package.

RESULTS

Table 1 shows the clinical and metabolic characteristics of the whole group of subjects, by sex. Among 201 subjects, 111 (55.2%) showed abnormal oral glucose tolerance, either as IGT (76 subjects, 37.8%) or as diabetes (35 subjects, 17.4%). Male and female uric acid levels, in the NGT, IGT, and DM groups, are listed in Table 2. As expected, uric acid concentrations were significantly higher in men than in women. Uric acid levels above saturation point (≥412 μmol/L) were observed in 30% of all subjects.

Table 3 shows the characteristics of the subjects according to their oral glucose tolerance. NGT subjects were significantly younger than IGT and diabetic subjects. No differences in terms of sex distribution and BMI was found in any of the glucose tolerance categories. Fasting glucose was higher in diabetic subjects and in IGT subjects than in NGT subjects. Average fasting insulin levels were lower in NGT subjects, intermediate in diabetic subjects, and higher in IGT subjects; significant differences were observed only between NGT and IGT subjects. The %S values revealed that those subjects with an abnormal glucose tolerance were more insulin-resistant than NGT subjects. The highest levels of insulin were measured in the IGT group. The OGTT showed that %β tended to be lower in subjects with diabetes in the OGTT; however, no significant differences were found. Triglyceride levels were significantly higher in IGT subjects than in NGT subjects, and no differences in cholesterol levels were observed. Uric acid levels were higher in those subjects with an abnormal glucose tolerance, and this difference was significant between IGT and NGT subjects.

Table 1. Clinical and Metabolic Characteristics of the Subjects, According to Sex

Characteristic	Men	Women
Age (yr)	48.5 ± 10.2	51.2 ± 12.0
BMI (kg/m^2)	27.8 ± 3.8	30.1 ± 5.6
SBP (mm Hg)	130.1 ± 16.2	127.1 ± 16.1
DBP (mm Hg)	84.7 ± 10.1	82.2 ± 9.7
Fasting glucose (mmol/L)	5.9 ± 0.9	5.7 ± 0.9
2-h OGTT glucose (mmol/L)	8.1 ± 3.1	8.7 ± 3.6
β%	110.5 ± 64.1	126.7 ± 54.2
S%	64.8 ± 31.4	58.8 ± 31.9
Cholesterol (mmol/L)	6.0 ± 1.2	5.9 ± 1.0
Triglycerides (mmol/L)	1.92 ± 1.59	1.39 ± 0.77
Uric acid (μmol/L)	400.5 ± 100.1	318.1 ± 100.1

NOTE. Data are expressed as the mean ± SD.

Abbreviations: BMI, body mass index; SBP/DBP, systolic/diastolic blood pressure; OGTT, oral glucose tolerance test; S%, insulin sensitivity; β%, insulin secretion.

Table 2. Uric Acid Levels According to Sex and Glucose Tolerance Category

	Men	Women	*P*
NGT, uric acid (μmol/L)	377.6 ± 82.6	259.6 ± 62.5	<.001
IGT, uric acid (μmol/L)	426.0 ± 107.4	347.5 ± 105.0	.002
DM, uric acid (μmol/L)	400.0 ± 103.2	368.2 ± 115.0	NS

NOTE. Data are expressed as the mean ± SD.

Abbreviation: NS, not significant.

A multiple regression analysis established that creatinine ($R = 0.48$, $P < .001$), but not gender, contributed independently to uric acid concentrations. However, all multiple regression analysis were adjusted by sex because uric acid levels were significantly lower in women than in men and are more strongly associated with morbity/mortality in women.[11] The analysis of the influence of insulin resistance syndrome components on uric acid levels revealed that BMI ($R = 0.20$, $P = .001$), triglycerides ($R = 0.17$, $P = .022$), DBP ($R = 0.29$, $P = .001$), and 2-hour OGTT glycemia ($R = 0.41$, $P < .001$) were independent contributors to uric acid levels ($R^2 = 0.595$). Uric acid concentrations did not influence either %S or glucose tolerance (fasting or 2-hour OGTT glucose) in our sample.

The results from the recovery tests demonstrated that triglyceride concentrations ≥ 3 mmol/L could lead to an erroneously high measurement of uric acid levels when a colorimetric method was used, thus confirming the relevance of interference associated with the presence of high triglyceride levels. This was not the case for dry-chemistry methods. Eighteen of 201 subjects had triglyceride values above 3 mmol/L.

DISCUSSION

In the present study we have demonstrated that, in a group of subjects at risk of DM, uric acid levels are higher in those with either IGT or DM than in those with NGT. We have also shown that some components related to the metabolic syndrome independently contributed to uric acid concentrations. In contrast with this result, uric acid concentration did not affect insulin sensitivity.

As expected, high triglyceride concentrations interfered with uric acid measurements taken using colorimetric enzymatic method, inducing a false increase in these measurements. The importance of the interference caused by hypertriglyceridemia (and its turbidity) in the measurement of uric acid levels using an enzymatic colorimetric method was described by Glick et al.[7] The addition of Intralipid (2.3 mmol/L; Kabifrimmer, Argentoina, Spain) to serum increased uric acid levels by about 20%. The dry-chemistry method that we used to measure uric acid levels in all subjects was absolutely free of interference due to the presence of triglycerides, thus decreasing the probability of obtaining false uric acid measurements due to hyperlipemia.[12] We believe that these conclusions are relevant, as dyslipemia defined as high triglyceride levels in plasma is a main component of the metabolic syndrome.

Among the subjects with abnormal glucose tolerance, those included in the IGT group showed the highest uric acid concentrations, especially when compared with NGT subjects. IGT subjects were also characterized by high fasting insulin levels, high triglyceride concentrations, and the lowest insulin sensitivity as expressed by the HOMA index. These findings are not unexpected, since hyperinsulinemia has negative effects on uric acid clearance.[13] Moreover, we have shown

Table 3. Characteristics of the Subjects According to Glucose Tolerance

Characteristic	TNG (n = 90)	ITG (n = 76)	DM (n = 35)	*P* Values		
				NGT *v* IGT	NGT *v* DM	IGT *v* DM
Sex (F/M)	32 F/58 M	29 F/47 M	16 F/19 M	NS	NS	NS
Age (yr)	45.9 ± 11.7	50.8 ± 9.5	56.9 ± 7.9	<.001	<.001	<.001
BMI (kg/m^2)	28.2 ± 4.9	28.9 ± 4.2	29.8 ± 5.2	NS	NS	NS
SBP (mm Hg)	126.4 ± 14.1	130.0 ± 17.6	131.6 ± 16.5	NS	NS	NS
DBP (mm Hg)	82.6 ± 9.6	84.9 ± 9.8	82.3 ± 11.2	NS	NS	NS
Basal glycemia (mmol/L)	5.4 ± 0.7	6.0 ± 0.7	6.6 ± 1.1	<.001	<.001	<.001
Glycemia 2 h (mmol/L)	5.7 ± 1.3	9.1 ± 1.2	13.8 ± 2.9	<.001	<.001	<.001
Insulinemia (pmol/L)	77.4 ± 38.4	107.4 ± 63.0	96.6 ± 42.6	.001	NS	NS
β%	122.5 ± 73.3	119.4 ± 51.3	98.5 ± 40.8	NS	NS	NS
S%	73.2 ± 34.4	54.9 ± 29.2	52.8 ± 20.9	<.001	<.001	NS
Cholesterol (mmol/L)	5.8 ± 1.1	6.2 ± 1.2	5.8 ± 1.0	NS	NS	NS
Triglycerides (mmol/L)	1.43 ± 0.96	2.01 ± 1.81	1.80 ± 0.85	<.005	NS	NS
Creatinine (μmol/L)	79.6 ± 17.7	88.4 ± 17.7	79.6 ± 8.84	NS	NS	NS
Uric acid (μmol/L)	335.7 ± 94.2	394.6 ± 111.9	382.8 ± 106.2	<.001	NS	NS

NOTE. Data are expressed as the mean ± SD. $P < .05$ was considered to be statistically significant. All variables not normally distributed were log-transformed for all statistics. However, all results are presented untransformed to improve comprehension.

that some components of the metabolic syndrome (oral glucose tolerance, blood pressure, triglyceride concentrations, and BMI) contributed positively to explaining the uric acid concentrations found in the multiple regression analysis. Although not significant, IGT subjects tended to be more obese and displayed higher DBP values than NGT subjects. Unfortunately, we did not get more precise information concerning visceral fat accumulation in our population, but some studies have associated the presence of central obesity to overproduction of uric acid.[14]

Differences in uric acid concentrations due to gender have been observed and reported by others; women have lower rates that tend to be similar to those of men at menopause, probably due to hormonal regulation.[11] It seems that uric acid concentrations are kept lower in women due to the presence of steroid hormones.[15] In some studies, the highest percentages of uric acid levels have been related to adverse events in women but not in men.[11,16] In our study, despite finding significant differences in uric acid levels between men and women (lower in women, as expected), other factors determined the concentration of uric acid in serum independently. This is probably due to the dilution of the gender effect in a population characterized by features related to insulin resistance, a primary contributor to uric acid concentration.

In subjects with a high risk of DM, the levels of metabolic syndrome components are expected to increase as glucose tolerance decreases. Likewise, the metabolic syndrome is associated with an increased risk of cardiovascular morbidity and mortality in such a population; this is the basis of the clinical relevance of the syndrome.[17] The precise role of uric acid in this setting is far from determined. A high serum antioxidant capacity has been observed in subjects with atherosclerosis and it was almost entirely explained by increased serum concentration of uric acid.[18] Uric acid has a peroxyl radical-trapping activity and it is part of the total peroxyl radical-trapping antioxidant parameter (TRAP).[19,20] This leads to speculation that high uric acid concentrations could reflect a compensatory mechanism counteracting oxidative damage involved in the pathogenesis of atherosclerosis.[18] However, it remains to be determined whether uric acid represents more than an epiphenomenon in the metabolic syndrome and in high-risk conditions of CVD.

In conclusion, our study demonstrates that uric acid concentrations are higher in subjects at a high risk of DM and displaying abnormal glucose tolerance, either as IGT or DM. In addition, in this population, uric acid concentrations are independently determined by components of the metabolic syndrome, especially when glucose tolerance is impaired.

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