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Hyperuricemia and Incidence of Hypertension Among Men Without Metabolic Syndrome

Eswar Krishnan, C. Kent Kwoh, H. Ralph Schumacher, Lewis Kuller

Abstract—The aim of this project was to study the risk of developing hypertension over a 6-year follow-up in normotensive men with baseline hyperuricemia (serum uric acid >7.0 mg/dL) but without diabetes/glucose intolerance or metabolic syndrome. We analyzed the data on men without metabolic syndrome or hypertension at baseline from the Multiple Risk Factor Intervention Trial. These men (n=3073; age: 35 to 57 years) were followed for an average of 6 years by annual examinations. Follow-up blood pressure among those with baseline was consistently higher than among those with normal serum uric acid concentration. We used Cox regression models for adjustment for the effects of serum creatinine, body mass index, age, blood pressure, proteinuria, serum cholesterol and triglycerides, alcohol and tobacco use, risk factor interventions, and use of diuretics. In these models, normotensive men with baseline hyperuricemia had an 80% excess risk for incident hypertension (hazard ratio: 1.81; 95% CI: 1.59 to 2.07) compared with those who did not. Each unit increase in serum uric acid was associated with a 9% increase in the risk for incident hypertension (hazard ratio: 1.09; 95% CI: 1.02 to 1.17). We conclude that the hyperuricemia–hypertension risk relationship is present among normotensive middle-aged men without diabetes/glucose intolerance or metabolic syndrome. (*Hypertension*. 2007; 49:298-303.)

Key Words: uric acid ■ hypertension ■ etiology ■ epidemiology ■ risk

An estimated 5.1 million Americans have gout resulting in ≈3.9 million ambulatory care visits annually.^{1,2} Many more have asymptomatic hyperuricemia, a risk factor for gout and for higher cardiovascular risk.³ Hypertension is also very common, affecting ≈1 in every 4 adults.⁴ Among those with prehypertension, those in the highest uric acid quartile were at >2 times greater risk for microalbuminuria than those in the lowest quartile, but this relationship was not found among normotensive subjects.⁵ Animal and human studies have repeatedly shown a statistically independent association between serum uric acid and risk for hypertension.^{6–13} In a recent review, Johnson et al⁸ have marshaled evidence that fulfills all of the Bradford Hill criteria for causality.¹⁴ However, the issue of causality has been challenged. Skeptics cite studies that point to the strong coincidence of other cardiovascular risk factors, such as metabolic syndrome as a whole and its individual components as potential confounders.^{15–17} Furthermore, many studies have linked a single baseline measurement of serum uric acid to onset of hypertension many years later: a limitation considering the fact that hyperuricemia, not necessarily a “trait,” like serum cholesterol, can fluctuate up and down over time in response to common environmental changes such as diet, medications, and so forth.

One way to overcome the above limitations would be to assemble a cohort of subjects who are at risk for hypertension

but not hypertensive (thereby affording statistical power to detect small risk differences) and free of renal disease, diabetes, and metabolic syndrome. These individuals should then be followed over time with several repeated measures of blood pressure, as well as serum uric acid measurements, and analysis of the serum uric acid–hypertension risk using time-varying covariates in multivariable models. This article reports the results from such a study performed in middle-aged men in the United States.

Methods

Detailed descriptions of the Multiple Risk Factor Intervention Trial (MRFIT) Study have been published.^{18–20} Briefly, the MRFIT study was a randomized, controlled trial designed to examine the efficacy of a program of coronary risk reduction among men at high risk for adverse coronary events. The subjects were eligible to join this study if the combination of 3 risk factors (smoking, hyperlipidemia, and hypertension) were of sufficient magnitude to place them in the upper 15% of a risk score distribution based on data from the Framingham Heart Study.²¹ Screening for this study began in 1973 and was completed in 1976 in 22 US clinical centers. Blood pressure, smoking history, and cholesterol measurements were taken at the first screening visit. Subjects were excluded from the trial if they had diabetes mellitus requiring medication, a history of acute myocardial infarction, elevated serum cholesterol of ≥350 mg/dL, or if diastolic blood pressure was ≥115 mm Hg. A medical history, 4 blood pressure measurements, a resting ECG, fasting blood draw for uric acid, lipid panel and glucose, and a 75-g glucose tolerance test were

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performed at the second screening visit. The average time interval between the first and second visit was 6 weeks. Subjects were also excluded at this stage based on an ECG-determined previous myocardial infarction, body weight >150% of desirable, angina by Rose questionnaire, untreated symptomatic diabetes, a diet incompatible with the diet prescribed as a part of the intervention, lipid-lowering treatment, or treatment with hydralazine, insulin, guanethidine, or oral hypoglycemic agents. A third screening visit included a resting and exercise ECG, a detailed smoking questionnaire, and a 24-hour dietary recall. If no major changes in cardiovascular status had occurred since the second screening visit, subjects were enrolled in the trial into either the usual care group or the special intervention group. Detailed risk factor assessments, including serum uric acid concentrations, were performed at baseline and on subsequent visits. All of the subjects who were randomly assigned were eligible for this study provided they met all following criteria at the baseline: (1) no evidence of hypertension as per the Seventh Joint National Committee criteria²² (defined as systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg or use of any antihypertensive medication, regardless of the recorded blood pressure); (2) no evidence of left ventricular hypertrophy by electrocardiography criteria²³; (3) no evidence of diabetes mellitus²⁴ (defined as a fasting glucose level >125 mg/dL or use of antidiabetic medications); (4) no evidence of metabolic syndrome (defined as per the 1999 World Health Organization criteria²⁵ using a body mass index >30 instead of waist circumference); and (5) availability of serum uric acid measurement at baseline.

Special interventions performed in the original MRFIT study were aimed at diastolic measurements of ≤ 89 mm Hg or a 10-mm Hg reduction, whichever was lower. Subjects already on medication at study entry were assigned a goal of ≤ 80 mm Hg. Pharmacotherapy included diuretics such as hydrochlorothiazide and reserpine. Dietary recommendations were made to reduce saturated fat intake to 10% of calories (8% starting in 1976), increase polyunsaturated fat to 10% of calories, and to reduce dietary cholesterol to 300 mg per day (250 mg per day starting in 1976). Weight reduction was sought for subjects whose weight was $\geq 115\%$ of the desirable body weight by reductions in caloric intake and moderate increases in physical activity. Behavioral modification techniques, including hypnosis in some cases, were used to promote smoking cessation.

Statement of Ethical Aspects of the Study

The MRFIT was a study performed in the 1970s. Limited access to these data was available through the National Heart, Lung, and Blood Institute. The approval for performing the posthoc analysis of this study was obtained from the institutional review board at the University of Pennsylvania.

Blood Pressure Measurement During the Study

At baseline, a detailed medical history was taken, including medication history, social history, and a full physical examination. Standard blood pressure measurements were recorded as the average of 2 measurements. Body mass index was calculated as the weight in kilograms divided by the square of the height in meters. Subjects received laboratory tests including lipid profiles, blood glucose after fasting and 1-hour postglucose load, peripheral blood count, urinalysis, and chemistry tests, including serum uric acid and serum creatinine on the same day. Blood samples were sent to a central laboratory, and results were determined as described previously.²⁶

Definition of Hyperuricemia

There is no universally accepted definition for hyperuricemia. Therefore, we studied serum uric acid at baseline both as a continuous variable and as a dichotomous variable. Statistically speaking, information is lost when continuous variables are dichotomized. On the other hand, this process helps to categorize serum uric acid levels to clinically meaningful strata and to better model any underlying nonlinear relationship between serum uric acid and hypertension. Accordingly, we defined hyperuricemia as a serum uric acid concentration >7.0 mg/dL. This is a cutoff commonly used in clinical laboratories and

has been used in published literature to define hyperuricemia.^{15,27} Furthermore, this cutoff approximates a serum urate concentration exceeding the limit of solubility (≈ 6.8 mg/dL).²⁸

Definition for Incident Hypertension

Incident hypertension was defined as systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or use of antihypertensive medications at any of the follow-up visits. For calculating incidence rates, we used the first occasion of documented hypertension per subject as the index event. The denominator for the rates was the person years of observation defined as the time of the first screening visit to date of death or the last visit.

Statistical Analyses

Statistical analyses were performed using Stata (Stata Corp). All of the SEs were calculated using the Huber-White Sandwich method.²⁹ By this technique, the effect of clustering of patients across randomization arms/clinic centers was accounted for. We used the Mantel-Haenszel method for evaluating interaction, trend testing, and evaluation of pooled relative risk.³⁰

We first cross-sectionally examined the correlation between the various risk factors for hypertension (both established and putative) at baseline. These relations were examined using a scatter plot matrix. Subsequently, we used Pearson's correlation coefficient (r) to measure the strength of association. P values were obtained for testing if correlation coefficients were different from 0 by random chance.

In the second step, after verifying that the condition of proportionality had been met, we fitted Cox proportional hazards regression models for the risk of incident hypertension. These time-oriented models have specified observations starting from the time of the baseline visit through the last visit or incidence of hypertension. In the first year, data from the subjects were collected over 3 sequential screening visits. We have chosen the second screening visit as the baseline visit for primary analyses, because this was when most of the clinical examination and laboratory testing were performed. The observation for the Cox model ended when the subject developed hypertension. Once hypertension was documented, subsequent observations were censored. The independent variable of interest was serum uric acid level. Laboratory values for the few tests that were not performed were either carried forward from the first screening visit or carried backward from the third screening visit. The randomization group variable was retained in all of the models, and the SEs were adjusted for clustering within the 22 clinic recruitment centers. The baseline serum uric acid was modeled both as continuous and dichotomized variables. There were separate but parallel regression models with the following covariates: baseline hyperuricemia (dichotomized), baseline values of age, systolic and diastolic blood pressure, serum creatinine, serum total cholesterol, alcohol use, smoking status, proteinuria, and body mass index (model 1). Separate sets of regression used time-varying values of proteinuria, serum creatinine, serum total cholesterol, alcohol use, smoking status, body mass index, and baseline values of systolic and diastolic blood pressure (model 2).

The third step of our analyses was targeted at evaluation of the role of serum uric acid level on the risk of hypertension in the next annual study visit using panel data analysis techniques. For this, we fitted generalized estimating equations (GEE)³¹ in which the independent variable was serum uric acid in the previous visit (ie, a lagged uric acid variable), and the dependent variable of interest was the corresponding systolic and diastolic blood pressure. These regressions calculate the change in blood pressure per incremental change in serum uric acid measured in the preceding visit. To avoid the confounding effect of hypertension medications, we excluded all of the study visits where individuals were on them. The covariates used in the GEE models were all time varying (except the randomization arm), which included age, proteinuria, serum creatinine, serum total cholesterol, serum triglyceride, alcohol use, smoking status, and body mass index.

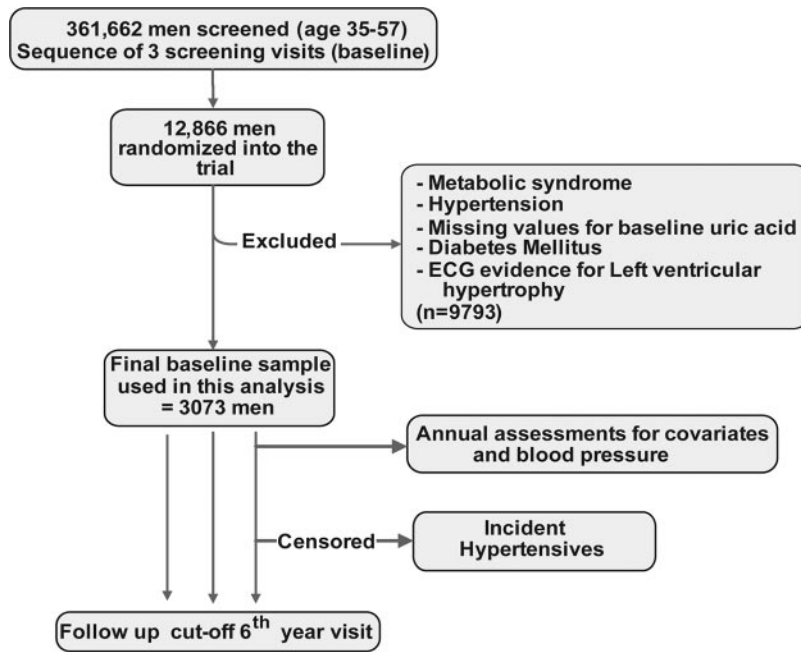


Figure 1. Study profile.

Results

Overall, 361 662 men were screened for recruitment into the MRFIT Study, and 12 866 men were randomly assigned into the study. Of the 12 866, 3073 individuals (24%) were free of hypertension, metabolic syndrome, and diabetes and had usable serum uric acid measurements at baseline (Figure 1).

Table 1 shows the characteristics of the study sample. Overall, there were 3073 men with 21 511 visits where measurements were performed. Correlation coefficients between serum uric acid and other cardiovascular risk factors used in this analysis were statistically significant. However, based on examination of the scatter plots and the magnitude of coefficients (all correlation coefficients <0.20), the intercorrelations of covariates were determined to be of minor clinical significance.

Follow-Up

The participants of the MRFIT Study were followed for an average 6 years each and 12 727 person-years overall. The

response rates and completeness of follow-up for the 6 annual visits were high (>90%). The ascertainment of hospitalization and availability of hospitalization records overall was 97% for both arms of the trial. Dropouts from the study, that is, those who survived through year 4 of the study but did not attend any of the last 4 annual visits (n=434) did not differ from those who remained in the study in terms of baseline characteristics with the exception that they were more likely to smoke and drink more alcohol and were less likely to have a positive ischemic response to exercise stress testing.³²

Variation of Serum Uric Acid and Hyperuricemia Status

To determine the extent of fluctuation in serum uric acid, we calculated transition probabilities between each instance of hyperuricemia status and normal uric acid status. The probability of an individual with normal serum uric acid developing hyperuricemia in the subsequent annual visit was 14%,

TABLE 1. Baseline Characteristics of the Study Population

Characteristics	Baseline Serum Uric Acid, mg/dL									
	First Quartile (1 to 5.6)		Second Quartile (5.6 to 6.3)		Third Quartile (6.3 to 7.1)		Fourth Quartile (7.1 to 11.6)		Overall (1 to 11.6)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age, y	45.3	5.8	44.7	5.7	44.3	5.9	44.4	5.9	44.7	5.8
Body mass index, kg/m ²	25.9	3.1	26.8	3.2	27.6	3.4	28.2	3.4	27.2	3.4
Mean no. of years of education	13.9	2.9	13.9	2.8	14	3	14.1	3	14	2.9
Serum cholesterol, mg/dL	259.9	38.6	259.2	37.8	262.8	37.4	259.4	35.6	260.4	37.3
LDL cholesterol, mg/dL	170.5	36.4	168	37.4	166.2	35.8	163.1	35.3	166.8	36.3
HDL cholesterol, mg/dL	41.4	11.4	40.3	11.3	39.6	10	39.8	10.3	40.2	10.7
Serum triglyceride, mg/dL	173.3	108.6	204.1	150.6	217.4	138.3	246.1	171.6	211.8	147.3
Systolic blood pressure, mm Hg	123	8.8	122.9	8.8	122.9	8.6	123.6	8.4	123.1	8.6
Diastolic blood pressure, mm Hg	81.9	5.8	82.1	5.5	82.2	5.2	82.8	5.1	82.3	5.4

LDL indicates low-density lipoprotein; HDL, high-density lipoprotein.

TABLE 2. Incidence Rates of Hypertension by Tertiles of Mean Serum Uric Acid Level

Randomization Group	Tertiles of Baseline Serum Uric Acid	Mean Serum Uric Acid	N	n	Person Years	Rate	95% CI
Special intervention	I	5.2	503	294	1960	15.0	13.4 to 16.8
	II	6.3	546	329	2072	15.9	14.3 to 17.7
	III	7.7	534	365	1833	19.9	18.0 to 22.1
Usual care	I	5.2	517	322	1908	16.9	15.1 to 18.8
	II	6.3	540	341	2018	16.9	15.2 to 18.8
	III	7.7	529	373	1795	20.8	18.8 to 23.0
Overall*	I	5.2	1020	616	3868	15.9	12.2 to 17.9
	II	6.3	1086	670	4090	16.4	15.4 to 17.4
	III	7.0	1063	738	3628	20.3	19.5 to 21.2

N indicates the number of individuals at risk; n, number of incident cases of hypertension. Serum uric acid tertile I is 1 to 5.8 mg/dL, tertile II is 5.8 to 6.8 mg/dL, and tertile III is 6.8 to 14.2 mg/dL.

*Adjusted for clustering within study arms.

whereas the mean probability of a hyperuricemic person to stay in that category in the subsequent annual visit was 68%.

Incidence of Hypertension

During the follow-up period, 1569 men (51%) developed hypertension. This translated into an incidence rate of 12.3 per 100 person-years (95% CI: 11.7 to 13.3). Table 2 shows the incidence rates of hypertension in men randomly assigned to either arm of the trial and overall.

Figure 2 shows that the age and risk-adjusted Kaplan–Meier estimates for hypertension-free survival for those with normal uric acid and those with hyperuricemia diverge widely. Assuming that an exponential extrapolation of Kaplan–Meier survival curves was valid, we estimated that the mean time to onset of hypertension was 8.6 years for those without hyperuricemia and 4.9 years for those with hyperuricemia ($P<0.001$).

In the univariable Cox regression model, baseline hyperuricemia increased the risk of hypertension (hazard ratio: 1.6; 95%

CI: 1.5 to 1.8). In the first set of multivariable Cox regressions where baseline values of the covariates (age, body mass index, serum creatinine, serum cholesterol, proteinuria, systolic and diastolic blood pressure, alcohol use, serum triglyceride, fasting glucose levels, smoking, randomization group, and the interaction term between baseline hyperuricemia and randomization group) were included, hyperuricemia was associated with a hazard ratio of 1.81 (95% CI: 1.59 to 2.06; $P<0.001$) compared with those with normal serum uric acid levels (Table 3). Baseline diuretic use was an exclusion criterion for cohort entry and, hence, was not used in the model. Overall, there was a consistent and substantial risk for the development of hypertension among those normotensive men with hyperuricemia at baseline. This was observed in model 2 as well.

In multivariable GEE models, there were 9618 observations from 2809 men. Here, a unit increase in serum uric acid was associated with a statistically significant increase in

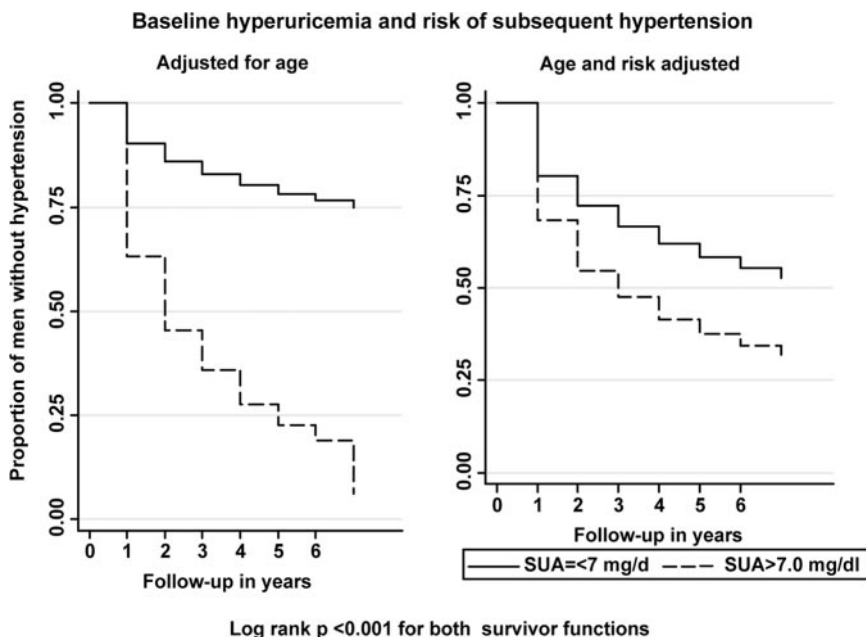


Figure 2. Time to develop hypertension among 803 men with baseline hyperuricemia (serum uric acid >7.0 mg/dL) compared with 2270 men without hyperuricemia, adjusted for baseline values of age, systolic and diastolic blood pressure, serum creatinine, proteinuria, serum triglycerides, total cholesterol, alcohol use, smoking, and body mass index.

TABLE 3. Multivariable Cox Regressions

Multivariable Cox Regression Models	Hazards		<i>P</i>
	Ratio	95% CI	
Model 1: Covariate values at baseline			
Hyperuricemia vs no hyperuricemia	1.81	1.59 to 2.07	<0.001
Each unit increase in serum uric acid	1.09	1.02 to 1.17	0.013
Each standard deviation increase in serum uric acid (1.14 mg/dL)	1.10	1.02 to 1.19	0.013
Model 2: Time varying values of covariates			
Hyperuricemia vs no hyperuricemia	1.14	1.09 to 1.20	<0.001
Each unit increase in serum uric acid	1.02	1.01 to 1.04	0.02
Each standard deviation increase in serum uric acid (1.14 mg/dL)	1.03	1.01 to 1.05	0.02

Model 1 was run with the following covariates: baseline uric acid and baseline values of age, systolic and diastolic blood pressure, serum creatinine, serum total cholesterol, alcohol use, smoking status, proteinuria, and body mass index. Model 2 was run with the following covariates: time-varying values of proteinuria, serum creatinine, serum total cholesterol, alcohol use, smoking status, body mass index, and baseline values of systolic and diastolic blood pressure. Both models were adjusted for randomization arm and interaction between it and hyperuricemia.

subsequent systolic blood pressure (β coefficient: 0.33; 95% CI: 0.10 to 0.57; $P=0.006$) and diastolic blood pressure (β coefficient: 0.16; 95% CI: 0.0013 to 0.33; $P=0.048$).

Sensitivity Analyses

For determining whether the choice of timing of blood pressure measurement influenced our results, we performed 2 separate analyses using the first and third screening visit blood pressure measurements for deciding on exclusions, as well as for baseline values. In separate analyses, we explored the potential effect of high-risk individuals on our study results. All of those who developed a cardiovascular event (fatal or nonfatal) at any time during the trial or a fatal cardiovascular event on follow-up through 1985 were excluded. Lastly, we reran the regressions in the primary analyses on all of the data without excluding those with metabolic syndrome. The link between hyperuricemia at baseline and as a time-varying measurement with the incidence of hypertension remained robust in all of the above analyses.

Discussion

We have presented evidence demonstrating that hyperuricemia increases the risk of developing hypertension by $\approx 80\%$, independent of baseline blood pressure measurements, renal function, serum lipid levels, body mass index, proteinuria, alcohol use, and age. This risk relationship was observed in both arms of the MRFIT Study. Using serum uric acid measurements as a continuous measure or a dichotomous variable did not change our findings. There were consistent findings across the various adjusted and unadjusted analyses. There have been suggestions that the effect of hyperuricemia may be more pronounced in younger subjects,^{8,13} but in our cohort with an age range 35 to 57 years, such an age effect was not discernible.

The link between hyperuricemia and hypertension has been reported in several studies.^{5–13,16,17} Among children newly diagnosed with hypertension, serum uric acid was highly correlated with both systolic and diastolic blood pressure.⁸ In the Framing-

ham cohort, subjects with hypertension have been noted to have a 3-fold increased risk of gout.⁹ A more recent 4-year study from the same cohort showed that hyperuricemia preceded onset of hypertension.¹³ The magnitude of risk that they observed (odds ratio: 1.17 for each increase in serum uric acid by 1.3 mg) is comparable to our findings. However, this magnitude is much smaller than that observed by Masuo et al,³³ who reported that for every unit rise in serum uric acid, the systolic and diastolic blood pressure increased by a magnitude of 28 mm Hg and 15 mm Hg, respectively. Another study showed that a 1.16-fold increase in serum uric acid was associated with an odds ratio of 1.4 for the development of diastolic hypertension.³⁴ The magnitude of the risk, however, varied substantially, reflecting underlying heterogeneity in study design, subject selection, and the distribution of serum uric acid.

Despite these and similar observations in cross-sectional analyses^{8–10} and longitudinal studies,^{11–13} it has been unclear whether causality can be inferred because of the possibility of unadjusted confounders, such as impaired renal function, endocrine factors, such as insulin resistance, and diuretic use, alcohol use, and baseline blood pressure measurement. Other potential difficulties in interpreting these data have included exclusion of subjects with gouty arthritis¹³ (a marker for severe/chronic hyperuricemia) and reliance on a single baseline measurement of serum uric acid, not accounting for the use of diuretics.

The pathophysiological links between hyperuricemia and hypertension have been investigated both in vivo and in vitro. Hyperuricemia can be associated with increased renal vascular resistance.^{35,36} An Italian study of 568 men has shown that hyperuricemia increased salt retention.³⁷ Although a role of insulin/insulin resistance has been put forward as a putative mechanism,³⁷ the presence of insulin resistance does not explain the findings in our study, because we excluded those with diabetes and insulin resistance at baseline.

Strengths and Limitations

The main strengths of the MRFIT data that strengthen our study are as follows: the large number of subjects that enabled exclusion of subjects with metabolic syndrome, baseline hypertension, and diabetes; the wealth of serial measurements of serum uric acid, blood pressure, and other covariates; and availability of all of the relevant confounders. The data were analyzed in a prospective fashion by both time-to-event regressions and panel-data models, such as the generalized estimating equation. The main limitation of this study is in the restricted generalizability of the results, because the men were highly selected. Furthermore, our epidemiological study cannot answer the pathophysiological question of whether the uric acid-hypertension association is directly because of a toxic effect of the uric acid molecule.⁸ Lastly, removal of individuals meeting the criteria for metabolic syndrome does not leave behind a sample completely devoid of confounding factors but rather reduces the extent of potential confounding.

Perspectives

The available evidence from epidemiological studies, including ours, points toward a role for hyperuricemia as an independent risk factor for hypertension. Regardless of the pathophysiological

cal explanations, these observations raise an important clinical question: is it possible to prevent/postpone the onset of hypertension by reducing serum uric acid? If so, even a small reduction in the relative risk of hypertension can translate into large public health gains considering that a quarter of the population in the United States suffers from hypertension. Such a question can only be answered in a randomized, controlled trial of uric acid reduction treatments.

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Disclosures

C.K.K. and H.R.S. have served on advisory boards and are consultants for TAP Pharmaceutical Products. H.R.S. is a consultant for Savient Pharmaceuticals. L.K. has no conflicts of interest to disclose.

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