Diabetes associated with a low serum uric acid level in a general Chinese population

Hairong Nan a,b,c,*, Yanhu Dong a, Weiguo Gao a,b,c, Jaakko Tuomilehto b,c,d, Qing Qiao b,c

a Qingdao Diabetes Epidemiology Study Group, Qingdao Endocrine and Diabetes Institute, Qingdao, China
b Department of Public Health, University of Helsinki, Helsinki, Finland
c Diabetes and Genetic Epidemiology Unit, National Public Health Institute, Helsinki, Finland
d South Ostrobotnia Central Hospital, Seinäjoki, Finland

Received 8 July 2005; accepted 28 July 2006
Available online 11 September 2006

Abstract

Objective: Serum uric acid (UA) is reported as an important marker of hypertension, coronary heart disease, and diabetes; diabetic subjects have low UA levels. The relationship between UA and fasting plasma glucose (FPG) and 2-h plasma glucose concentrations in non-diabetic subjects as well as in diabetic subjects in general population is not well known. This was investigated in a general Chinese population.

Methods: A stratified, random cluster sampling method was performed to select a representative sample of general population aged 20–74 years in Qingdao in 2002. A total of 1288 men and 2344 women participated in the survey. The mean UA concentration was calculated for small glucose intervals and the trend was tested using general linear model.

Results: The mean concentrations of UA were 381, 393, 371, and 345 μmol/l in men with FPG of <6.1, 6.1–6.9, ≥7.0 mmol/l (newly diagnosed diabetes), and in those with prior history of diabetes. They were 308, 322, 301, and 293 μmol/l, respectively, in women. The UA levels declined with increasing FPG levels in individuals with newly diagnosed diabetes, with standardized coefficient of −0.26 in men and −0.20 in women, after multivariate adjustment for age, body mass index, triglycerides, and cardiovascular disease history. The relationship between 2-h glucose and UA was not as clear as that for FPG.

Conclusion: Serum UA levels tended to increase with increasing FPG levels in non-diabetic individuals, but decrease in diabetic individuals.

Keywords: Fasting plasma glucose; Serum uric acid; Impaired fasting glycaemia; Diabetes mellitus

1. Introduction

Serum uric acid (UA) is an end product of purine metabolism and related to the purine bases of nucleic acids. It is likely to be determined by both genetic and environmental factors. The importance of asymptomatic hyperuricemia in the general population remains unclear. If the gouty symptom does not occur, people with hyperuricemia are usually unaware of their condition and of subsequent complications such as hypertension, coronary heart disease, renal disease, and diabetes. Recent evidence from many clinical and epidemiological researches suggests that serum UA
Table 1
Characteristics of the study population by fasting plasma glucose categories (mmol/l) in individuals without prior history of diabetes and by previously diagnosed diabetes status

<table>
<thead>
<tr>
<th></th>
<th>Men, fasting plasma glucose (mmol/l)</th>
<th>Diagnosed DM</th>
<th>Women, fasting plasma glucose (mmol/l)</th>
<th>Diagnosed DM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;6.1</td>
<td>6.1–6.9</td>
<td>≥7.0</td>
<td>6.1–6.9</td>
</tr>
<tr>
<td>Number</td>
<td>852</td>
<td>169</td>
<td>147</td>
<td>120</td>
</tr>
<tr>
<td>Age (year)</td>
<td>51.3 (0.41)</td>
<td>54.0 (0.91)</td>
<td>54.1 (0.98)</td>
<td>58.5 (1.12)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>26.0 (0.12)</td>
<td>27.6 (0.27)†</td>
<td>27.4 (0.29)‡</td>
<td>26.0 (0.33)</td>
</tr>
<tr>
<td>Waist to hip ratio</td>
<td>0.90 (0.00)</td>
<td>0.92 (0.00)</td>
<td>0.92 (0.01)</td>
<td>0.91 (0.01)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>129 (0.67)</td>
<td>136 (1.48)‡</td>
<td>131 (1.60)</td>
<td>128 (1.85)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>85 (0.42)</td>
<td>88 (0.92)‡</td>
<td>85 (1.00)</td>
<td>84 (1.16)</td>
</tr>
<tr>
<td>Serum uric acid (μmol/l)</td>
<td>378 (3.22)</td>
<td>392 (7.12)¶</td>
<td>375 (7.70)</td>
<td>355 (8.87)</td>
</tr>
<tr>
<td>Serum total cholesterol (mmol/l)</td>
<td>5.50 (0.04)</td>
<td>5.51 (0.09)</td>
<td>5.67 (0.10)</td>
<td>5.51 (0.11)</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>1.36 (1.02)</td>
<td>1.63 (1.04)</td>
<td>1.74 (1.05)¶</td>
<td>1.56 (1.05)</td>
</tr>
<tr>
<td>HDL-C (mmol/l)</td>
<td>1.54 (0.01)</td>
<td>1.44 (0.03)¶</td>
<td>1.57 (0.03)¶</td>
<td>1.46 (0.04)</td>
</tr>
<tr>
<td>Education ≥9 years (%)</td>
<td>54.2</td>
<td>52.4</td>
<td>41.8</td>
<td>36.8</td>
</tr>
<tr>
<td>Family history of diabetes (yes, %)</td>
<td>15.3</td>
<td>21.3</td>
<td>19.7</td>
<td>33.3</td>
</tr>
<tr>
<td>History of Hypertension</td>
<td>16.3</td>
<td>32.0</td>
<td>21.8</td>
<td>34.2</td>
</tr>
<tr>
<td>History of cardiovascular disease</td>
<td>13.6</td>
<td>17.8</td>
<td>7.5</td>
<td>27.5</td>
</tr>
<tr>
<td>History of dyslipidimia</td>
<td>7.7</td>
<td>8.9</td>
<td>10.9</td>
<td>15.0</td>
</tr>
<tr>
<td>Current smoking (%)</td>
<td>49.9</td>
<td>47.3</td>
<td>50.3</td>
<td>45.0</td>
</tr>
<tr>
<td>Current alcohol drinking (%)</td>
<td>43.4</td>
<td>40.2</td>
<td>49.7</td>
<td>41.7</td>
</tr>
</tbody>
</table>

*p < 0.05 † for the difference between FPG of 6.1–6.9 mmol/l and FPG of ≥7.0 mmol/l of the same gender after adjusting for age and resident areas, ‡ for the difference between diagnosed DM and FPG of 6.1–6.9 mmol/l or diagnosed DM and FPG of ≥7.0 mmol/l of the same gender after adjusting for age and resident areas, respectively. DM, diabetes mellitus; HDL-C, high-density lipoprotein cholesterol.
level is an important marker of these diseases [1–7]. Relationships between serum UA and diabetes have been studied and the conclusions from these studies was that the serum UA level decreased in diabetic subjects, particularly in diabetic men [8–11]. In a study in Taiwan, Chou et al. [12] found that the association of serum UA with FPG and hyperinsulinemia was stronger in women than in men in non-diabetic subjects. However, the relationship between fasting plasma glucose (FPG) and 2-h post-load plasma glucose (2-h PG) concentration and serum UA level in non-diabetic population is still less known.

We set out to study the relationship between glucose levels and serum UA concentrations in an urban Chinese adult population.

2. Materials and methods

2.1. Study population

A stratified, random cluster sampling method was used to select a representative sample of the general population aged 20–74 years in Qingdao in 2002. Street blocks were randomly drawn from rural and urban communities to serve as clusters for the survey. From each selected block, families were randomly selected, and a total of 10,258 eligible subjects were invited to take part in the survey. Two screening strategies for diabetes were performed except in one urban community, Zhan Shan. In Zhan Shan community a standard 75 g 2-h oral glucose tolerance test (OGTT) was administered to all 2438 (903 men and 1535 women) participants. The response rate for OGTT was 87.8%. Among the 2438 participants, 416 subjects were excluded due to missing data on glucose or other lab measurements, leaving 2022 subjects in the current data analysis. For the rest of the study population of 7820 participants, a two-step screening strategy was applied. A fasting capillary whole blood glucose test was first administered to the target population of 7820 subjects between 7:00 and 9:30 in the morning. The participation rate for the capillary whole blood test was 82.9%. The 1645 subjects who had a capillary blood glucose value of ≥6.1 mmol/l were further invited to an OGTT; 1610 subjects with complete data for the current data analysis were included. Therefore, a total of 3632 (1288 men and 2344 women) subjects with data on both FPG and serum UA were included in the current data analysis.

2.2. Laboratory methods and physical examination

The specimens were put into ice-cooled containers and transported immediately to a clinical lab at the Qingdao Endocrinology and Diabetes Hospital. The plasma glucose was determined by a glucose oxidase method within 3 h after the blood sample was collected. Serum UA was measured by the uricase method in the same clinical lab. Fasting serum lipid profile, including triglycerides, total, and high-density lipoprotein cholesterol (HDL-C) was determined by enzymatic method. Height and weight was measured with light clothes and without shoes. The body mass index (BMI) was calculated by dividing the weight (kg) by the height (m) squared. Waist girth at the mid-point between the lower margin of the ribs and the iliac crest, and hip circumference at the maximal horizontal girth between the waist and thigh were measured. The measurements were made to the nearest 0.5 cm. Two consecutive measurements were performed. If there was a variation greater than 2.0 cm between the two readings, a third measurement was taken. The two most consistent readings were used in analysis. Waist to hip ratio was calculated by the waist circumference divided by the hip circumference. Three consecutive blood pressure readings, taken at least 5 min apart, were taken from the right arm of seated subjects; the average of the three readings was used in subsequent data analysis.

Subjects who had a history of diabetes and who were under treatment with either insulin or oral anti-diabetic agents were considered to have known diabetes, regardless of their plasma glucose levels. Participants without known DM were divided into glucose categories according to either FPG or 2-h PG

<table>
<thead>
<tr>
<th>Adjustment for</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FPG &lt; 7.0</td>
<td>FPG ≥ 7.0</td>
</tr>
<tr>
<td>N</td>
<td>1015</td>
<td>146</td>
</tr>
<tr>
<td>Model 1: age + resident area</td>
<td>0.12***</td>
<td>−0.28**</td>
</tr>
<tr>
<td>Model 2: 1 + triglycerides</td>
<td>0.08**</td>
<td>−0.27**</td>
</tr>
<tr>
<td>Model 3: 1 + body mass index</td>
<td>0.05</td>
<td>−0.26**</td>
</tr>
<tr>
<td>Model 4: 1 + body mass index + triglycerides</td>
<td>0.03</td>
<td>−0.26***</td>
</tr>
<tr>
<td>Model 5: 4 + others*</td>
<td>0.03</td>
<td>−0.26***</td>
</tr>
</tbody>
</table>

* Previous history of hypertension, cardiovascular disease and dyslipidemia.
** p < 0.05.
*** p < 0.001.
distributions. Data on history of dyslipidemia and cardiovascular disease were based on a self-reported questionnaire. Dyslipidaemia was defined as triglycerides $\geq 1.7 \text{ mmol/l}$ and/or HDL-cholesterol $<0.9 \text{ mmol/l}$ (male) and $<1.0 \text{ mmol/l}$ (female). Hypertension was defined as systolic blood pressure $\geq 140$ and/or diastolic blood pressure $\geq 90 \text{ mmHg}$ and/or being on antihypertensive therapy.

2.3. Statistical analysis

Data were summarized as mean (standard error) for continuous variables and proportions for categorical variables. FPG and triglycerides were logarithmically transformed for all analyses and the geometric means were presented. The mean values of BMI, waist to hip ratio, blood pressure, lipids, and serum UA were estimated using the general linear model adjusting for age; the difference between FPG categories and known DM was also tested. The $\chi^2$-test was employed to estimate the difference in categorical variables.

The data were further analysed for the small FPG intervals of $<4.5$, $4.5--5.5$, $5.6--6.0$, $6.1--6.9$, $7.0--7.9$, $8.0--9.9$, and $\geq 10.0 \text{ mmol/l}$, and for the small 2-h PG intervals of $<4.5$, $4.5--5.5$, $5.6--6.0$, $6.1--6.9$, $7.0--7.9$, $8.0--8.9$, $9.0--9.9$, $10.0--10.9$, $11.0--11.9$, $12.0--12.9$ and $\geq 13.0 \text{ mmol/l}$ in subjects without previously diagnosed diabetes and gout. The general linear model was employed to test the relationships between these small FPG and 2-h PG intervals and serum UA separately for men and women, adjusting for age, BMI, log-triglycerides, and a history of hypertension and cardiovascular disease before the survey. Systolic blood pressure and diastolic blood pressure was added in the Model, separately. Stratified analyse by history of hypertension (yes/no) was performed to test the possible interaction between history of hypertension and UA concentrations. A $p$-value of $<0.05$ (two-tailed) was considered to be statistically significance. All analyses were performed using SPSS for Windows, version 12.0.

3. Results

Because the relationship between serum UA and FPG or 2-h PG was similar in the two screening sets, we presented here the results based on the pooled data analysis of the two parts. BMI, waist to hip ratio, triglycerides, and blood pressure were all higher in subjects with impaired fasting glycaemia (IFG) or newly diagnosed diabetes (FPG of $>7.0 \text{ mmol/l}$) than in those with FPG of $<6.1 \text{ mmol/l}$, in either men or women ($p<0.05$) (Table 1). A family history of

Fig. 1. Mean serum uric acid (mmol/l) and their 95% confidence intervals (bar) in men (solid line) and women (dashed line) according to fasting plasma glucose categories, after adjustment for age and resident areas (A); additional adjustment for body mass index and triglycerides (B); further adjustment for previous history of hypertension, cardiovascular disease, and dislipidemia (C).
diabetes was more common in previously diagnosed diabetes subjects than in others. Current alcohol drinking and smoking did not differ among the four subgroups for men. Individuals with IFG had the highest serum UA levels, and those with previously diagnosed diabetes had the lowest UA levels in both genders.

There was an increasing trend in serum UA concentration when the levels of FPG increased from low to high, up to the FPG of 7.0 mmol/l; thereafter, the UA concentration started to decrease with further increases in FPG levels (Fig. 1A). The standardized coefficient ($\beta$) between FPG and UA was 0.12 for men and women at FPG < 7.0 mmol/l, whereas the $\beta$ was $-0.28$ in men ($p < 0.001$) and $-0.21$ in women ($p < 0.01$) when FPG was $\geq 7.0$ mmol/l, after adjusting for age and resident areas (Table 2). After multivariable adjustments for age, resident areas, BMI, and log-triglycerides, the increasing trend in UA at low FPG level (<7.0 mmol/l) levelled off in men but still remained in women (Fig. 1B). The declining trend of UA at the higher FPG concentration remained significant after further adjusting for the previous disease history of hypertension, cardiovascular disease, or dyslipidemia in both genders, with a $\beta$-value of $-0.26$ in men and $-0.20$ in women ($p < 0.01$) (Fig. 1C, Table 2). The lowest UA level appeared in subjects with the highest FPG concentrations ($\geq 10.0$ mmol/l) in previously undiagnosed diabetic men and women ($p < 0.001$). Adjustment for blood pressure did not change the trend; a history of hypertension did not alter the observed relationship either.

As shown in Fig. 2, a decreasing trend of serum UA levels with increasing 2-h PG at 2-h PG concentration $\geq 8.0$ mmol/l approximately was also observed, with a multivariate adjusted $\beta$ coefficient of $-0.13$ ($p < 0.05$) in men and $-0.15$ in women ($p < 0.001$). We did not, however, observed an upward positive relationship between UA and 2-h PG at low 2-h PG range.

4. Discussion

In this population-based cross-sectional study we found that serum UA increased with increasing FPG levels up to the FPG level of 7.0 mmol/l; but decreased when FPG over 7.0 mmol/l. There was an inverse relationship between 2-h PG and serum UA when 2-h post-load plasma glucose categories, after adjustment for age and resident areas (A); additional adjustment for body mass index and triglycerides (B); further adjustment for previous history of hypertension, cardiovascular disease, and dislipidemia (C).
PG higher than 8.0 mmol/l, but an upward increasing trend in UA levels was not observed in low 2-h PG range.

It has been reported previously that serum UA is significantly elevated in non-diabetic range of FPG distribution, and reduced after the onset of diabetes [10,13,14]. Whitehead et al. [11] found an increase in mean serum UA with increasing glucose concentrations up to 7.0 mmol/l in men and to 9.0 mmol/l in women in Caucasians. Subsequently, increases in glucose values were accompanied by a statistically significant decrease in UA concentrations. A study of a biracial population in Fiji showed that Melanesian and Asian Indian men and women with impaired glucose tolerance (per the WHO 1980 criteria) had the highest plasma uric acid levels. A study among Chinese in Taiwan [12] revealed that among non-diabetic subjects, FPG increased with increasing uric acid levels in both pre-menopausal and post-menopausal women, but not in men. Our current study further confirmed previous findings despite of the differences in assays used for UA and in diagnostic criteria for diabetes in different studies. Few studies have investigated the relationship between 2-h PG and UA due to the fact that 2-h OGTT have not been widely performed. We found UA decline with increasing 2-h PG at upper range of the 2-h PG distribution, but did not find an increasing trend at lower 2-h PG range. The association between FPG and serum UA was stronger than that for 2-h PG in our study. The finding needs to be further examined. The underlying mechanism leading to fasting or post-load hyperglycemia differs; the former attributable to the defect in insulin function at basal status while the latter to the deficiency of first-phase insulin secretion after meals [15]. To what extent the difference in glucose regulations at fasting and post-prandial conditions has contributed to the observed relationship between UA and glucose levels also require further investigation.

In humans, UA exists in blood at a concentration close to maximum solubility owing to the lack of the enzyme uricase, which oxidises uric acid to allantoin in other animals. Normally, UA is totally filtered in the renal glomerular and almost completely reabsorbed in the proximal tubular, while glucose competitively inhibits UA reabsorption and enhances its excretion at the same anatomic position, given normal renal function [10,14,16]. Nevertheless, the mechanisms leading to the increased urate excretion are not clear. The alteration of the proximal tubule related to the elevated levels of glucose seems to be the most possible mechanism, which may involve, in part, an osmotic diuretic effect (though the influence of glycosuria is not clear), leading to excessive uric acid excretion [16]. Alternatively, hyperinsulinaemia and insulin resistance enhances the tubular sodium–hydrogen exchange and facilitates the active absorption of uric acid in humans [17–19]. More recent studies suggest that oxidant stress could precede the development of endothelial dysfunction, and occurs when blood glucose concentrations are moderately elevated above normal levels [20,21]. It was suggested that the serum UA acts as an antioxidant and may be one of the strongest determinates of plasma antioxidative capacity in the early stages of the atherosclerotic process [22]; later, advancing with the atherosclerotic process when serum UA levels are known to be elevated, this previous antioxidant paradoxically becomes pro-oxidant [23]. Thus, hyperuricemia turns to induce endothelial dysfunction via impairing nitric oxide generation in cultured rat endothelial cells, provided insight into a pathogenic mechanism by which UA may induce hypertension and vascular disease [24]. The role of “antioxidative capacity” of UA in the process of deterioration of glucose metabolism is not clear. Is the failure in further compensable increase in UA levels partly contributed to the development of diabetes? All these are not known.

BMI and triglyceride appeared to be strong confounding factors in our study as indicated by others [12,25–28]. After adjusting for BMI or log-triglycerides, the increasing trend in UA at lower FPG concentration was reduced, particularly in men, but still remained significance in women. Other factors that affect the UA concentration such as use of diuretics and plasma creatinine are not available in this study and cannot be addressed. But we checked the effect of previous history of hypertension (yes/no), and the relationship between UA and glucose was not altered after individuals with hypertension were excluded.

In summary, serum UA levels tended to increase with increasing FPG concentration in the non-diabetic individuals, but decreased in diabetic individuals defined based on FPG criteria. The relationship between UA and 2-h PG levels was not as strong as that for FPG.

Acknowledgements

This study has been approved and supported by the Bureau of Science and Technology of Qingdao (2001KNS-E-5), Lifescan of Johnson & Johnson Company in China, the academy of Finland (46558, 118492), the Paulo Foundation in Finland, the Future Forum Grant 2004 and the Novo Nordisk Foundation 2005.
References


