High Serum Uric Acid as a Novel Risk Factor for Type 2 Diabetes

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OBJECTIVE — To investigate the association between serum uric acid level and risk of type 2 diabetes.

RESEARCH DESIGN AND METHODS — The population for analysis consisted of 4,536 subjects free from diabetes at baseline. During a mean of 10.1 years of follow-up, 462 subjects developed diabetes.

RESULTS — The age- and sex-adjusted hazard ratios (HRs) (95% CIs) for diabetes were 1.30 (0.96–1.76) for the second, 1.63 (1.21–2.19) for the third, and 2.83 (2.13–3.76) for the fourth quartile of serum uric acid, in comparison with the first quartile. After adjustment for BMI, waist circumference, systolic and diastolic blood pressure, and HDL cholesterol, the HRs decreased to 1.08 (0.78–1.49), 1.12 (0.81–1.53), and 1.68 (1.22–2.30), respectively.

CONCLUSIONS — The results of this population-based study suggest that serum uric acid is a strong and independent risk factor for diabetes.

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Serum uric acid is positively associated with serum glucose in healthy subjects.(1,2) However, this association is not consistent between healthy and diabetic individuals (3–5), as a low serum level of uric acid is reported in the hyperglycemic state (6). Since most individuals experience a phase of impaired glucose tolerance before progression to diabetes, it is not clear whether raised serum uric acid predicts the risk of type 2 diabetes (4,5). We investigated the association between serum uric acid and risk of diabetes in the Rotterdam Study, a large population-based, prospective cohort study among subjects aged 55 years and older.

RESEARCH DESIGN AND METHODS

— The Rotterdam Study has been described in detail elsewhere (7). Written informed consent was obtained from all participants, and the Medical Ethics Committee of Erasmus Medical Center approved the study. At baseline, serum uric acid was measured (8,9) and prevalent diabetes cases were excluded (10). Incident cases of diabetes were diagnosed during follow-up based on the guidelines of the American Diabetes Association (11) and World Health Organizatioin (12) using the information from general practitioners, pharmacies' databases, and fasting blood samples that were taken during follow-up examinations (10). The association was assessed by Cox regression analysis. The population-attributable risk and 95% CIs were calculated with use of the Interactive Risk Assessment Program (IRAP) (13).

RESULTS

— Serum uric acid was ranged from 107 to 756 μmol/l with a mean ± SD of 323.7 ± 82.2 μmol/l. Age BMI, waist circumference, systolic and diastolic blood pressure, and HDL cholesterol were significantly correlated with serum uric acid. The correlation coefficient ranged from 0.03 for diastolic blood pressure to 0.35 for waist circumference. Except for HDL cholesterol, the correlations were positive.

During a mean follow-up of 10.1 years, 462 of 4,536 participants developed diabetes (incidence rate 10.1 per 1,000 person-years). The age- and sex-adjusted hazard ratios (HRs) (95% CIs) for diabetes were 1.30 (0.96–1.76) for the second, 1.63 (1.21–2.19) for the third, and 2.83 (2.13–3.76) for the fourth quartile of serum uric acid, in comparison with the first quartile. In a multivariate-adjusted model (Table 1), the HRs (95% CIs) decreased to 1.08 (0.78–1.49), 1.12 (0.81–1.53), and 1.68 (1.22–2.30), respectively. The population-attributable risk of high serum uric acid for diabetes was 0.24 (95% CI 0.17–0.30) for the fourth quartile, 0.09 (0.3–0.15) for the third quartile, and 0.04 (−0.01 to 0.10) for the second quartile.

CONCLUSIONS

— We showed that the subjects with higher levels of serum uric acid are more at risk of developing type 2 diabetes. We also found that one-quarter of diabetes cases can be attributed to a high serum uric acid level.

Our finding is in agreement with previous studies. At least two studies in 1980s reported on the association of serum uric acid with the risk of diabetes (14,15); however, the association was not adjusted for any potential confounder. Lately, it has been shown in middle-aged Japanese men (4) that serum uric acid level is significantly associated with the risk of diabetes. However, another study in middle-aged Japanese men in Osaka showed that the association was not significant after adjustment for BMI, alcohol consumption, smoking, physical activity, fasting blood glucose, and parental history of diabetes. The absence of an independent effect in this study could be explained by the fact that the study population only consisted of men. We observed in our study that, although not significantly, the association was weaker in men than in women (data not shown).

Recognition of high serum uric acid as a risk factor for diabetes has been a matter of debate for a few decades, since hyperuricemia has been presumed to be a consequence of insulin resistance rather than its precursor. However, recent findings sug-

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Table 1—*HR (95% CI) for diabetes according to level of serum uric acid*

Serum uric acid quartile	Participants (cases)	HR (95% CI) Model 1	Model 2	Model 3
1 (≤267 μmol/l)	1,153 (77)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
2 (268–310 μmol/l)	1,141 (94)	1.30 (0.96–1.76)	1.14 (0.83–1.57)	1.08 (0.78–1.49)
3 (311–370 μmol/l)	1,175 (120)	1.63 (1.21–2.19)	1.23 (0.89–1.67)	1.12 (0.81–1.53)
4 (>370 μmol/l)	1,067 (171)	2.83 (2.13–3.76)	1.92 (1.41–2.62)	1.68 (1.22–2.30)
P for trend		<0.001	<0.001	<0.001
1 SD increment	4,536 (462)	1.53 (1.39–1.67)	1.37 (1.23–1.52)	1.31 (1.18–1.46)

Model 1: adjusted for age and sex. Model 2: model 1 + BMI and waist circumference. Model 3: model 2 + systolic and diastolic blood pressure and HDL cholesterol.

gest that uric acid could be related to the development of diabetes. Serum uric acid has been shown to be associated with oxidative stress (16) and production of tumor necrosis factor-α (16), which are both related to the development of diabetes. In addition, a recent study in rats showed that fructose-induced hyperuricemia plays a pathogenic role in the metabolic syndrome (17). These findings support high serum uric acid as a precursor of type 2 diabetes.

Currently, gout and renal disorders are the only consequences considered for hyperuricemia. Recent studies have introduced serum uric acid as a potential risk factor for hypertension (18), stroke (8), and cardiovascular diseases (19). Our findings suggest that type 2 diabetes is another consequence of hyperuricemia. The importance of this finding is even clearer when considering that lowering serum uric acid in subjects in the highest quartile may decrease the incidence of diabetes by 24%, if the relationship is causal. Hence, the public health impact of high serum uric acid may be larger than currently thought. Even so, uric acid is neither a target for treatment in asymptomatic hyperuricemia nor a risk marker in clinical practice (20), but methods for assessment of serum uric acid are widely available and inexpensive. Moreover, xanthine oxidase inhibitors, which are currently used to decrease serum uric acid, are safe and inexpensive.

In conclusion, our findings, together with those from previous literature, indicate that lowering uric acid may be a novel treatment target for preventing diabetes and justify a prospective clinical trial on the possible benefits of the measurement and lowering of serum uric acid on multiple chronic disease end points.

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