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Serum Uric Acid Levels and the Risk of Type 2 Diabetes: A Prospective Study

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Abstract

Purpose—To evaluate the impact of serum uric acid levels on the future risk of developing type 2 diabetes independent of other factors.

Methods—We used prospective data from the Framingham Heart Study original (n=4,883) and offspring (n=4,292) cohorts to examine the association between serum uric acid levels and the incidence of diabetes. We used Cox proportional hazards models to estimate the relative risk (RR) of incident diabetes adjusting for age, sex, physical activity, alcohol consumption, smoking, hypertension, body mass index, and blood levels of glucose, cholesterol, creatinine, and triglycerides.

Results—We identified 641 incident cases of diabetes in the original cohort and 497 cases in the offspring cohort. The incidence rates of diabetes per 1000 person-years for serum uric acid levels <5.0, 5.0–5.9, 6.0–6.9, 7.0–7.9 and ≥8.0 mg/dL were 3.3, 6.1, 8.7, 11.5, and 15.9 in the original cohort, and 2.9, 5.0, 6.6, 8.7, 10.9 in the offspring cohort, respectively (*P*-values for trends <0.001). Multivariable RRs per mg/dL increase in serum uric acid levels were 1.20 (95% CI, 1.11 to 1.28) for the original cohort and 1.15 (95% CI, 1.06 to 1.23) for the offspring cohort.

Conclusions—These prospective data from two generations of the Framingham Heart Study provide evidence that individuals with higher serum uric acid, including younger adults, are at a higher future risk of type 2 diabetes independent of other known risk factors. These data expand on cross-sectional associations between hyperuricemia and the metabolic syndrome, and extend the link to the future risk of type 2 diabetes.

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Keywords

Uric acid; type 2 diabetes

The prevalence of diabetes in the U.S (2007) was estimated to be 10.7% (23.5 million) among adults aged 20 years or older and 23.1% (12.2 million) among those aged 60 years and older.¹ Hyperuricemia, the precursor of gout, is strongly associated with insulin resistance syndrome, an established risk factor for type 2 diabetes.^{2, 3} This link may be translated into an independent association between hyperuricemia and the future risk of type 2 diabetes, but little prospective data on the topic are available, particularly in the general population. Indeed, studies of individuals with impaired glucose levels have suggested that hyperuricemia is an independent risk factor for diabetes.^{4, 5} Furthermore, the Rotterdam study of individuals 55 years and older reported similar results.⁶ These findings call for confirmation by prospective, general-population-based data, particularly with the inclusion of young individuals who tend to have fewer confounding pathophysiologic conditions associated with uric acid levels and type 2 diabetes.

To address this issue, we examined the independent association between serum uric acid levels and the future risk of incident type 2 diabetes among men and women in two well-established, population-based, prospective cohorts, the Framingham Heart Study original and offspring cohorts.

MATERIALS AND METHODS

Study Population

We conducted analyses of the prospectively collected data in the Framingham Heart Study original and offspring cohorts, using the datasets obtained from the National Heart, Lung and Blood Institute (NHLBI). The Framingham Heart Study-original cohort is an ongoing longitudinal study of 5,209 men and women from the town of Framingham, Massachusetts, aged 29-62 years at time of recruitment in 1948. Subjects have been followed biennially, with data from a detailed medical history, a physical examination, and laboratory tests collected at each examination. The offspring cohort, initiated in 1971, includes 5,124 men and women aged 5-70 years at baseline, and is comprised of the offspring of members of the original cohort and their spouses. Offspring cohort members are followed at intervals of approximately 4 years (except for an 8-year gap between the first and the second examinations). Additional details of the cohorts are described elsewhere.^{7, 8} We limited our analyses to 2,690 women and 2,193 men from the original cohort and 2,243 women and 2,049 men from the offspring cohort who had complete follow-up data and were free of diabetes at baseline using our same case definition of type 2 diabetes as described below.

Assessment of Exposure Variables

We evaluated serum uric acid levels and purported risk factors for diabetes obtained in the Framingham Heart Study. Serum uric acid levels were measured with an autoanalyzer using a phosphotungstic acid reagent⁹ in the original (first four and the thirteenth examinations) and offspring (first two examinations) cohorts. Height and weight were measured at each examination, and body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters. Information on medication use, alcohol consumption, smoking and physical activity was obtained by self-report. A composite score for the physical activity index was calculated by summing up the products at each level of activity times a weight based on oxygen consumption required for that activity.¹⁰ Systolic and diastolic blood pressures were measured twice in the left arm in a sitting position using

mercury-column sphygmomanometer positioned near eye level. The average of the two readings was used for each blood pressure variable. Hypertension was defined by a systolic blood pressure of 140 mm Hg or higher, a diastolic blood pressure 90 mm Hg or higher, or use of antihypertensive drugs.¹¹ Blood glucose levels were determined by Nelson's method,¹² cholesterol levels were determined according to the Abel-Kendall method,¹³ creatinine levels were determined by the modified Jaffe's method and triglyceride levels were measured enzymatically as previously described.¹⁴

Ascertainment of Type 2 Diabetes

Type 2 diabetes was defined as fasting plasma glucose ≥ 126 mg/dL (offspring cohort), casual plasma glucose ≥ 200 mg/dL (original cohort), or treatment with insulin or oral hypoglycemic agents (both cohorts) among individuals aged ≥ 35 years at the time of diagnosis.¹⁵

Statistical Analysis

We calculated the incidence rates of type 2 diabetes according to serum uric acid level categories. We computed person-time of follow-up from the baseline examination to the diagnosis of type 2 diabetes at a subsequent examination, day of the last attended examination, or end of the study period (26th examination [2000-2002] for the original cohort and 7th examination [1998-2002] for the offspring cohort), whichever came first.

For each cohort, we used Cox proportional hazards models to estimate the relative risk (RR) of incident type 2 diabetes associated with updated serum uric acid levels in a time-dependent manner. We categorized serum uric acid levels into <5.0 , 5.0 - 5.9 , 6.0 - 6.9 , 7.0 - 7.9 and ≥ 8.0 mg/dL to reflect the range in both genders as serum uric acid levels in men are substantially higher than in women during adulthood. These integer categories of serum uric acid are consistent with widely-cited previous studies about the impact of serum uric acid on related disease outcomes such as gout and metabolic syndrome.^{16, 17} Multivariable models evaluated the following purported risk factors in a time-dependent manner in addition to uric acid level: sex (male, female), age (continuous, per 5 years), BMI (<25 , 25 - 29.9 or ≥ 30 kg/m²), physical activity level (light, moderate, heavy [physical activity index score ≤ 28 , 29 - 36 or >36 , respectively]), alcohol consumption (abstinent/light [zero to one ounce, 29.57 ml, per week], moderate [two to six ounces per week], or heavy [seven or more ounces per week]), smoking (yes or no), hypertension (yes or no), blood glucose level (continuous, per 10 mg/dL), blood cholesterol level (continuous, per 10 mg/dL), creatinine level (continuous, per 1 mg/dL) and triglyceride level (continuous, per 10 mg/dL). We conducted additional analyses using incident impaired fasting glucose status as an outcome in the offspring cohort, where the fasting blood glucose levels were measured. For this analysis, we used both the original¹⁸ and revised¹⁹ American Diabetes Association definitions of impaired fasting glucose (between 110 and 125 mg/dL vs. between 100 and 125 mg/dL). We also conducted additional analyses after excluding individuals with a history or treatment or diagnosis of gout or a history of treatment with uric acid lowering drugs ($n=416$ in the original cohort and $n=215$ in the offspring cohort). We assessed the trend in the risk of type 2 diabetes across the uric acid categories using the median value of uric acid level in each category to minimize the influence of outliers. We also modeled serum uric acid as a continuous variable and calculated the RRs per mg/dL increase in serum uric acid level. We explored a potential interaction by gender by testing the significance of interaction terms added to our final multivariable models. We calculated 95% confidence intervals (CI) for all RRs. All *P*-values are two-sided. All statistical analyses were conducted using SAS (Version 9.1, SAS Institute Inc, Cary, NC). Ethical approval for this study was obtained from the University of British Columbia Behavioural Research Ethics Board.

RESULTS

The baseline characteristics of original and offspring cohorts are shown in Table 1. The mean baseline ages were 45 years in the original cohort (45% men) and 37 years in the offspring cohort (48% men).

We identified 641 incident type 2 diabetes cases (320 men) in the original cohort over a 28 year median follow-up and 497 incident cases (287 men) in the offspring cohort over a 26 year median follow-up. In both cohorts, the incidence of type 2 diabetes increased with increasing serum uric acid levels (both *P* values for trend <0.001) (Table 2). The incidence rates of diabetes according to serum uric acid categories were higher in the original cohort than those in the offspring cohort (Table 2), likely reflecting the older age of the original cohort. The age- and sex-adjusted RRs for type 2 diabetes corresponding to the serum uric acid levels <5.0, 5.0-5.9, 6.0-6.9, 7.0-7.9 and ≥8.0, were 1.00, 1.69, 2.37, 3.11, 4.48 for the original cohort (*P* for trend <0.001) and 1.00, 1.82, 2.50, 3.57, 4.50 for the offspring cohort (*P* for trend <0.001), respectively. After we additionally adjusted for BMI, alcohol consumption, smoking, physical activity, hypertension, and levels of glucose, cholesterol, creatinine, and triglycerides, the RRs were attenuated but remained significant (*P* for trend <0.001 in both cohorts) (Table 2). When we used serum uric acid as a continuous variable, the multivariable RRs conferred by per mg/dL increase of serum uric acid levels were 1.20 (95% CI, 1.11 to 1.28) for the original cohort and 1.15 (95% CI, 1.06 to 1.23) for the offspring cohort. Furthermore, in the offspring cohort, the multivariable RR for incident impaired fasting glucose was 1.10 (95% CI, 1.02 to 1.18) per mg/dL increase of serum uric acid levels using the revised criterion¹⁹ of fasting blood glucose between 100 to 125 mg/dL. The corresponding RR was 1.09 (95% CI, 1.01 to 1.18) using the original criterion¹⁸ (fasting blood glucose between 110 to 125 mg/dL). When we excluded individuals with a history or treatment or diagnosis of gout or a history of treatment with uric acid lowering drugs, the multivariable RRs per mg/dL increase of serum uric acid levels were 1.22 (95% CI, 1.12 to 1.32) in the original cohort and 1.16 (95% CI, 1.07 to 1.27) in the offspring cohort. The incidence of type 2 diabetes rose with increasing levels of serum uric acid for both men and women (all *P*-values for trends among both genders in both cohorts <0.001). There was no significant interaction by gender (*P* for interaction in both cohorts >0.4).

DISCUSSION

In this prospective study of two generations of the Framingham Heart Study, we found that higher levels of serum uric acid were associated with an increasing risk of developing type 2 diabetes. Specifically, for every mg/dL increase in serum uric acid level, the risk of type 2 diabetes was increased by 20% in the original cohort and 15% in the offspring cohort. These associations persisted in both genders and were independent of other known risk factors of type 2 diabetes, including age, BMI, alcohol consumption, smoking, physical activity level, hypertension, and levels of glucose, cholesterol, creatinine and triglycerides. Overall, these findings provide prospective evidence that individuals with higher serum uric acid, including younger adults, are at an increased future risk of type 2 diabetes independent of other known risk factors.

Our data provide prospective confirmation of recent findings⁴⁻⁶ on the relationship between serum uric acid levels and the risk of type 2 diabetes. The Finnish Diabetes Prevention Study,⁴ based on 475 overweight or obese individuals with impaired glucose tolerance found that having a serum uric acid level within the top tertile (≥6.4 mg/dL) was associated with a twofold increase in the risk of type 2 diabetes compared with the lowest tertile (<5.2 mg/dL). Similarly, the Rancho Bernardo Study with 566 participants (mean age 68 years) found a 65% increase in the risk of incident type 2 diabetes per mg/dL increase in uric acid level.⁵

The Rotterdam study, a prospective cohort of individuals aged 55 years and older,⁶ showed that the risk of developing type 2 diabetes in the top quartile of uric acid (>6.2 mg/dL) was 1.68 times that in the lowest quartile (uric acid ≤4.5 mg/dL). According to a recent review article of published data on the topic,²⁰ no studies had a mean baseline age below 40 years. As there are strong associations between serum uric acid level and several important covariates that are also associated with the risk of type 2 diabetes (e.g. hypertension, alcohol use, BMI, and levels of glucose, triglycerides, and cholesterol), particularly in older populations, our findings from both older and younger populations substantially bolster the evidence for the link between serum uric acid and type 2 diabetes. Furthermore, in view of the alarmingly high burden of diabetes, particularly in the US,¹ our results provide relevant general population data.

The biological mechanisms underlying the association between serum uric acid and development of diabetes remain a matter of debate. Hyperuricemia may lead to endothelial dysfunction and nitric oxide inhibition, which in turn contribute to insulin resistance and thus diabetes.²¹ This is supported by findings that fructose-induced hyperuricemia in rats leads to insulin resistance along with other components of metabolic syndrome, and these conditions are improved by decreasing uric acid levels.^{21, 22} However, it is also conceivable that elevated serum acid levels may reflect prediabetes status, particularly at the renal level, although our observed association was independent of fasting glucose, triglycerides, and serum creatinine. Higher insulin levels associated with prediabetes can reduce renal excretion of uric acid,²³⁻²⁵ as insulin can stimulate the urate-anion exchanger²⁶ and/or the Na⁺-dependent anion co-transporter in brush border membranes of the renal proximal tubule²⁷ and increase renal urate reabsorption. Thus, although our study provides support for the independent association between serum uric acid levels and the risk of incident type 2 diabetes, any causal inference remains to be clarified by future studies. In particular, randomized trial data on the effect of urate lowering medications on insulin resistance or type 2 diabetes would be particularly valuable to clarify this question.

Strengths and limitations of our study deserve comment. Because this study was based on community-based prospective data from the Framingham Heart Study, findings are likely to be generalizable to US population. Potential recall bias was avoided because the exposure assessment was completed before the diagnosis of diabetes. The long follow-up of the original cohort reflects life-time risk of diabetes, whereas offspring cohort bolstered the validity of this study by adding more contemporary evidence from younger adults. Nevertheless, our study was observational; thus we cannot rule out the possibility that unmeasured factors or residual confounding might contribute to the observed associations.

In conclusion, these prospective data from two generations of the Framingham Heart Study provide evidence that individuals with higher serum uric acid, including younger adults, are at a higher future risk of type 2 diabetes independent of other known risk factors. These data expand on well-established, cross-sectional associations between hyperuricemia and the metabolic syndrome, and extend the link to the future risk of type 2 diabetes.

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Table 1

Baseline Characteristics according to Framingham Heart Study Cohorts

Characteristics		Original Cohort (n=4,883)	Offspring Cohort (n= 4,292)
Age (yrs), mean $\pm$ SD		45 $\pm$ 9	37 $\pm$ 10
Males, %		44.9	47.7
BMI	<25 kg/m ² , %	49	53
	25-29.9 kg/m ² , %	38	35
	$\geq$ 30 kg/m ² , %	13	12
Alcohol,*	Abstinent/light, %	60	35
	Moderate, %	26	50
	Heavy, %	14	15
Smoking, %		52	44
Physical Activity,**	Light, %	33	02
	Moderate, %	55	75
	Heavy, %	12	23
Hypertension, %		14	8
Serum Uric Acid (mg/dL), mean $\pm$ SD		4.3 $\pm$ 1.1	5.7 $\pm$ 1.4
Blood Glucose Level (mg/dL), mean $\pm$ SD		80.9 $\pm$ 13.2	97.6 $\pm$ 12.1
Blood Cholesterol Level (mg/dL), mean $\pm$ SD		221.0 $\pm$ 34.6	196.0 $\pm$ 38.0
Triglycerides (mg/dL), mean $\pm$ SD		152.4 $\pm$ 62.1	92.5 $\pm$ 75.1
Creatinine (mg/dL), mean $\pm$ SD		1.0 $\pm$ 0.3	1.1 $\pm$ 0.3

* Alcohol use first assessed at original cohort examination 2.

** Physical activity measured for the first time at offspring cohort examination 2.

Table 2

Incidence Rate and Relative Risk of Type 2 Diabetes

		Uric Acid, Categorical (mg/dL)				Uric Acid, Continuous (per mg/dL)	
		< 5.0	5.0-5.9	6.0-6.9	7.0-7.9	≥8.0	
Original Cohort	No. of Diabetes Cases	299	174	106	43	19	---
	Person-Years of Follow-up	91436	28405	12202	3753	1194	---
	Incidence/1000 Person-Years	3.3	6.1	8.7	11.5	15.9	4.7**
	Univariate RR (95% CI)	1.00	1.84 (1.53, 2.23)	2.62 (2.09, 3.29)	3.57 (2.56, 4.96)	4.82 (3.00, 7.73)	1.44 (1.36, 1.53)
	Age- and sex-adjusted RR (95% CI)	1.00	1.69 (1.39, 2.06)	2.37 (1.86, 3.02)	3.11 (2.21, 4.38)	4.48 (2.76, 7.26)	1.40 (1.31, 1.50)
Offspring Cohort	Multivariable RR (95% CI)*	1.00	1.46 (1.20, 1.78)	1.59 (1.24, 2.04)	1.72 (1.21, 2.44)	2.36 (1.44, 3.89)	1.20 (1.11, 1.28)
	No. of Diabetes Cases	131	121	119	75	51	---
	Person-Years of Follow-up	45139	24369	18097	8580	4674	---
	Incidence/1000 Person-Years	2.9	5.0	6.6	8.7	10.9	4.9**
	Univariate RR (95% CI)	1.00	1.90 (1.48, 2.43)	2.68 (2.09, 3.44)	3.79 (2.85, 5.04)	4.83 (3.49, 6.69)	1.42 (1.34, 1.50)
	Age- and sex-adjusted RR (95% CI)	1.00	1.82 (1.40, 2.36)	2.50 (1.89, 3.31)	3.57 (2.59, 4.93)	4.50 (3.15, 6.43)	1.40 (1.31, 1.49)
	Multivariable RR (95% CI)*	1.00	1.00 (0.77, 1.31)	1.05 (0.78, 1.40)	1.71 (1.24, 2.36)	1.61 (1.10, 2.37)	1.15 (1.06, 1.23)

* Multivariate models adjusted for sex (male, female), age (continuous), BMI (<25, 25-29.9, ≥30 kg/m²), alcohol consumption (light, moderate, heavy), smoking (yes, no), physical activity (light, moderate, heavy), hypertension (yes, no), blood glucose level (continuous; casual glucose for original cohort, fasting glucose for offspring cohort), blood cholesterol level (continuous), creatinine level (continuous), and serum triglyceride level (continuous).

** Overall incidence rate.