Analysis of the relationship between fasting serum uric acid and the insulin sensitivity index in a population-based sample of 380 young healthy Caucasians

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Abstract

Aim: To determine whether fasting serum uric acid is associated with the insulin sensitivity index or with other anthropometric, metabolic or environmental features of the insulin resistance syndrome in a population-based sample of young healthy Caucasians.

Methods: The protocol included 380 unrelated Caucasian subjects (age 18–32 years) who had their insulin sensitivity index and glucose effectiveness measured during a combined intravenous glucose (0.3 g/kg body weight) and tolbutamide (3 mg/kg body weight) tolerance test. A number of anthropometric and biochemical tests, including the level of fasting serum uric acid, were carried out.

Results: In univariate analyses the concentration of fasting serum uric acid was negatively correlated to the insulin sensitivity index in both men ($r^2 = -0.25$, $P = 0.001$) and women ($r^2 = -0.25$, $P < 0.001$). In multivariate analysis controlling for age, gender, body mass index, waist to hip ratio, maximal aerobic capacity, fasting serum triglyceride and creatinine, daily intake of alcohol, smoking, use of oral contraceptives, and disposition for non-insulin dependent diabetes mellitus, the insulin sensitivity index was not significantly associated with fasting serum uric acid. However, 51% of the variation in the fasting serum uric acid level could be explained, and fasting serum triglyceride was the most important determinant of fasting serum uric acid.

Conclusion: The major determinant of the fasting serum uric acid level in young healthy Caucasians is the fasting concentration of serum triglyceride, which has been shown to be a biochemical feature of the insulin resistance syndrome. Thus, hyperuricaemia appears to be an indirect part of the insulin resistance syndrome through its association with fasting hypertriglyceridaemia.

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Introduction

The clustering in some individuals of impaired glucose tolerance, obesity, hypertension, and dyslipidaemia, all states which separately or in combination are characterized by reduced whole body insulin sensitivity, has been designated the insulin resistance syndrome (1). Low insulin sensitivity, defined as a high fasting or stimulated serum insulin value, has in some studies been found to predict subsequent cardiovascular disease, especially in men (2–9). Hyperuricaemia is also associated with obesity, hypertriglyceridaemia, impaired glucose tolerance, and hypertension (10–13). Moreover, several epidemiological studies have shown that increased fasting serum levels of uric acid is a risk factor for cardiovascular disease (14–16). The resemblance of the insulin resistance syndrome and hyperuricaemia has led to the suggestion that hyperuricaemia is a part of the insulin resistance syndrome (17–20).

The relationship between insulin sensitivity and fasting serum uric acid has not been examined in a population-based sample of young subjects. Young healthy subjects

are an ideal population to examine relationships between insulin sensitivity and variables in the insulin resistance syndrome, because in young healthy subjects insulin resistance-associated variables are not influenced by chronic diseases. The objectives of the present investigation were to evaluate whether hyperuricaemia correlates with a low insulin sensitivity index and the cluster of metabolic, anthropometric and environmental features closely associated with impaired insulin sensitivity in a population-based sample of young, healthy Caucasians. Furthermore, we wanted to study whether impaired insulin sensitivity or another component of the insulin resistance syndrome was independently associated with elevated levels of fasting serum uric acid.

Subjects and methods

Subjects

The present investigation was population based. The study participants were randomly recruited from a

population of young individuals aged 18–32 years, who in 1979 and again in 1984/85 as children had participated in blood pressure surveys in a representative and specified part of Copenhagen city (21–23). All were Danish Caucasians by self-identification. The present examination took place in 1992 and 1993. All subjects from the initial cohort except one could be traced in the Danish Central Population Register ($n = 1389$). Subjects with insulin dependent diabetes mellitus, pregnant women, and subjects now living in the western part of Denmark or abroad were excluded from the study ($n = 89$). A random sample of unrelated subjects in the initial cohort was invited to participate in the present examination. The participation rate was 56% (380 of 697) and altogether 380 non-related individuals were included in the protocol (Table 1). Two lean subjects (body mass index (BMI) $<25 \text{ kg/m}^2$) were treated with inhalation of β -2 adrenergic agonists for their asthma and 50 females were on oral contraceptives. No study participants were taking any other drugs on a regular basis and all were asked not to take aspirin, paracetamol or non-steroidal anti-inflammatory drugs on the day of examination. Parental history of non-insulin dependent diabetes mellitus (NIDDM) was considered present if the subjects reported that one or both of their parents had NIDDM. Informed consent was obtained from all study participants. The study protocol was approved by the Ethical Committee of Copenhagen and was in accordance with the Helsinki Declaration.

Anthropometric measurements, alcohol consumption and smoking

Waist circumference was measured midway between the lower rib margin and the iliac crest in the horizontal

plane. Hip circumference was measured at the point yielding the maximum circumference over the buttocks. The variables were measured with the individuals in an upright position and taken to the nearest 0.5 cm. Height was measured to the nearest 0.5 cm with the subjects standing without shoes, the heels together and the head in the horizontal plane. Body weight was measured to the nearest 0.1 kg, subjects wearing only light clothes. BMI was calculated as weight divided by squared height (kg/m^2). Maximal aerobic capacity (VO_2max) was measured by means of a submaximal bicycle exercise test as described by Åstrand & Ryhning (24).

Blood pressure was determined by means of a London School of Hygiene sphygmomanometer (25), making the readings unbiased, as the scale is not visible during deflation of the cuff. Recording of blood pressure took place between 1200 and 1400 h, when the subjects had participated in the study for a minimum of 4 h and were in a relaxed state and after they had eaten lunch. All blood pressure measurements were done in the supine position by the same nurse. Systolic and diastolic blood pressure measurements (read at the disappearance of the fifth Korotkoff sound) were recorded. The standard blood pressure cuff was $12 \times 35 \text{ cm}$. In subjects having an upper arm circumference of more than 35 cm, a cuff measuring $15 \times 43 \text{ cm}$ was used, and in subjects having an upper arm circumference of less than 20 cm, a cuff measuring $9 \times 25 \text{ cm}$ was used.

The total daily alcohol consumption was calculated from questionnaire items about average alcohol consumption. Intakes of beer, wine, and spirits were reported separately. Most of the alcohol consumed was in beer. One drink corresponded to 12 g ethanol. Smoking was assessed by a questionnaire.

Table 1 Clinical and biochemical characteristics (means $\pm$ s.d.) of men and women in the population-based sample of 380 healthy Danish Caucasians.

	Men	Women	Significance level: men versus women (<i>P</i>)
Number	186	194	—
Age (years)	25.5 (3.5)	25.0 (3.5)	—
BMI (kg/m^2)	24.2 (3.5)	23.0 (3.9)	0.0001
Waist to hip ratio	0.86 (0.05)	0.77 (0.06)	<0.0001
Systolic blood pressure (mmHg)	121 (12)	109 (9)	<0.0001
Diastolic blood pressure (mmHg)	67 (8)	62 (8)	<0.0001
VO_2max ($\text{ml O}_2/(\text{kg} \times \text{min})$)	44 (9)	38 (8)	<0.0001
Alcohol consumption (g/day)	15 (15)	6 (7)	<0.0001
Smoking (%)	41	49	0.12
Fasting serum uric acid* ($\mu\text{mol/l}$)	333 (66)	236 (54)	<0.0001
Fasting serum triglyceride (mmol/l)	1.2 (0.9)	1.0 (0.5)	0.0006
Fasting plasma glucose (mmol/l)	5.2 (0.5)	4.8 (0.4)	<0.0001
Fasting serum creatinine ($\mu\text{mol/l}$)	93 (11)	82 (14)	<0.0001
Disposition for NIDDM (%)	6.6	8.3	0.53
Insulin sensitivity index ($10^{-5} \times (\text{min} \times \text{pmol/l})^{-1}$)	15.2 (8.9)	15.2 (9.7)	0.68
Glucose effectiveness ($10^{-2} \times \text{min}^{-1}$)	2.0 (0.6)	2.3 (0.6)	<0.0001
Glucose disappearance constant (min^{-1})	2.1 (0.9)	2.6 (1.2)	0.0001

* Four men and one woman did not have uric acid measured due to lack of serum.

Biochemical studies

After 12 h overnight fasting venous blood samples were drawn in the morning. Serum levels of triglyceride, uric acid and creatinine were analysed using standardized methods. The concentration of insulin was determined by ELISA with a narrow specificity excluding des[31,32]- and intact proinsulin, employing the Dako insulin kit with overnight incubation (Code No K6219 Dako Diagnostics Ltd, Ely, UK) (26).

Measurements of the insulin sensitivity index and glucose effectiveness

Each subject underwent an intravenous glucose tolerance test (IVGTT) after an overnight fasting period of 12 h. After insertion of a venous cannula into the antecubital vein all subjects rested in a quiet room for at least 20 min. Baseline values of serum insulin and plasma glucose were taken in duplicate at 5 min intervals. Glucose was injected i.v. in the contralateral antecubital vein over a period of 60 s (0.3 g/kg body weight of 50% glucose). At 20 min following the end of the glucose injection, a bolus of 3 mg tolbutamide/kg body weight (Rastinon, Hoechst, Germany) was injected during 5 s to elicit a secondary pancreatic β -cell response. Venous blood was sampled at 2, 4, 8, 19, 22, 30, 40, 50, 70, 90 and 180 min, timed from the end of the glucose injection, for measurements of plasma glucose and serum insulin. All the IVGTTs were done by the same investigator. The insulin sensitivity index and glucose effectiveness were calculated using the Bergman MINMOD computer program developed specifically for the combined intravenous glucose and tolbutamide tolerance test (27–30). The insulin sensitivity index represents the increase in net fractional glucose clearance rate per unit change in plasma insulin concentration following the intravenous glucose load. Glucose effectiveness represents the net fractional glucose clearance rate simply due to the increase in glucose itself without any increase in insulin concentration above baseline. Importantly, both the insulin sensitivity index and glucose effectiveness involve an inhibition of hepatic glucose output and an acceleration of peripheral glucose uptake due to insulin and glucose, respectively (27, 28). Furthermore, glucose effectiveness includes a contribution mediated by the pre-existing basal insulin status and a contribution from hyperglycaemia *per se* without insulin. The tolbutamide-boostered protocol for frequently sampled IVGTT with minimal model analysis has been validated in normal subjects against the euglycaemic, hyperinsulinaemic clamp (28, 31, 32).

Statistics

Differences of continuous variables between the groups were tested by the Mann–Whitney test. Differences of categorical variables were tested using chi-square.

Spearman correlation coefficients between fasting serum uric acid and the insulin sensitivity index, glucose effectiveness, age, gender, BMI, waist to hip ratio, VO_2max , fasting serum triglyceride and creatinine, systolic and diastolic blood pressure, daily intake of alcohol, smoking, disposition of NIDDM, and use of oral contraception, were calculated in the whole population and stratified in men and women as appropriate. Multiple linear regression analysis was used to elucidate any independent effect of any variable on fasting serum uric acid. Interaction variables between gender and all continuous explanatory variables (the insulin sensitivity index, age, gender, BMI, waist to hip ratio, VO_2max , fasting serum triglyceride and creatinine and daily intake of alcohol) were constructed and included in a multiple regression analysis. All interaction variables were without significant effect and were excluded in the final multiple regression analysis. Statistical Package of Social Science (SPSS) for Windows, version 6.01, was used for statistical analyses. A *P* value <0.05 (two-tailed) was considered significant.

Results

Fasting serum uric acid was significantly higher in men than in women (Table 1). As reported previously (23), BMI, waist to hip ratio and fasting serum triglyceride were higher in men compared with women, whereas glucose effectiveness was significantly lower. The insulin sensitivity index did not differ between men and women despite the higher fasting serum uric acid in men compared with women (23).

In the univariate analyses in men the strongest associations to fasting serum uric acid were found with BMI and fasting serum triglyceride (Table 2). The strongest associations in women with fasting serum uric acid were found with BMI and the insulin sensitivity index. In women the associations with fasting serum uric acid were weaker than in men. In both men and women, significantly negative associations with fasting serum uric acid were found regarding the insulin sensitivity index and the maximal aerobic capacity (Table 2). No significant association was found between fasting serum uric acid and glucose effectiveness in either men or women (Table 2).

In the multiple regression analysis including the insulin sensitivity index, age, gender, BMI, waist to hip ratio, VO_2max , fasting serum triglyceride and creatinine, daily intake of alcohol, smoking, use of oral contraceptives, and disposition for NIDDM as explanatory variables, fasting serum uric acid was significantly positively associated with fasting serum triglyceride, BMI, gender and, in women, the use of oral contraceptives. No other variable was significantly associated with fasting serum uric acid (Table 3). Fasting serum triglyceride was the variable that was most strongly associated with fasting serum uric acid. The importance

Table 2 Spearman correlation coefficients between fasting serum uric acid and the insulin sensitivity index, glucose effectiveness, glucose disappearance constant, age, gender, BMI, waist to hip ratio, VO_2max , blood pressure, fasting plasma glucose, fasting serum triglyceride and creatinine, daily intake of alcohol, smoking, use of oral contraceptives and disposition for NIDDM in the population-based sample of 380 young healthy Danish Caucasians.

	Men (<i>n</i> = 186)		Women (<i>n</i> = 194)		All (<i>n</i> = 380)	
	r^2	<i>P</i>	r^2	<i>P</i>	r^2	<i>P</i>
Age	0.12	0.010	0.05	0.45	0.11	0.040
BMI	0.40	<0.001	0.24	0.001	0.37	<0.001
Waist to hip ratio	0.32	<0.001	0.19	0.008	0.60	<0.001
Systolic blood pressure	0.10	0.17	0.10	0.18	0.41	<0.001
Diastolic blood pressure	0.33	<0.001	0.23	0.002	0.33	<0.001
VO_2max	-0.27	<0.001	-0.22	0.003	0.04	0.45
Alcohol consumption	-0.04	0.62	0.07	0.34	0.23	<0.001
Smoking	0.09	0.22	-0.10	0.17	-0.05	0.29
Use of oral contraceptives	—	—	-0.12	0.11	—	—
Fasting serum triglyceride	0.39	<0.001	0.15	0.037	0.32	<0.001
Fasting plasma glucose	0.16	0.032	-0.04	0.58	0.29	<0.001
Fasting serum creatinine	0.15	0.042	-0.00	0.97	0.36	<0.001
Disposition for NIDDM	-0.08	0.28	-0.08	0.28	-0.04	0.40
Insulin sensitivity index	-0.25	0.001	-0.25	<0.001	-0.17	0.001
Glucose effectiveness	-0.04	0.62	-0.02	0.80	-0.19	<0.001
Glucose disappearance constant	0.07	0.37	-0.03	0.65	-0.11	<0.001

of gender is seen by the fact that the explained variation, r^2 , in the fasting serum uric acid level in the multiple regression analyses stratified for gender was 24% in men and 17% in women but 51% in the multiple regression analysis including both men and women. The gender-stratified multiple regression analyses gave the same results in men and women, and especially we found no significant association between fasting serum uric acid and the insulin sensitivity index in either men or women.

Discussion

Hyperuricaemia is commonly associated with obesity, glucose intolerance, dyslipidaemia and coronary artery

disease (14–16). It has therefore been argued that elevated fasting serum uric acid levels might be yet another facet of the insulin resistance syndrome (11, 17–20). This idea has been supported by several epidemiological studies. Thus Modan *et al.* (11) found in a representative sample of 1016 Jewish subjects aged 37–70 years a highly significant positive correlation between fasting serum uric acid levels and plasma insulin responses (sum of 1- and 2-h post oral glucose levels) in both males and females. Facchini *et al.* (19) found in 36 glucose-tolerant volunteers aged 23–69 years, independent of age, gender, overall obesity and abdominal obesity, a positive relationship between fasting serum uric acid levels and insulin resistance

Table 3 The relationship between the fasting serum uric acid and the insulin sensitivity index controlling age, gender, BMI, waist to hip ratio, VO_2max , fasting serum triglyceride and creatinine, daily intake of alcohol, smoking, use of oral contraceptives, and disposition for NIDDM in the population-based sample of 380 young Caucasians.

Response variable: fasting serum uric acid		
	Regression coefficients (95% confidence interval)	<i>P</i> value
Insulin sensitivity index ($10^{-5} \times (\text{min} \times \text{pmol/l})^{-1}$)	-3.7×10^{-2} (-10.6–3.1)	0.29
Gender (0 = male, 1 = female)	-7.1×10^{-1} (-9.0–5.1)	<0.0001
Age (years)	-2.0×10^{-2} (-19.1–15.0)	0.81
Waist to hip ratio	9.0 (-4.1–22.0)	0.18
VO_2max ($\text{ml O}_2/(\text{min} \times \text{kg})$)	-3.5×10^{-2} (-11.4–4.3)	0.38
Alcohol consumption (g/day)	3.2×10^{-1} (-56.6–63.0)	0.92
Smoking (0 = no, 1 = yes)	1.3×10^{-1} (-10.7–13.4)	0.92
Fasting plasma triglyceride (mmol/l)	2.4 (1.4–3.4)	<0.0001
Fasting serum creatinine ($\mu\text{mol/l}$)	3.9×10^{-2} (-0.1–8.7)	0.11
BMI (kg/m^2)	3.1×10^{-1} (1.0–5.2)	0.0032
Disposition for NIDDM (0 = no, 1 = yes)	-1.4 (-3.6–0.7)	0.18
Use of oral contraceptives (0 = no, 1 = yes)	-2.6 (-4.5–0.75)	0.0062
r^2 (adjusted) = 0.51		

as measured by the insulin suppression test. Also Vuorinen-Markkola & Yki-Järvinen (17) showed in 37 healthy subjects aged 30–68 years, independent of age and BMI, positive correlations between insulin resistance as determined by the euglycaemic, hyperinsulinaemic clamp technique and fasting levels of serum uric acid. Furthermore, in a study of 40 healthy males Zavaroni *et al.* (18) reported that subjects with asymptomatic hyperuricaemia had a higher blood pressure, when matched for age and overall obesity and were more hyperinsulinaemic and dyslipidaemic compared with a group of volunteers with normal serum levels of uric acid. Finally, Cigolini *et al.* (20) demonstrated in a random sample ($n = 181$) of 38-year-old healthy and non-obese subjects that both abdominal fat distribution and hypertriglyceridaemia, rather than fasting hyperinsulinaemia, play a major role in the relationship between hyperuricaemia and other components of the insulin resistance syndrome.

In a population-based sample of 380 young healthy individuals we have examined the associations between fasting serum uric acid on the one hand and the insulin sensitivity index and features of the insulin resistance syndrome on the other hand. Methodologically, the importance of stratifying the sample by gender in the univariate analysis is shown by the fact that very different strengths of correlations are found when the sample is either analysed as a whole or stratified by gender. Fasting serum triglyceride, BMI, use of oral contraceptives and gender were the only variables which were independently associated with fasting serum uric acid in the multiple regression analysis.

Some unmeasured factor related to gender must be a major determinant of fasting serum values of uric acid as gender is a major determinant of fasting serum uric acid. In another population based study by Cigolini *et al.* (20) fasting serum triglyceride was also independently associated with fasting serum uric acid. In contrast, however, the estimate of abdominal distribution of fat in men was not a major determinant of fasting serum uric acid in our study. This may be explained by the lower waist to hip ratio in the present study compared with the study by Cigolini (20) (0.86 versus 0.96). The lack of subjects with a high amount of abdominal fat diminishes the effect of abdominal fat on fasting serum uric acid levels. Sinagra *et al.* (33) also found insulin sensitivity to be independently associated with fasting serum uric acid in a case-control study comparing non-hyperuricaemic and hyperuricaemic obese female subjects. As in our study, Vuorinen-Markkola & Yki-Järvinen (17) found that fasting serum uric acid was associated with both fasting serum triglyceride and insulin sensitivity in the univariate analysis. In contrast with our study, fasting serum uric acid was independently associated with fasting serum values of triglyceride and insulin sensitivity in the multiple regression analysis. The strength of the association between fasting serum uric acid and the insulin

sensitivity index was, however, relatively weak ($P < 0.05$) whereas the association with triglyceride was stronger ($P < 0.005$) (17).

One reason for the weaker association found in our study between insulin sensitivity and fasting serum uric acid compared with the studies of others (17, 19) could be the different methodology applied for measuring insulin sensitivity, as the use of the 12 samples minimal model technique gives less accurate estimate of insulin sensitivity than the glucose clamp technique. Another reason for the weaker association between insulin sensitivity and fasting serum uric acid found in our study could be that the range for the serum level of uric acid is relatively narrow, as the examined subjects are young and healthy. In the study by Modan *et al.* (11) fasting triglyceridaemia was of minor importance compared with the insulin response after an oral glucose tolerance test. The overall explained variation, however, was lower compared with our study (17 versus 51%), which may be related to the fact that the study participants were not representative of the general population and the insulin response after an oral glucose tolerance test is a poor measure of insulin sensitivity.

It has been suggested that the positive association between the insulin resistance syndrome and fasting hyperuricaemia is partly explained by the fact that hyperinsulinaemia may decrease the renal excretion of uric acid (19, 34). In our study, the association between fasting serum values of uric acid and creatinine did not reach statistical significance. Previously, fasting serum values of uric acid and creatinine have been shown to be positively associated in a population-based study (35), where no measurements of fasting serum triglyceride or the insulin sensitivity index were undertaken.

Serum uric acid is likely to be determined by both genetic and environmental factors (35, 36). The potential mechanisms relating fasting hyperuricaemia to fasting hypertriglyceridaemia are unknown. Moreover, why is the insulin sensitivity index and the fasting serum uric acid level more strongly associated in the univariate analysis than in the multivariate analysis? Obesity, waist to hip ratio, BMI and fasting serum triglyceride are all reported to be important determinants of fasting serum uric acid (12), and thus it has been speculated that the positive association between fasting serum values of uric acid and triglyceride could be due to an increase in NADPH requirement for *de novo* fatty acid synthesis in obese man (17). When NADPH production is increased, then an enhanced uric acid production is the result, and this might increase the serum uric acid level (17). Fasting serum triglyceride and obesity are inherent parts of the insulin resistance syndrome (35). Therefore, the association between the fasting serum uric acid level and the insulin sensitivity index may be secondary to the association with BMI and hypertriglyceridaemia.

In conclusion, we have found that the most important determinant of the fasting serum uric acid

level in young healthy Caucasians is the fasting serum triglyceride level. Therefore, by its association to hypertriglyceridaemia, hyperuricaemia appears to be a feature of the insulin resistance syndrome.

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