Introduction

Hyperuricaemia is considered the precursor of gout, which is the most common inflammatory arthritis in adult men [1]. Several studies have shown that a moderate degree of hyperglycaemia is associated with higher serum uric acid levels, while a higher degree of hyperglycaemia is most common inflammatory arthritis in adult men [1]. Several previous studies have described relationships between insulin levels, insulin resistance and serum uric acid levels. Furthermore, although several previous studies have described a relationship between lower serum uric acid levels and the association was larger among men (P-value for interaction, 0.007). Serum uric acid levels increased linearly with increasing fasting serum C-peptide levels, serum insulin levels or insulin resistance (multivariate P-values for trend, <0.001).

Conclusions. Individuals with moderately elevated HbA1c levels (i.e., pre-diabetes) may be at a higher risk of hyperuricaemia and gout, particularly in women, whereas individuals with diabetes or highly elevated HbA1c levels may be at a lower risk of these conditions, particularly in men.

Key words: Uric acid, Gout, Haemoglobin A1c, C-peptide, Insulin, Insulin resistance, NHANES III.

Materials and methods

Study population

Conducted between 1988 and 1994, the NHANES III included a representative sample of the non-institutionalized civilian US population, which was selected by using a multistage, stratified sampling design [12]. After a home interview, participants were invited to attend examination sessions where blood and urine specimens were obtained. For participants unable to attend the examination for health reasons, a blood sample was obtained during the home interview. We limited our analyses for HbA1c levels to participants 20 yrs or older who attended the medical examination and included the 14,664 participants (6861 men and 7803 women) with complete information in our analyses. We repeated our analyses among 14,223 participants after excluding those who self-reported gout or were taking allopurinol or uricosuric agents (n = 441). For the blood tests that required fasting (i.e., fasting C-peptide, blood glucose, insulin levels), we limited our analyses to the 9023 participants (4255 men and 4768 women) who had fasted at least 8 h prior to the blood collection.

The NHANES III study underwent institutional review board approval, and written informed consent was obtained from participants prior to starting the study.

Measurements

Glycosylated haemoglobin concentration was measured by ion-exchange HPLC with a glycosylated haemoglobin analyser system (DIAMAT; Bio-Rad Laboratories, Hercules, CA, USA). C-peptide levels by use of a RIA (Bio-Rad Laboratories), plasma glucose levels by a hexokinase enzymatic reference method (COBAS MIRA; Roche Diagnostics Corporation, Laboratory Systems, Montclair, New Jersey, USA) and serum insulin levels by means of an RIA (Pharmacia Diagnostics, Uppsala, Sweden) [12, 13]. Analytical protocols for other serum analytes and
laboratory quality-assurance procedures were described elsewhere [13, 14]. A Homeostasis Model Assessment (HOMA) was used to evaluate insulin resistance [15, 16]. Assuming that normal subjects aged 35 with normal weight have an insulin resistance of 1, the values for a patient can be calculated from the fasting concentration of insulin and glucose using the following formula: fasting serum insulin (µU/ml) × fasting plasma glucose (mmol/l)/22.5 [15, 16].

Serum uric acid was measured by oxidation with the specific enzyme uricase to form allantoin and H₂O₂ (Hitachi Model 737 Multichannel Analyzer, Boehringer Mannheim Diagnostics, Indianapolis, IN, USA). Details about quality-control procedures have been published elsewhere [13]. Values are reported in micromoles per litre; to convert to milligrams per decilitre, divide by 59.48.

**Assessment of co-variates**

The average daily intakes of total meat, seafood and dairy foods were derived from responses to a food frequency questionnaire. Food frequency questionnaire assessment of dietary intake has been shown to be a valid and reliable method for assessing average dietary consumption [17, 18]. The NHANES III collected information on body measurements (including height and weight), medication use (including diuretics, anti-hypertensives, allopurinol and uricosuric agents), medical conditions (including self-reported physician-diagnosed diabetes, hypertension and gout) and serum creatinine. Glomerular filtration rate (GFR) was estimated by using the simplified Modification of Diet in Renal Disease study equation: GFR (ml/min/1.73 m²) = 186 × (serum creatinine level [mg/dl])⁻¹.₅⁴ × (age)⁻₀.₂₀³ × [0.742, if female] × [1.212, if black] [19–21]. BMI was calculated by dividing the weight in kilograms by the square of the height in metres.

**Statistical analysis**

All statistical analyses were computed using survey commands of STATA (e.g. SVYMEAN and SVYREG) to incorporate sample weights and adjust for clusters and strata of the complex sample design (Version 8.2, STATA Corporation, College Station, TX, USA).

We used linear regression modelling to evaluate the relationship between HbA1c levels, other glucose-insulin markers and uric acid levels. Percentage of HbA1c was categorized into six groups: <5, 5–5.9, 6–6.9, 7–7.9, 8–8.9 and ≥9. Serum C-peptide levels were categorized into five groups: <0.5, 0.5–0.9, 1–1.4, 1.5–1.9 and ≥2 nmol/l. Because previous reports suggested significant differences between sexes in the relation between glucose-insulin markers and serum uric acid levels [10], our analyses were stratified by sex. We evaluated the significance of the potential interaction by sex by testing the significance of interaction terms added to our final multivariate models. These models were adjusted for age, smoking status, BMI, use of diuretics, β-blockers, allopurinol and uricosuric agents, self-reported hypertension, GFR, and intake of total energy, total meats, seafood, dairy foods, sugar-sweetened soft drinks and coffee. When categorical analyses suggested linear trends across categories, statistical significance of trends were assessed in the final multivariate linear regression models by using the median values of each category to minimize the influence of outliers. We also performed logistic regression with a dichotomous outcome of hyperuricaemia (i.e. serum uric acid >416 µmol/l [7 mg/dl] among men and serum uric acid >339 µmol/l [7 mg/dl] among women) and 18% were hyperuricaemic (19% with serum uric acid >416 µmol/l among men and 17% with serum uric acid >339 µmol/l among women [13]). The characteristics of the study population according to HbA1c levels are shown in Table 1. With increasing HbA1c levels, fasting blood glucose levels, and serum uric acid levels, we plotted the predicted values of quadratic models (using continuous values) and CIs, reflecting the relation suggested by the categorical analyses. For serum C-peptide, insulin and insulin resistance levels, we plotted the predicted values of linear regression models with CIs. For all difference estimates and odds ratios (ORs), we calculated 95% CIs. All P-values are two-sided.

**Results**

The population’s mean age was 45 yrs. The mean serum uric acid was 316.4 µmol/l (361.0 µmol/l among men and 276.6 µmol/l among women) and 18% were hyperuricaemic (19% with serum uric acid >416 µmol/l among men and 17% with serum uric acid >339 µmol/l among women [13]). The characteristics of the study population according to HbA1c levels are shown in Table 1. With increasing HbA1c levels, age, BMI and frequency of hypertension, diuretic use and uric acid lowering medication use tended to increase, particularly up to the HbA1c level 7–7.9%, but alcohol consumption tended to decrease.

The serum uric acid level increased with increasing serum HbA1c levels up to the category of 6–6.9%, and thereafter decreased with further increasing HbA1c levels (a bell-shaped relation) (Table 2 and Fig. 1). Compared with an HbA1c level of <5%, the multivariate differences among women were 26.8 µmol/l (95% CI 16.7, 37.5) for HbA1c 6–6.9% and −25.6 µmol/l (95% CI −42.8, −8.3) for HbA1c ≥9%. The corresponding multivariate differences among men were 8.3 µmol/l (95% CI −3.0, 19.6) and −64.8 µmol/l (95% CI −45.8, −84.5) (Table 2), both of which were significantly different from those among women (P-values for interaction by sex <0.001).

The multivariate ORs for hyperuricaemia for an HbA1c level of ≥9%, as compared with HbA1c <5%, were 0.51 (95% CI 0.25, 1.03) among women and 0.24 (95% CI 0.09, 0.67) among men. Corresponding ORs using an alternative definition of hyperuricaemia (serum uric acid level >357 µmol/l [6 mg/dl] regardless of sex) were 0.61 (95% CI 0.28, 1.32) among women and 0.14 (95% CI 0.07, 0.28) among men.

When we repeated our analyses after excluding participants who self-reported gout or were taking allopurinol or uricosuric agents (n = 441), compared with an HbA1c level of <5%, the multivariate differences among women were 25.6 µmol/l (95% CI

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**Table 1. Characteristics of the study participants according to categories of HbA1c**

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>Age (yr)</th>
<th>Men (%)</th>
<th>BMI (kg/m²)</th>
<th>Diuretic use (%)</th>
<th>History of hypertension (%)</th>
<th>Alcohol (servings/day)</th>
<th>Total meat (servings/day)</th>
<th>Seafood (servings/day)</th>
<th>Dairy foods (servings/day)</th>
<th>Urate-lowering agents (%)</th>
<th>Creatinine (µmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>&lt;5</td>
<td>3032</td>
<td>36</td>
<td>40</td>
<td>25</td>
<td>3</td>
<td>16</td>
<td>0.3</td>
<td>1.0</td>
<td>0.2</td>
<td>1.5</td>
<td>0</td>
<td>88.4</td>
</tr>
<tr>
<td>5–5.9</td>
<td>9193</td>
<td>46</td>
<td>51</td>
<td>27</td>
<td>6</td>
<td>24</td>
<td>0.3</td>
<td>1.1</td>
<td>0.2</td>
<td>1.4</td>
<td>1</td>
<td>97.2</td>
</tr>
<tr>
<td>6–6.9</td>
<td>1538</td>
<td>59</td>
<td>50</td>
<td>29</td>
<td>17</td>
<td>45</td>
<td>0.2</td>
<td>1.1</td>
<td>0.2</td>
<td>1.4</td>
<td>2</td>
<td>106.1</td>
</tr>
<tr>
<td>7–7.9</td>
<td>290</td>
<td>82</td>
<td>53</td>
<td>30</td>
<td>22</td>
<td>54</td>
<td>0.2</td>
<td>1.1</td>
<td>0.2</td>
<td>1.3</td>
<td>5</td>
<td>97.2</td>
</tr>
<tr>
<td>8–8.9</td>
<td>203</td>
<td>59</td>
<td>52</td>
<td>30</td>
<td>21</td>
<td>47</td>
<td>0.1</td>
<td>1.0</td>
<td>0.2</td>
<td>1.5</td>
<td>3</td>
<td>97.2</td>
</tr>
<tr>
<td>≥9</td>
<td>408</td>
<td>55</td>
<td>40</td>
<td>31</td>
<td>21</td>
<td>49</td>
<td>0.1</td>
<td>1.1</td>
<td>0.2</td>
<td>1.5</td>
<td>2</td>
<td>97.2</td>
</tr>
<tr>
<td>Total</td>
<td>14644</td>
<td>45</td>
<td>48</td>
<td>27</td>
<td>7</td>
<td>24</td>
<td>0.3</td>
<td>1.1</td>
<td>0.2</td>
<td>1.5</td>
<td>1</td>
<td>97.2</td>
</tr>
</tbody>
</table>

*Data are presented incorporating sample weights and adjusted for clusters and strata of the complex sample design of NHANES III. *Allopurinol and uricosuric agents.
14.9, 36.3) for HbA1c 6–6.9% and −27.4 μmol/l (95% CI −45.8, −8.9) for HbA1c ≥9%. The corresponding multivariate differences among men were 5.9 μmol/l (95% CI −5.9, 17.8) and −70.2 μmol/l (95% CI −87.4, −52.3), both of which were significantly different from those among women (P-values for interaction by sex < 0.001).

Fasting glucose levels showed a similar, bell-shaped relation with serum uric acid levels (Fig. 1). History of physician-diagnosed diabetes was associated with a lower serum uric acid level by 13.1 μmol/l (95% CI 0.1, 16.7) among women and by 20.8 μmol/l (95% CI 4.8, 37.5) among men in our multivariate analyses (P-values for interaction by sex = 0.007). These differences increased and remained significant after additional adjustment for serum C-peptide levels (21.4 and 26.2 μmol/l, respectively), but became insignificant after additional adjustment of HbA1c levels (P > 0.2).

Serum uric acid levels increased linearly with increasing fasting serum C-peptide levels (Table 2 and Fig. 2) (P-values for trend < 0.001) in both sexes, although the association was significantly stronger among women (P-values for interaction by sex < 0.001). After adjusting for age, serum uric acid levels associated with the largest category of serum C-peptide levels (≥2 nmol/l) were higher than in the lowest by 130.3 μmol/l (95% CI 107.7, 152.9) among women and 110.6 μmol/l (95% CI 75.5, 145.7) among men (P-values for trend, < 0.001) (Table 3). After adjusting for other co-variates, the difference was attenuated but remained significant (P-values for trend, < 0.001) (Table 3). When hyperuricaemia was examined as a dichotomous outcome, the results were similar. The multivariate ORs for hyperuricaemia according to the categories of fasting serum C-peptide levels (<0.5, 0.5-0.9, 1–1.4, 1.5–1.9 and ≥2 nmol/l) were 1.00, 2.04, 5.47, 9.33 and 19.34 (95% CI 7.20, 52.00; P-values for trend < 0.001) among women, respectively. The corresponding ORs among men were 1.00, 1.75, 3.05, 3.84 and 5.12 (95% CI 1.79, 14.69; P-values for trend < 0.001). Similarly, serum insulin levels and insulin resistance by HOMA showed a linearly increasing association both with serum uric acid levels and odds of hyperuricaemia (both multivariate P-values for trend < 0.001) (Fig. 2).

**Discussion**

In this nationally representative sample of US men and women, we found that the serum uric acid levels and the frequency of hyperuricaemia increased with moderately increasing levels of HbA1c (6–6.9%) and then decreased with further increasing levels of HbA1c (a bell-shaped relation). Serum uric acid levels showed a similar bell-shaped relation with fasting glucose levels. In comparison, serum uric acid levels and frequency of hyperuricaemia monotonically increased with increasing fasting C-peptide levels, as with increasing serum insulin levels and insulin resistance. These associations were independent of other risk factors for hyperuricaemia such as age, sex, BMI, dietary factors, alcohol intake, renal function, hypertension and diuretic use.

A biological mechanism underlying the bell-shaped relation between blood glucose levels and serum uric acid levels is thought to be due to the uricosuric effect of glycosuria, which occurs when the blood glucose level is greater than ~10 mmol/l (180 mg/dl) [2]. This level of blood glucose was consistent with that of HbA1c that corresponded to the peak of serum uric acid in our data, further

![Fig. 1. Serum uric acid levels in relation to HbA1c and fasting glucose levels. Grey areas indicate 95% CIs. Data are presented incorporating sample weights of NHANES III.](image-url)
supporting this notion. Correspondingly, history of diabetes was significantly associated with lower levels of serum uric acid in this study as well as in previous studies [2–5]. Our extended multivariate analyses showed that this inverse association became larger and stronger after adjusting for C-peptide, but became smaller and insignificant after adjusting for HbA1c, suggesting that the inverse link was due to average blood glucose levels. Collectively, these results indicate that individuals with pre-diabetes may be at a higher risk of developing gout, but once they develop diabetes their risk may drop to a lower level than that of normal individuals. This potential impact on the eventual risk of gout was also supported by our results with hyperuricaemia as a dichotomous outcome using various definitions.

The strong, linear and independent association between fasting serum C-peptide levels and serum uric acid levels in this nationally representative sample further adds to the close link between insulin levels, insulin resistance and serum uric acid levels found in previous studies [6–10] as well as in this study. Higher insulin levels are known to reduce renal excretion of urate [7–9, 22]. For example, exogenous insulin can reduce the renal excretion of urate in both healthy and hypertensive subjects [7, 8, 23]. Insulin may enhance renal urate reabsorption via stimulation of

TABLE 3. Gender-segregated differences in serum uric acid levels (μmol/l) according to categories of C-peptide levels

<table>
<thead>
<tr>
<th>C-peptide (nmol/l)</th>
<th>&lt;0.5</th>
<th>0.5-0.9</th>
<th>1-1.4</th>
<th>1.5-1.9</th>
<th>≥2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Participants (n)</td>
<td></td>
<td></td>
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<tr>
<td>Age-adjusted difference (95% CI)</td>
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<tr>
<td>Multivariate difference (95% CI)</td>
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<td></td>
<td></td>
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<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Participants (n)</td>
<td></td>
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<td>Age-adjusted difference (95% CI)</td>
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<tr>
<td>Multivariate difference (95% CI)</td>
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</table>

*Uric acid levels are reported in micromoles per litre; to convert to milligrams per decilitre, divide by 59.48. Data are presented incorporating sample weights and adjusted for clusters and strata of the complex sample design of NHANES III. Additional adjustments for intake of alcohol, total meat, seafood, dairy foods, sugar-sweetened soft drinks, coffee and total energy.

Fig. 2. Serum uric acid levels in relation to fasting C-peptide, insulin and HOMA insulin resistance levels. Grey areas indicate 95% CIs. Data are presented incorporating sample weights of NHANES III.

FIG. 2. Serum uric acid levels in relation to fasting C-peptide, insulin and HOMA insulin resistance levels. Grey areas indicate 95% CIs. Data are presented incorporating sample weights of NHANES III.
the urate-anion exchanger URAT1 [24] and/or the Na\(^+\)-dependent anion co-transporter in brush border membranes of the renal proximal tubule [25]. Collectively, these data provide a strong mechanism underlying the close link between the metabolic syndrome, hyperuricaemia and gout [26–29]. The increased insulin levels in individuals with insulin resistance syndrome could conceivably contribute to their elevated serum uric acid levels to the point where the effect is offset by subsequent development of diabetes, leading to glosycuria, uricosuria and lower uric acid levels.

We found that the positive associations between HbA1c (levels <7%) serum C-peptide levels, and serum uric acid levels were larger among women than men. These data closely agree with a population study of non-diabetic adults [10]. This Chinese community-based study reported a stronger association between fasting plasma glucose, serum insulin levels and serum uric acid levels among women than among men [10]. Furthermore, our results revealed that the inverse association between diabetes (or a level of HbA1c ≥7%) and serum uric acid levels was significantly stronger among men than among women. The mechanism behind these apparent gender differences remains unclear, although the role of female sex hormones has been suspected [10]. It also remains to be studied whether these differences could translate into a differential risk of gout between sexes.

Strengths and limitations of our study deserve comment. This study was performed in a nationally representative sample of US women and men; thus, the findings are likely to be generalizable to US men and women. Although previous reports and biological plausibility consistently suggest that blood glucose and insulin levels would affect the serum uric acid levels as observed [2–10], a cross-sectional study design tends to leave uncertainty regarding the temporal sequence of exposure-outcome relations. Thus, confirming the relation with prospective longitudinal data (e.g. relation between prior HbA1c, diabetes and incident hyperuricaemia or gout) would be valuable. Furthermore, it would be interesting to study whether controlling diabetes by reducing glycosuria would raise serum urate levels and increase the risk of gout in this high-risk group.

In conclusion, individuals with moderately elevated HbA1c levels (i.e. pre-diabetes) may be at a higher risk of hyperuricaemia and gout, particularly in women, whereas individuals with highly elevated HbA1c levels or diabetes may be at a lower risk of these conditions, particularly in men.

Rheumatology key messages

- Individuals with moderately elevated HbA1c levels (i.e. pre-diabetes) may be at a higher risk of hyperuricaemia and gout.
- However, individuals with highly elevated HbA1c levels or diabetes may be at a lower risk of these conditions.

Disclosure statement: The authors have declared no conflicts of interest.

References