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The predictive value of mean serum uric acid levels for developing prediabetes

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ABSTRACT

Aims: We aimed to assess the predictive value of mean serum uric acid (SUA) levels for incident prediabetes.

Methods: Normoglycemic adults (n = 39,353) were followed for a median of 3.0 years. Prediabetes is defined as impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or impaired HbA1c (IA1c), based on the American Diabetes Association criteria. Serum SUA levels were measured annually. Four diagnostic strategies were used to detect prediabetes in four separate analyses (Analysis 1: IFG. Analysis 2: IFG+IGT. Analysis 3: IFG+IA1c. Analysis 4: IFG +IGT+IA1c). Cox proportional hazards regression models were used to assess the relationship between SUA quintiles and prediabetes. C-statistic was additionally used in the final analysis to assess the accuracy of predictions based upon baseline SUA and mean SUA, respectively.

Results: After adjustment for potential confounders, the hazard ratios (95% confidence interval) of prediabetes for the highest versus lowest quintile of mean SUA were 1.22 (1.10, 1.36) in analysis 1; 1.59 (1.23, 2.05) in analysis 2; 1.62 (1.34, 1.95) in analysis 3 and 1.67 (1.31, 2.13) in analysis 4. In contrast, for baseline SUA, significance was only reached in analyses 3 and 4. Moreover, compared with baseline SUA, mean SUA value was associated with a significant increase in the C-statistic ($P < 0.001$).

Conclusions: Mean SUA value was strongly and positively related to prediabetes risk, and showed better predictive ability for prediabetes than baseline SUA.

1. Introduction

Prediabetes is defined as having impaired fasting glucose (IFG), or impaired glucose tolerance (IGT), or impaired hemoglobin A1c (impaired HbA1c, IA1c) of 5.7–6.4% (39–46 mmol/mol), according to the American Diabetes Association (ADA) criteria [1]. It is a common antecedent to diabetes that has reached epidemic proportions worldwide

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[2]. Though without overt symptoms, various pathological changes have already occurred in prediabetes [3–5]. As a result, individuals with prediabetes are at higher risk for subsequent diabetes and cardiovascular disease (CVD) [6,7]. Fortunately, prediabetes can be reversed, and future risk of diabetes and CVD can be reduced if decisive action is taken before the development of diabetes [8,9]. Nevertheless, little attention has previously been paid to early prediction and timely intervention of prediabetes, which is critical to ease the long-term healthcare burden.

Uric acid is the metabolic end-product of purine metabolism in humans. Accumulating evidence suggested that serum uric acid (SUA) is causally involved in the pathogenesis of diabetes [10–12]. In addition, several prospective studies have investigated the relationship between SUA and IFG, but they yield inconsistent results [11,13–15]. This may be due to the fact that these previous studies simply used baseline value of SUA. SUA levels are relatively unstable. The variability of SUA may be caused by its biorhythm [16] and by things in daily life like diet and exercise [17–19]. Thus one measurement of SUA at baseline may be temporary, and may not fully reflect the actual SUA levels in a long-term follow-up. Furthermore, the utility of baseline SUA may result in inaccurate estimation of the relationship between SUA and prediabetes. Therefore, it is hypothesized that mean SUA value is more appropriate than baseline SUA value when investigating the relationship between SUA and prediabetes. On the other hand, there is a paucity of data available on the relationships between SUA and IGT, or between SUA and IA1c. Noteworthily, discrepancy exists among IFG-, IGT-, and IA1c-based criteria for prediabetes, and different diagnostic strategies lead to discordant diagnoses of prediabetes [20–22]. Thus, when investigating the relationship between SUA and prediabetes, bias would certainly be introduced if one diagnostic criterion alone is used.

Therefore, we designed the present study to investigate whether a relationship does exist between SUA and prediabetes in Asian adults.

2. Subjects

The Tianjin chronic low-grade systematic inflammation and health (TCLSIH) cohort study has been introduced elsewhere [23]. The TCLSIH data from 2007 to 2014 was used in this study. Totally, there were 82,159 participants who had received at least one health examination, and had given informed consent for participation and with available data on age, body mass index (BMI) measurements, SUA concentration, and glucose parameters. All the participants had their fasting glucose measured once per year in annual health examinations, but only some of them had undergone HbA1c measurements or oral glucose tolerance test (OGTT) tests. We excluded those with a history of CVD ($n = 5477$), cancer ($n = 1128$), or diabetes ($n = 4175$), or those who had only received a health examination in 2014 ($n = 17,742$), or those who had baseline IFG ($n = 5558$), or those who did not complete health examinations during follow-up ($n = 8510$), or those who were diagnosed with diabetes during follow-up without previous detection of prediabetes ($n = 101$), or those who didn't have SUA measurements during follow-up ($n = 115$). Owing to these exclusions, 39,353 participants were eligible for the first cohort analysis focusing on the relationship between SUA and IFG (follow-up rate: 81.9%, median duration: 3.0, 95% confidence interval (95% CI): 2.94–2.98 y, range: 1–7 y; mean ± standard deviation age: 43.2 ± 12.9 years, age range: 18.0–100.0; male: 52.4%). In addition, since some of them had data on OGTT or HbA1c, we used those extra data, and performed 3 other cohort analyses. The second cohort analysis ($n = 5044$) investigated the relationship between SUA and prediabetes according to IFG- and/or IGT-based criteria (mean ± standard deviation age: 49.9 ± 9.6 years, age range: 22.3–91.0; male: 57.8%). The third cohort analysis ($n = 8021$) investigated the relationship between SUA and prediabetes according to IFG- and/or IA1c-based criteria (mean ± standard deviation age: 45.8 ± 11.2 years, age range: 16.3–92.3; male: 60.9%), and the fourth cohort analysis ($n = 3744$) investigated the relationship between SUA and prediabetes according to IFG- and/or OGTT- and/or IA1c-based criteria (mean ± standard deviation age: 48.8 ± 9.4 years, age range: 22.3–87.0; male: 57.3%).

The study conformed to STROBE guidelines for cohort studies, and was approved by the Institutional Review Board of Tianjin Medical University, and all the participants had given written informed consent.

3. Materials and methods

3.1. Assessments of SUA and glycemic parameters

Measurements of SUA and other biochemical indexes were provided during annual health examinations once per year. For each participant, data of the first examination during follow-up was used as their baseline information. Participants received examinations after an overnight fast. Serum SUA levels were measured by enzymatic colorimetric test using the Roche 912 analyzer (Roche Diagnostics, Indianapolis, IN), and were expressed as μmol/L. The lower detection limit of the test was 11.9 μmol/L; the measuring range was 11.9–1487 μmol/L; and the intermediate coefficients of variation (CV) were ⩽1.7%. Fasting serum glucose was measured by glucose oxidase method. Blood samples for analysis of HbA1c were mixed with ethylenediaminetetraacetic acid (as an anticoagulant) prior to testing. The HbA1c separation and quantification were performed by high-performance liquid chromatography analyzer (HLC-723 G8; Tosoh, Tokyo, Japan) with the intra- and inter-assay coefficients of variation less than 3% (http://www.diagnostics.eu.tosohbioscience.com/solutions/hplc+solutions/G8+analyser/). In order to measure postprandial glucose, a blood sample was drawn 2 h after the administration of an oral glucose load (a standard 75-g glucose solution) as part of an OGTT.

3.2. Assessment of other variables

Triglycerides (TG) and total cholesterol (TC) were measured by enzymatic methods. Low density lipoprotein (LDL) was measured by the polyvinyl sulfuric acid precipitation method while high density lipoprotein (HDL) was measured by the