Serum uric acid and incident DM2

Serum uric acid levels improve prediction of incident Type 2 Diabetes in individuals with impaired fasting glucose: The Rancho Bernardo Study

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Objective: To determine whether serum uric acid (UA) predicts incident Type 2 Diabetes Mellitus (DM2) by glucose tolerance status in older community-dwelling adults.

Research design and methods: Participants without diabetes at baseline were evaluated for incident DM2 13 years later. Baseline glucose tolerance status was defined as normoglycemia, impaired fasting glucose (IFG), and impaired post-challenge glucose tolerance.

Results: 566 participants were included (mean age 63.3±8.6 yrs; 41% men). Regression models adjusted for age, sex, body mass index, diuretic use, and estimated glomerular filtration rate showed that for each 1 mg/dL increment in UA levels, incident DM2 risk increased by approximately 60%. When analyses were stratified by glucose status, UA levels independently predicted incident DM2 among participants who had IFG (OR 1.75 95%CI 1.1-2.9, P=0.02).

Conclusion: UA may be a useful predictor of DM2 in older adults with IFG.
Increased levels of serum uric acid (UA) have been associated with insulin resistance (1) and with established Type 2 Diabetes (DM2) (2). Previous studies demonstrated that UA is an independent predictor of incident DM2 in general populations (3; 4), but whether UA predicts incident DM2 in individuals who have abnormal glucose tolerance is unknown. We examined whether baseline UA levels predict incident DM2 by glucose tolerance status in older adults.

**RESEARCH DESIGN AND METHODS**

Participants were older adults who had an oral glucose tolerance test (OGTT) and UA measured between 1984 and 1987. The 566 participants without baseline diabetes by history and OGTT were evaluated for incident diabetes an average of 13 years later (±0.85 yrs; maximum 22 yrs). Baseline glucose tolerance status was defined by ADA criteria as 1) normoglycemia (NG; n=276): fasting plasma glucose <100 mg/dL and 2-h post-challenge glucose <140 mg/dL; 2) impaired fasting glucose (IFG; n=152): fasting plasma glucose ≥100 mg/dL and <126 mg/dL; and 3) impaired glucose tolerance (IGT; n=167): 2-h post-challenge glucose ≥140 mg/dL and <200 mg/dL.

Participants provided written informed consent. The Human Research Protection Program at the University of California, San Diego approved the study protocol.

Laboratory and anthropometric data were collected as described (5). Incident DM2 was defined as: fasting blood glucose ≥126 mg/dL and/or post-challenge glucose ≥200 mg/dL and/or physician-prescribed medication for DM2. Estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease formula: $186 \times \frac{\text{plasma creatinine (mg/dl)}}{\text{age (years)}}^{0.203} \times (1.212 \text{ if black}) \times (0.742 \text{ if female})$.(6).

Analyses were performed using SPSS (version 13.1, Chicago, IL). The association between UA and incident DM2 was examined using multivariate regression models after adjustment for potential confounding variables (age, sex, body mass index, diuretic use, and eGFR). Receiver-operating characteristic (ROC) curves were constructed to calculate sensitivity and specificity of UA in identifying incident DM2 by glucose tolerance status. P values <0.05 were considered significant.

**RESULTS**

Mean age at baseline was 63.3 (±8.6) years; 41% were men. During follow-up, there were 55 (9.7%) new cases of DM2 (8, 25, and 22 among NG, IFG, and IGT groups, respectively). At baseline, participants who developed DM2 during the follow-up had higher body mass index (27±3.2 vs. 24.6±3.2 kg/m², $P<0.001$), blood pressure levels (systolic: 136.8±16.1 vs. 129.4±17.7 mmHg, $P=0.003$; diastolic: 80±8.5 vs. 75.7±8.5 mmHg, $P<0.001$), total cholesterol/HDL ratio (4.3±1.2 vs. 3.7±1.1, $P <0.001$), and UA levels (6.8±1.3 vs. 5.6±1.2 mg/dL, $P <0.001$) compared with those who did not develop diabetes.

In regression models adjusted for age, sex, body mass index, diuretic use, and eGFR, the risk for incident DM2 in the cohort overall increased by approximately 60% for each 1 mg/dL increment in UA levels (OR 1.65 95%CI 1.25-2.18, $P <0.001$). UA still predicted incident DM2 (OR 1.63 95%CI 1.21-2.19, $P=0.001$) after including IFG and/or IGT in the model (OR 4.7 95%CI2-11, $P <0.001$). In the same adjusted analyses stratified by glucose status, UA levels independently predicted incident DM2 among the 152 subjects who had IFG (OR 1.75 95%CI 1.1-2.9, $P=0.02$) but not among those with NG (OR 2.1 95%CI 0.93-4.84, $P = 0.07$) or IGT (OR 1.42 95%CI 0.9-2.3, $P=0.15$).
Further adjustment for regular physical exercise, family history of DM2, and triglycerides levels did not materially change the results.

Among participants with IFG, a UA level above 6.35 mg/dL had 80% sensitivity and 70% specificity to identify individuals who later developed DM2 (area under ROC curve 0.751) (figure). The negative predictive value of a UA level below 5.35 mg/dL was 100%; this value was calculated using its ROC curve sensitivity (100%) and specificity (40%) based on the prevalence of diabetes in the U.S population (7). In our sample 30% of those who had IFG also had UA levels below 5.35 mg/dL.

CONCLUSIONS

In this population-based study, UA levels independently predicted incident DM2 (after adjustment for variables known to be associated with DM2) only among individuals with IFG.

The association of UA levels and DM2 incidence has been reported in two other populations: In a 6-year follow-up study of 2310 Japanese male adults, the odds ratio for DM2 incidence of the highest UA quintile compared to lower quintiles was 1.63 (95%CI 1.2-2.2, P <0.001) after adjustments for age, sex, BMI, and other covariates (4). The highest quartile of UA was also associated with incident DM2 in the Rotterdam study (4536 adults followed for 10 years) (3). Although these studies demonstrated an association of UA with DM2 incidence, neither addressed the association of UA with incident DM2 by glucose tolerance status.

UA levels had high specificity for persons with IFG. The current recommendation is to perform an oral glucose tolerance test in those with IFG, to better define the risk of DM2 (8); but testing glucose tolerance is unpleasant and expensive. In this small cohort a simple measurement of UA below 5.35 mg/dL demonstrated a 100% negative predictive value of incident DM2 over a maximum 22-year follow-up. If confirmed, this simple inexpensive test might help to identify older adults with IFG who are at little risk for developing DM2 and would not need an OGTT. This observation would be important since in the United States the elderly have the greatest current burden and expected increase in prevalence of DM2 (9; 10).

This study has limitations. The Rancho Bernardo cohort is a homogeneous population (largely Caucasian and middle class) so results may not be generalizable to other populations. The average age of participants was 68 at baseline; the role of UA in predicting incident DM2 among younger adults needs further study. Due to the small number of new DM2 cases, this study had limited power to exclude completely effectiveness of UA prediction among IGT and NG groups. This does not obscure the main result, showing that UA adds to the prediction of DM2 among adults with IFG.

In conclusion, adding UA to fasting blood glucose may help identify older adults with IFG who are at low risk of diabetes and who do not need a glucose tolerance test.

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Figure Serum uric acid receiver-operating characteristic curve of individuals with impaired fasting glucose for DM2 incidence