Postprint of an Association Study Between Serum Uric Acid Levels and Type 2 Diabetes Risk

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Abstract

Background The high prevalence of hyperuricemia (HUA) caused by elevated serum uric acid (SUA) has become the fourth major metabolic disorder following hyperglycemia, hyperlipidemia, and hypertension, and the second largest metabolic disease after diabetes in China. Evidence has demonstrated that elevated SUA levels are significantly associated with the risk of type 2 diabetes mellitus (T2DM) incidence.

Objective To investigate the association between baseline SUA levels and T2DM incidence risk in health examination populations.

Methods A total of 17,626 participants without diabetes history at baseline who had at least two health examinations between January 2017 and December 2020 were selected. Demographic information, lifestyle data, physical examination results, and laboratory indicators were collected. The Cox proportional hazards regression model was used to analyze the association between different baseline SUA levels and T2DM incidence risk.

Results The median age of study participants was 38.15 (31.89, 49.59) years, the median baseline SUA level was 304.50 (248.00, 374.00) mol/L, and the overall prevalence of HUA was 13.12%. The cumulative follow-up was 54,634 person-years with a median follow-up duration of 3.10 years. There were 479 new-onset T2DM cases, with an incidence density of 8.76 per 1,000 person-years (95% CI: 8.00/1,000-9.59/1,000 person-years) and a cumulative incidence rate of 2.72% (95% CI: 2.48-2.97%). The cumulative incidence of T2DM was higher in subgroups of older age ($ $60 years), females, current smokers, current drinkers, BMI $ $28.0 kg/m^{2}$, those with hypertension, and those with dyslipidemia, and the risk of T2DM was also higher when accompanied by HUA. Multivariate-adjusted Cox proportional hazards regression model analysis showed that the risk of T2DM incidence increased in patients with HUA, with an HR of 1.32

(95% CI: 1.04, 1.67; P=0.023). Moreover, with increasing SUA levels, the high SUA group had a higher risk of T2DM incidence (P for trend <0.001). For every 10 mol/L increase in baseline SUA level, the risk of T2DM incidence increased by 3% (95% CI: 1%-4%, P<0.001).

Conclusion Elevated baseline SUA levels in health examination populations are associated with increased risk of T2DM incidence.

Full Text

Preamble

Association between Serum Uric Acid Levels and Risk of Type 2 Diabetes Mellitus: A Prospective Cohort Study

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Abstract

Background: Hyperuricemia (HUA) caused by elevated serum uric acid (SUA) has become the fourth most common chronic condition in China, following hyperglycemia, hyperlipidemia, and hypertension, and the second most prevalent metabolic disorder after diabetes mellitus. Evidence indicates that elevated SUA levels are significantly associated with increased risk of type 2 diabetes mellitus (T2DM). **Objective:** To investigate the association between baseline SUA levels and T2DM incidence risk in a health examination population. **Methods:** We selected 17,626 subjects without diabetes history at baseline who underwent at least two health examinations between January 2017 and December 2020. Demographic information, lifestyle data, physical examination measurements, and laboratory indicators were collected. Cox proportional hazards regression models were used to analyze the association between baseline SUA levels and T2DM risk. **Results:** The median age of participants was 38.15 (31.89, 49.59) years, with a baseline median SUA level of 304.50 (248.00, 374.00) mol/L. The overall HUA prevalence was 13.12%. During a cumulative follow-up of 54,634 person-years (median 3.10 years), 479 new T2DM cases were identified, yielding an incidence density of 8.76/1,000 person-years (95%CI: 8.00-9.59) and a cumulative incidence of 2.72% (95%CI: 2.48-2.97%). Higher cumulative T2DM incidence was observed in subgroups aged $ $60 years, females, current smokers, current drinkers, those with BMI $ 28.0$kg/m\^{}\{2\}$, hypertension, and dys-

lipidemia, with even greater risk when HUA was present. After multivariate adjustment, HUA was associated with increased T2DM risk (HR=1.32, 95%CI: 1.04-1.67; P=0.023), and risk increased with SUA levels (P-trend<0.001). Each 10 mol/L increase in baseline SUA was associated with a 3% increase in T2DM risk (95%CI: 1%-4%, P<0.001). **Conclusion:** Elevated baseline SUA levels are associated with increased T2DM risk in health examination populations.

Keywords: Type 2 diabetes mellitus; Serum uric acid; Hyperuricemia; Incident risk; Cohort study

Introduction

With socioeconomic development, lifestyle changes, and population aging, the prevalence of type 2 diabetes mellitus (T2DM) has been increasing annually. According to the International Diabetes Federation' s 2019 Global Diabetes Overview, 463 million adults aged 20-79 years worldwide had diabetes, with 90% being T2DM. In China, adult diabetes prevalence rose from 0.67% in 1980 to 11.2% in 2017. By 2019, China had 116.4 million adults with diabetes, accounting for 25% of the global total, and this number is projected to reach 147.2 million by 2045, making diabetes the country' s leading chronic disease.

Serum uric acid (SUA), the final product of purine metabolism, has increased in prevalence due to rising living standards and purine metabolism disorders. Hyperuricemia (HUA) has become China' s "fourth high" condition after hyperglycemia, hyperlipidemia, and hypertension, and the second most common metabolic disease after diabetes. Studies show that HUA prevalence is highest among T2DM populations, and evidence demonstrates a significant association between elevated SUA and T2DM risk. A US retrospective cohort study found that after a mean follow-up of 6.5 years, HUA patients had a 19% higher diabetes risk compared to non-HUA individuals, with nearly 8.7% of new diabetes cases attributable to HUA. Taiwanese research also identified high SUA as an independent risk factor for T2DM, with risk increasing alongside SUA levels. Therefore, this study examined the association between baseline SUA levels and T2DM risk in a Tianjin health examination population.

Methods

1.1 Study Population

We selected 18,968 individuals who underwent at least two health examinations at the Health Management Center of First Teaching Hospital of Tianjin University of Traditional Chinese Medicine between January 1, 2017 and December 31, 2020. Inclusion criteria were: (1) age >18 years; (2) complete baseline SUA data; (3) complete baseline and follow-up glucose measurements. Exclusion cri-

teria were: (1) history of gestational diabetes or T2DM at baseline (n=719); (2) baseline glucose meeting diabetes diagnostic criteria (n=530); (3) history of cancer (n=93). The final cohort included 17,626 participants [Figure 1: see original paper]. This study was approved by the Ethics Committee of First Teaching Hospital of Tianjin University of Traditional Chinese Medicine (Approval No.: TYLL2018[K]013), and all participants provided informed consent.

1.2 Sample Size Estimation

This prospective cohort study defined the exposed group as HUA patients and the unexposed group as non-HUA individuals, with incident T2DM as the primary outcome. Based on previous literature reporting T2DM incidence of 12.2%-26.9% in HUA populations, we used 12.2%. The hazard ratio for diabetes in HUA versus non-HUA patients ranged from 1.192-1.950, so we adopted 1.192. With α=0.05 (two-sided) and power=0.90, PASS 15.0 software calculated required sample sizes of N_1=5,418 for the HUA group and N_2=5,418 for the non-HUA group. Assuming 10% loss to follow-up, we needed N_1=6,020 and N_2=6,020, totaling 12,040 participants.

1.3 Data Collection

(1) Questionnaire Survey: Face-to-face interviews collected demographic characteristics (age, sex, education, marital status), lifestyle information (smoking and alcohol consumption), medical history (diabetes, hypertension, HUA/gout, cancer), and medication use. **(2) Physical Examination:** Trained staff measured height, weight, waist circumference, systolic blood pressure (SBP), and diastolic blood pressure (DBP), and calculated body mass index (BMI). **(3) Laboratory Tests:** After at least 8 hours of fasting, 5 ml of venous blood was collected in the morning for baseline and follow-up laboratory measurements. Fasting blood glucose (FBG) was measured by hexokinase method (Roche P800). Hemoglobin A1c (HbA1c) was measured by high-performance liquid chromatography (TOSOH G8). Participants consumed a standardized meal (milk, egg, two buns or bread slices, and vegetables) at the center' s restaurant, with timing recorded at first bite. Two-hour postprandial glucose (2hPG) was measured from fingerstick blood 2 hours later. SUA was measured by ARCHITECTci 16000 autoanalyzer. Total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) were measured by autoanalyzer (Roche Cobas C501).

1.4 Follow-up

The endpoint was T2DM incidence. Follow-up examinations mirrored baseline assessments, with annual questionnaires collecting disease onset and diagnosis timing. Follow-up ended at T2DM diagnosis or study completion (December 31, 2020).

1.5 SUA Classification Criteria

(1) Based on the *Practice Guideline for Hyperuricemia/Gout Patients*, baseline SUA was categorized as: <360 mol/L, 360-419 mol/L, 420-480 mol/L, and $ 480$\mu mol/L$.(2)$Quartilegroups : Q1 < 248\mu mol/L, Q2 = 248 - 303\mu mol/L, Q3 = 304 - 373\mu mol/L, Q4$ $374 mol/L. (3) HUA was defined as SUA>420 mol/L, self-reported HUA history, or urate-lowering medication use.

1.6 T2DM Diagnostic Criteria

(1) FBG $ $7.0 mmol/L; (2) or 2hPG $ $11.1 mmol/L; (3) or HbA1c $ $6.5%; (4) or physician-diagnosed T2DM or current antidiabetic medication use.

1.7 Classification Criteria for Other Chronic Diseases

Hypertension: SBP $ $140 mmHg, DBP $ $90 mmHg, self-reported hypertension history, or antihypertensive medication use. **Hypercholesterolemia:** TC $ $6.2 mmol/L. **Hypertriglyceridemia:** TG $ $2.3 mmol/L. **Low HDL-C:** HDL-C <1.0 mmol/L. Dyslipidemia included any of these three conditions.

1.8 Statistical Analysis

STATA 14.0 was used for all analyses. Continuous variables (non-normally distributed) were expressed as median (interquartile range) and compared using Mann-Whitney U tests. Categorical variables were expressed as frequency (percentage) and compared using ^{2} tests. Cumulative incidence was calculated as: (new T2DM cases during follow-up / total participants at baseline) × 100%. Incidence density was calculated as: new T2DM cases / total person-years. Cox proportional hazards models analyzed associations between baseline SUA (categorical and continuous) and HUA with T2DM incidence, adjusting for age, sex, BMI, waist circumference, smoking, alcohol consumption, hypertension, and dyslipidemia. Hazard ratios (HR) with 95% confidence intervals (CI) were reported. Proportional hazards assumptions were tested. Linear trend analysis used median values of SUA categories. Stratified analyses examined effect modification. Two-sided P<0.05 indicated statistical significance.

Results

2.1 Participant Characteristics

The cohort included 17,626 participants with median age 38.15 (31.89, 49.59) years; 8,117 (46.05%) were male. Baseline median SUA was 304.50 (248.00, 374.00) mol/L [males: 372.00 (325.00, 425.00); females: 257.00 (223.00, 297.00); Z=-90.07, P<0.001]. Overall HUA prevalence was 13.12% (males: 27.08%; females: 1.21%; ^{2}=2,570.26, P<0.001), including 107 participants (0.61%) with

self-reported HUA/gout history, of whom 37 (34.58%) used urate-lowering medications.

During 54,634 person-years of follow-up (median 3.10 years, range: 2.01-3.93), 479 new T2DM cases occurred, yielding an incidence density of 8.76/1,000 person-years (95%CI: 8.00-9.59) and cumulative incidence of 2.72% (95%CI: 2.48-2.97%). Participants who developed T2DM were older, more likely male, and had higher rates of smoking, alcohol consumption, obesity, hypertension, and dyslipidemia. They also had higher baseline waist circumference, SBP, DBP, TC, TG, LDL-C, FBG, 2hPG, HbA1c, and SUA, but lower HDL-C (all P<0.001) .

2.2 Cumulative T2DM Incidence in Subgroups

Subgroup analyses showed higher cumulative T2DM incidence in those aged $ $60 years, males, current smokers, current drinkers, BMI $ 28.0kg/m^{2}, hypertensive patients, and those with dyslipidemia (all P<0.001) .

2.3 Cox Regression Analysis of SUA and T2DM Risk

After multivariate adjustment, HUA was associated with increased T2DM risk (HR=1.32, 95%CI: 1.04-1.67; P=0.023), meeting proportional hazards assumptions (^{2}=14.22, P=0.287). T2DM risk increased with SUA levels (P-trend<0.001). Each 10 mol/L increase in baseline SUA was associated with a 3% increase in T2DM risk (95%CI: 1%-4%, P<0.001), also meeting proportional hazards assumptions (^{2}=13.01, P=0.368). Sex-stratified analysis showed similar associations in males (HR=1.02 per 10 mol/L, 95%CI: 1.01-1.03, P=0.001) and females (HR=1.05, 95%CI: 1.03-1.08, P=0.012) .

2.4 Stratified Analysis of HUA and T2DM Risk

Stratified analyses revealed that HUA conferred higher T2DM risk in subgroups aged $ $60 years [HR=6.78 (4.16-11.03)], females [HR=2.31 (1.54-3.45)], current smokers [HR=1.79 (1.23-2.60)], current drinkers [HR=1.61 (1.23-2.10)], BMI $ 28.0kg/m^{2} [HR=1.69 (1.07-2.68)], hypertensive patients [HR=2.89 (2.15-3.89)], and those with dyslipidemia [HR=2.39 (1.80-3.16)] .

Discussion

This study demonstrates that elevated SUA levels and HUA increase T2DM risk in health examination populations, with particularly high cumulative incidence and risk among older adults ($ $60 years), females, current smokers, drinkers, those with BMI $ 28.0kg/m^{2}, hypertension, and dyslipidemia when HUA is present.

SUA is a purine metabolite, and HUA is a metabolic disorder resulting from purine metabolism dysfunction. Elevated SUA can crystallize and deposit in organs and joints, causing gout arthritis or stones. Research has identified SUA as a risk factor for chronic kidney disease, hypertension, and T2DM, with elevated levels increasing cardiovascular disease risk in hypertensive and diabetic patients.

A Korean cohort study identified HUA as a strong independent predictor of incident T2DM, with a 78% increased risk over 5 years and elevated long-term cardiovascular risk. A European nested case-control study found that after adjusting for age, TG, obesity, and hypertension, the highest SUA quartile had 1.43-fold higher T2DM risk than the lowest. Yamada et al. reported that SUA was not associated with T2DM risk in Japanese men but was predictive in women, possibly related to SLC2A9 gene-mediated sex-specific effects. Wang et al. found that among 924 Chinese middle-aged and elderly participants followed for 3.5 years, HUA patients had 1.95-fold higher T2DM risk (95%CI: 1.11-3.44). Research in Chinese longevity areas showed HUA increased T2DM risk by 19%, with each 10 mol/L SUA increase raising risk by 1.1%, similar to our findings, though limited by its focus on adults over 80 years.

SUA has antioxidant properties that protect against oxidative damage, but under certain conditions can become pro-oxidant and damage tissues. Mechanisms linking elevated SUA to T2DM include: (1) reduced nitric oxide activity and endothelial dysfunction, impairing insulin uptake, GLUT4 translocation, and glucose uptake; (2) induction of reactive oxygen species (ROS) causing oxidative stress and inflammation, disrupting metabolic systems and insulin signaling pathways, reducing insulin sensitivity and secretion; (3) uric acid crystal deposition in pancreatic tissue reducing insulin production and secretion.

Study strengths include: (1) prospective cohort design enabling robust causal inference with minimal reverse causation bias; (2) large sample size with effective follow-up and reliable data; (3) comprehensive adjustment for lifestyle and biochemical confounders yielding stable results. Limitations include: (1) single-center health examination population limiting generalizability; (2) use of baseline SUA only, creating potential information bias as SUA is dynamic; (3) relatively short median follow-up of 3.10 years requiring continued monitoring to examine dynamic SUA changes.

In conclusion, elevated SUA and HUA increase T2DM risk, particularly when combined with older age, female sex, smoking, alcohol consumption, obesity, hypertension, and dyslipidemia. These high-risk subgroups require targeted risk factor control to prevent T2DM.

Conflict of Interest: All authors declare no conflicts of interest.

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Note: Figure translations are in progress. See original paper for figures.