Nephrolithiasis and Risk of Hypertension

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A positive association between nephrolithiasis and blood pressure has been suggested in previous studies. However, controversy remains, due to methodological problems in some of the previous studies and absence of prospective data. We evaluated the relationship between nephrolithiasis and the risk of hypertension in a cohort of 51,529 men followed prospectively for 8 years. Information was obtained by biennial mailed questionnaires. At baseline in 1986, 4111 (8.0%) subjects reported a history of nephrolithiasis and 11,623 (22.6%) a diagnosis of hypertension. A positive association was found between the two disorders (age adjusted odds ratio [OR]: 1.31; 95% confidence interval [CI]: 1.30 to 1.32). Among men who reported both disorders, 79.5% reported that the occurrence of nephrolithiasis was prior to or concomitant with the diagnosis of hypertension. Among men without hypertension at baseline, the odds ratio for incident hypertension in men with a history of nephrolithiasis compared with those without was 1.29 (95% CI: 1.12 to 1.41; adjusted for age, body mass index, and intake of calcium, sodium, potassium, magnesium, and alcohol). The occurrence of incident nephrolithiasis during follow-up was similar in men with hypertension at baseline compared with that in men without (adjusted OR: 0.99, 95% CI: 0.82 to 1.21). These data support the hypothesis that prior occurrence of nephrolithiasis increases the risk of subsequent hypertension. Am J Hypertens 1998;11:46–53

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Studies in animals and humans have suggested a positive association between nephrolithiasis and blood pressure. Although nephrolithiasis is rare in animals, strains of spontaneously hypertensive rats develop nephrolithiasis with greater frequency compared with nonhypertensive strains.[1] The few epidemiological studies that have addressed this association in humans[2–6] have suggested a significant association between nephrolithiasis and blood pressure. The prevalence of nephrolithiasis has been reported to be 30%[2] to 79%[5] greater in hypertensive than in normotensive subjects.

More than 85% of kidney stones in men contain calcium; among these, calcium oxalate stones are the most common.[7,8] Alterations in calcium metabolism may play an important role in the pathogenesis of both nephrolithiasis and hypertension and have been suggested as a plausible mechanism linking the two disorders.[9,10] A higher prevalence of hypercalciuria has been reported in patients with essential hyperten-

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sion,[11,12] and alterations of calcium metabolism such as primary hyperparathyroidism, that lead to hypercalciuria, have been associated with an increased prevalence of hypertension.[10,11] Several other mechanisms that may link nephrolithiasis and hypertension have been suggested, which include high dietary intake of sodium, low intake of potassium, and renal damage.[9,13,14]

The epidemiological evidence supporting an association between nephrolithiasis and hypertension remains limited, due to methodological problems in some previous studies and absence of prospective data. Using the current literature, inferences cannot be drawn about the temporal sequence of events. It is unclear whether normotensive subjects with a history of nephrolithiasis are more likely to develop hypertension in the future than are subjects with no history of nephrolithiasis or, conversely, whether patients with hypertension are more likely to develop nephrolithiasis than are normotensive individuals.

To examine these issues further, we prospectively studied the association between nephrolithiasis and blood pressure in a cohort of 51,529 men followed over an 8 year period.

METHODS

Study Population The Health Professionals Follow-up Study is a longitudinal study of cardiovascular disease, cancer, and other diseases among 51,529 male dentists, optometrists, osteopaths, pharmacists, podiatrists, and veterinarians who were 40 to 75 years of age in 1986. The participants returned a mailed questionnaire in 1986 concerning diet, medical history, and medications. Follow-up questionnaires were sent in 1988, 1990, 1992, and 1994. After up to six mailings for each follow-up period, the response rate was greater than 90%.

Assessment of Nephrolithiasis The baseline questionnaire inquired about history of nephrolithiasis prior to 1986. A study participant was considered to have a positive history of nephrolithiasis if this condition was reported on the initial questionnaire. Participants were also asked when the diagnosis of nephrolithiasis was made. The categories for the time of diagnosis were: prior to 1955, 1955 to 1964, 1965 to 1974, 1975 to 1979, and 1980 to 1986. The diagnosis of nephrolithiasis is reported reliably in this cohort.[15] In a random sample of 60 men who had reported having a history of nephrolithiasis, the diagnosis was confirmed in 97% of the cases by reviewing their medical records. Although no information was available on the type of nephrolithiasis, it is likely that >85% contain calcium.[8]

Assessment of Hypertension and Blood Pressure The baseline and biennial follow-up questionnaires inquired about physician diagnosed hypertension. A study participant was considered to have hypertension at baseline if physician diagnosed hypertension was reported on the 1986 questionnaire. The participants were also asked when the diagnosis of hypertension was made. The categories for the time of diagnosis were the same as for nephrolithiasis. The 1986 and 1992 questionnaires also inquired about the subjects' blood pressure during the preceding 2 years. The 1986 categories of systolic blood pressure responses (in mm Hg) were: <120, 120 to 139, 140 to 149, 150 to 159, 160 to 169, 170+, and unknown or not checked within the past 2 years. The 1986 categories of diastolic blood pressure were: <75, 75 to 84, 85 to 89, 90 to 94, 95 to 104, 105+, and unknown or not checked within the past 2 years. The 1992 categories of systolic blood pressure responses (in mm Hg) were: <105, 105 to 114, 115 to 124, 125 to 134, 135 to 144, 145 to 154, 155 to 164, 165 to 174, 175+, and unknown or not checked within the past 2 years. The 1992 categories of diastolic blood pressure were: <65, 65 to 74, 75 to 79, 80 to 84, 85 to 89, 90 to 94, 95 to 104, 105+, and unknown or not checked within the past 2 years. In this population, the diagnosis of hypertension is reported reliably, and self reported blood pressure is a strong predictor of stroke.[16] To assess the validity of self reported diagnosis of hypertension, we contacted 100 randomly selected participants reporting a diagnosis of hypertension to obtain confirmation of the diagnosis and permission for review of their medical records.[16] Among the 95 men who responded, 77 (81%) men confirmed having had a physician's diagnosis of hypertension. Medical records were obtained for 39 subjects. All had a diagnosis of high blood pressure reported in the medical history or were receiving antihypertensive treatment. In addition, blood pressure was measured in 139 health professionals living in the greater Boston area. The Spearman correlation coefficient between self-reported and measured systolic blood pressure was 0.50 ($P < .05$). Moreover, the relative risk of subsequent stroke was significantly higher in men who reported a systolic blood pressure of 120 to 139 mm Hg compared with those with reported blood pressure <120 mm Hg.[16]

Assessment of Other Parameters In 1986, the men provided information on age, height, weight, and average daily intake of alcohol. Dietary intake was assessed using a semiquantitative food frequency questionnaire that inquired about the average use of 131 foods and beverages during the previous year. Information on food intake allowed estimation of the average daily intake of various nutrients. Previous reports have demonstrated the reproducibility and validity of

this dietary questionnaire in this cohort.[17] Dietary data were available on 96.9% of the eligible study population.

Statistical Analysis The association between nephrolithiasis and hypertension was assessed using a cross-sectional analysis on 1986 baseline data. To further define the association and to evaluate the temporal sequence of events, two separate prospective analyses were also conducted. The first analysis excluded subjects with a history of nephrolithiasis at baseline and evaluated the risk of nephrolithiasis between 1986 and 1994 according to the subjects' 1986 hypertension status. The second analysis excluded men who reported hypertension at baseline or the use of any medication that might lower blood pressure (eg, diuretics, β-blockers, or calcium blockers), and evaluated the risk of a new diagnosis of hypertension between 1986 and 1994 according to the history of nephrolithiasis reported in 1986. The odds ratio—the odds of disease among the men in a particular category of exposure divided by the corresponding odds in the comparison category—was used as the measure of association. Age adjusted prevalence odds ratios were calculated after stratification according to 5-year age categories using the Mantel-Haenszel pooled estimate technique.[18] In addition, for the prospective analyses, odds ratios were adjusted simultaneously for potentially confounding variables by multiple logistic regression analysis.[19] The variables considered in these models were age at baseline (in 5-year categories), body mass index (BMI) at baseline (the weight in kilograms divided by the square of the height in meters; considered in quintile groups), alcohol intake (eight categories), and dietary intake of calcium, sodium, potassium, and magnesium (quintile groups) at baseline. Interactions between history of nephrolithiasis and age, body mass index, or family history of nephrolithiasis were also examined in these analyses. Odds ratios (OR) and 95% confidence intervals (CI) were calculated from the model covariate β-coefficients and standard errors, respectively.

Linear regression[20] was used to evaluate the relation between systolic and diastolic blood pressure in 1992 and history of nephrolithiasis at baseline. Systolic and diastolic blood pressure were the outcome variables and history of nephrolithiasis was the independent variable. The other independent variables considered in these models were age at baseline (in 5-year categories) and body mass index at baseline (considered in quintile groups).

All analyses were performed with the SAS statistical package (SAS Institute, Cary, NC). Means are shown ± SD.

RESULTS

Cross-Sectional Analysis in 1986 Of the 51,529 men responding to the 1986 baseline questionnaire, 4111 (8.0%) men reported a history of nephrolithiasis and 11,623 (22.6%) a diagnosis of hypertension. A positive association was found between the two disorders (age adjusted OR, 1.31; 95% CI, 1.30 to 1.32). Among the 1195 men who reported both a history of nephrolithiasis and a diagnosis of hypertension in 1986, 79.5% reported that the occurrence of nephrolithiasis was prior to or concomitant with the diagnosis of hypertension. In addition, of the 39,906 men who did not report a diagnosis of hypertension in 1986, 2097 reported the use of medication that may lower blood pressure (ie, diuretics, calcium blockers, β-blockers, nitrates, or any other antihypertensive agent).

Prospective Analyses

Incident Nephrolithiasis According to Baseline Hypertension Of the 47,418 men with no history of nephrolithiasis prior to 1986, 10,428 (21.9%) reported a diagnosis of hypertension. During the 8 years of follow-up, 960 men reported a new diagnosis of nephrolithiasis. After adjusting for age, body mass index, and the intake of calcium, sodium, potassium, and magnesium, the odds of incident nephrolithiasis in men with hypertension compared with those without hypertension was 0.99 (95% CI, 0.82 to 1.21).

Incident Hypertension According to Baseline History of Nephrolithiasis Of the 37,809 subjects who did not report a history of hypertension at baseline and who were not taking medication that might lower blood pressure, 2,676 (7.1%) reported a history of nephrolithiasis in 1986. The baseline characteristics of these participants are shown in Table 1. Compared with the men without a history of nephrolithiasis, those with a history of nephrolithiasis were on average 2 years older (55.0 ± 9.8 years *v* 53.1 ± 9.6 years) and had a slightly higher body mass index (24.9 ± 4.6 kg/m^2 *v* 24.7 ± 4.8 kg/m^2). The mean daily intake in 1986 of calcium, potassium, magnesium, and alcohol was slightly lower in men with nephrolithiasis. The systolic and diastolic blood pressure distribution were also comparable at baseline with >85% of the men in both groups having a value <140 mm Hg of systolic and <90 mm Hg of diastolic. Among the 35,045 men with available information on medical examination in 1990, 84.8% (2,109) of the men with a history of nephrolithiasis and 84.6% (27,554) of those without this condition had had a medical examination. Similar findings were observed in 1994.

During the 8 years of follow-up, 466 (17.4%) men with a history of nephrolithiasis and 4613 (13.1%) men without reported a new diagnosis of hypertension (Table 2). After adjusting for age, the odds of incident

TABLE 1. BASELINE CHARACTERISTICS IN 1986 ACCORDING TO HISTORY OF NEPHROLITHIASIS*†

Characteristic	No Nephrolithiasis	Nephrolithiasis
n (%)	35,133 (92.9%)	2676 (7.1%)
Age (years)	53.1 ± 9.6	55.0 ± 9.8
Body mass index (kg/m^2)	24.7 ± 4.8	24.9 ± 4.6
Dietary intake (mg/day)		
Calcium	907.6 ± 427.3	827.0 ± 394.4
Sodium	3300.7 ± 1130.1	3297.7 ± 1122.9
Potassium	3400.8 ± 687.3	3279.2 ± 683.8
Magnesium	355.5 ± 85.5	344.7 ± 84.3
Alcohol intake (g/day)	11.9 ± 15.8	10.9 ± 15.3
Systolic blood pressure (%)‡		
<120 mm Hg	8829 (28.8%)	606 (25.6%)
120–139 mm Hg	18,319 (59.8%)	1448 (61.3%)
140–149 mm Hg	2858 (9.3%)	253 (11.7%)
150–159 mm Hg	469 (1.5%)	36 (1.5%)
160–169 mm Hg	115 (0.4%)	14 (0.6%)
≥170 mm Hg	36 (0.1%)	5 (0.2%)
Diastolic blood pressure (%)‡		
<75 mm Hg	6753 (22.1%)	471 (20.0%)
75–84 mm Hg	17080 (55.8%)	1334 (56.6%)
85–89 mm Hg	4964 (16.2%)	407 (17.3%)
90–94 mm Hg	1607 (5.3%)	124 (5.3%)
94–104 mm Hg	168 (0.6%)	16 (0.7%)
≥105 mm Hg	40 (0.1%)	7 (0.3%)

** After excluding men who reported a history of hypertension at baseline and those who reported the use of medication that might lower blood pressure, n = 37,809.*

† Values for age, body mass index, and dietary and alcohol intake are expressed as means ± SD.

‡ Systolic and diastolic blood pressure at last physical exam reported in 1986. This information was available for 32,988 (systolic) and 32,969 (diastolic) of the 37,809 men. The percentages may total >100 because of rounding.

hypertension in men with a history of nephrolithiasis compared with those without was 1.30 (95% CI, 1.16 to 1.45). After further adjustment for body mass index and the intake of calcium, sodium, potassium, magnesium, and alcohol, the odds ratio was 1.29 (95% CI, 1.12 to 1.41). In men with a positive family history of nephrolithiasis, the odds ratio was 1.56 (95% CI, 1.24 to 1.98) and 1.18 (95% CI, 1.02 to 1.37) in those with no family history, but these were not significantly different. No significant interaction was observed between history of nephrolithiasis and age or body mass index.

When men with systolic blood pressure >155 mm Hg or diastolic blood pressure >90 mm Hg and men with missing data on blood pressure at baseline were excluded from the analysis, there was no change in the estimate of the odds ratio (OR, 1.29; 95% CI, 1.13 to 1.47). In addition, when the analysis was restricted to men who had had a physical examination between 1992 and 1994, there was no change in the estimate of the odds ratio (OR, 1.29; 95% CI, 1.14 to 1.47).

TABLE 2. ADJUSTED ODDS RATIO (OR) OF INCIDENT HYPERTENSION BETWEEN 1986 AND 1994 ACCORDING TO HISTORY OF NEPHROLITHIASIS IN 1986*

Variables	No Nephrolithiasis	Nephrolithiasis
Number of men	35,133	2676
Cases of incident hypertension (%)	4613 (13.1%)	466 (17.4%)
Age Adjusted OR (95% CI)	1.0 (referent)	1.30 (1.16 , 1.45)
Multivariate OR (95% CI)†	1.0 (referent)	1.29 (1.12 , 1.41)

** After excluding men who reported a history of hypertension at baseline and those who reported the use of medication that might lower blood pressure, n = 37,809.*

† Adjusted for age, body mass index, and dietary intake of calcium, sodium, potassium, magnesium, and alcohol, in 1986, using logistic regression.

Systolic and Diastolic Blood Pressure Among men without hypertension at baseline and during follow-up, and with available information on blood pressure (n = 31,803), there was a positive association between history of nephrolithiasis and diastolic blood pressure in 1992 (Table 3). After adjusting for age, history of nephrolithiasis was associated with an increase in diastolic blood pressure of 0.40 mm Hg (95% CI, 0.05 to 0.75) in 1992. After further adjustment for body mass index, the increase in diastolic blood pressure in 1992 was 0.33 mm Hg (95% CI, −0.01 to 0.67), only marginally significant. The increase in systolic blood pressure associated with a history of nephrolithiasis

TABLE 3. ESTIMATED DIFFERENCE IN SYSTOLIC AND DIASTOLIC BLOOD PRESSURE IN 1992 ASSOCIATED WITH A HISTORY OF NEPHROLITHIASIS*

Blood Pressure†	Age Adjusted‡ (95% CI)	Age and BMI Adjusted‡ (95% CI)
Systolic, 1992	+0.34 (−0.22 , 0.90)	+0.24 (−0.31 , 0.79)
Diastolic, 1992	+0.40 (0.05 , 0.75)	+0.33 (−0.01 , 0.67)

** After excluding men with hypertension at baseline and during follow-up, men who reported the use of medication that might lower blood pressure, and men without available information on blood pressure, n = 31,803.*

† Values are expressed in mm Hg.

‡ Using linear regression.

showed a similar trend but was not statistically significant (Table 3).

DISCUSSION

These data support the existence of an association between nephrolithiasis and hypertension, as suggested in previous cross-sectional studies.[2–6] Among the 51,529 men who responded to the 1986 baseline questionnaire, a positive association was found between the two disorders (age adjusted OR, 1.31; 95% CI, 1.30 to 1.32). This association was independent of factors known to have an impact on the occurrence of nephrolithiasis and hypertension, such as age, body mass index, alcohol intake, and dietary intake of calcium, sodium, potassium, and magnesium.

This study also allows inferences to be drawn about a temporal sequence of events for the occurrence of nephrolithiasis and hypertension, something that no previous study has provided. Among men with both disorders at baseline, 79.5% reported that the occurrence of nephrolithiasis was prior to or concomitant with the diagnosis of hypertension. In addition, men with a history of nephrolithiasis prior to 1986 were 29% more likely to report a diagnosis of hypertension in the following 8 years than were men without a history of nephrolithiasis (OR, 1.29, 95% CI, 1.12 to 1.41). However, men with hypertension at baseline were not more likely to develop nephrolithiasis during the follow-up (OR, 0.99, 95% CI, 0.82 to 1.21). These results suggest that prior occurrence of nephrolithiasis increases the risk of subsequent hypertension. Mechanisms that cause nephrolithiasis may thus contribute to the development of hypertension at an older age. Such a temporal sequence of events is not unexpected, as hypertension generally tends to occur at an older age than does nephrolithiasis. However, these undefined factors are unlikely to be major causes of hypertension, as a substantial proportion (close to 90%) of hypertensive subjects have never presented with nephrolithiasis. Thus, hypertension develops in the majority of patients by mechanisms that are not likely related to those involved in the pathogenesis of kidney stones.

In addition to the association with physician diagnosed hypertension, a history of nephrolithiasis was also associated with an increase in diastolic blood pressure even among men with hypertension. Although the magnitude of the increase in systolic and diastolic blood pressure was similar, only the association with diastolic blood pressure was statistically significant. The magnitude of the association between history of nephrolithiasis and hypertension may appear to be inconsistent with the small increase in diastolic blood pressure in those men with a history of nephrolithiasis. The absolute difference in the frequency of hypertension between those men with and without a history of nephrolithiasis was 4.3%. Thus, the additional fraction of hypertensive men may have had only a slight impact on the mean systolic and diastolic blood pressure in those with a history of nephrolithiasis.

The present prospective study supports the results of previous cross-sectional studies that evaluated the association between nephrolithiasis and blood pressure.[2–6] In 1967 in Göteborg, Sweden, a random sample of 895 men aged 50 years were interviewed about their medical history and received a physical examination including measurement of blood pressure.[2] The prevalence of nephrolithiasis increased significantly, from 1.1% in the lowest blood pressure class up to 13.3% in the highest. However, each subject was seen only once, and no longitudinal data were available.

Two cross-sectional surveys were performed in Italy by the same group of investigators.[4,5] In both studies, participants were interviewed about their medical history and received a physical examination along with measurement of blood pressure. In the first study, which included 4516 adults living in the town of Gubbio,[4] a higher prevalence of nephrolithiasis was observed among individuals in the highest quintile of the diastolic blood pressure distribution compared with those in the first four diastolic pressure quintiles (5.22% *v* 3.36%, $p = .009$). This observation remained significant after adjustment for age. The second study involved 688 male workers from an Olivetti factory in a suburban area of Naples.[5] The age-adjusted prevalence of a history of nephrolithiasis was 14% in the normotensive subjects (ie, blood pressure $<160/95$ mm Hg), 18% in the untreated hypertensives (ie, blood pressure >160 or >95 mm Hg), and 29% in the treated hypertensives ($P = .011$). Of note, the prevalences of nephrolithiasis in this study were much higher than those reported elsewhere, even in normotensive subjects.

A cross-sectional study collected data in 1982 on 1,167,009 US men and women, aged > 30 years.[6] The study was aimed primarily at evaluating geographic variability and risk factors associated with nephrolithiasis. Information was obtained by self-administered questionnaires. The prevalence of a history of nephrolithiasis was 10.2% in hypertensive subjects compared with 8.2% in normotensive subjects (odds ratio adjusted for age and race, 1.2; 95% CI, 1.2 to 1.3).

The significant association between nephrolithiasis and hypertension does not necessarily imply a causal relationship; rather, one or more pathogenic mechanisms common to nephrolithiasis and hypertension may be responsible for the development of both. Several possible mechanisms may link nephrolithiasis and blood pressure. Alterations in calcium metabolism have been suggested to play an important role in

the pathogenesis of both nephrolithiasis and hypertension.[9,10,12]

Calcium metabolism is important in the pathogenesis of nephrolithiasis. The majority of stones contain calcium, and elevated urinary calcium excretion (hypercalciuria) is one of the most important risk factors for the development of nephrolithiasis.[8] Dietary calcium intake has also been shown to play an important role in stone formation. Although increased dietary calcium intake will lead to a slight increase in urinary calcium, the cause of hypercalciuria in most patients is not related to excessive calcium intake.[8] In fact, calcium restriction rarely normalizes urinary calcium excretion in individuals with idiopathic hypercalciuria.[8] Dietary calcium intake appears to play an important role in stone formation independent of its effect on urinary calcium excretion. Two recent large epidemiologic studies found an inverse association between diet calcium intake and risk of stone formation.[15,21]

Calcium metabolism is also central in the pathogenesis of hypertension. Alterations in calcium metabolism, such as increased intracellular calcium concentration in vascular smooth muscle cells, have been described in subjects with essential hypertension.[9,10,22] Dietary calcium intake has also been shown to have a substantial effect on blood pressure. High dietary calcium intake has been reported in several studies to be associated with lower blood pressure.[23–25] Hypercalciuria has also been reported with higher frequency in patients with essential hypertension.[9–12,26] Because hypercalciuria represents a very important risk factor for nephrolithiasis,[8] several investigators have proposed that hypercalciuria might be the mechanism linking nephrolithiasis and hypertension.[9,10,11]

Several observations have linked hypercalciuria to hypertension. First, in the spontaneously hypertensive rat (SHR) model of hypertension, the animals develop hypertension responsive to manipulation of dietary sodium, potassium, and calcium intake.[27] The animals may also have several alterations of calcium metabolism, including hypercalciuria.[28–30] Second, clinical studies have shown that individuals with hypertension have a higher urinary calcium excretion than do normotensive subjects, and dietary calcium intake and intestinal absorption of calcium cannot explain this observation.[9–12,26] Moreover, normotensive children with familial predisposition to hypertension (with one or two hypertensive parents) have been shown to have higher urinary calcium excretion than children of normotensive parents.[31] The latter observation supports the view that alterations in calcium metabolism may predate the development of hypertension and that hypercalciuria does not occur as a consequence of high blood pressure. In some individuals, elevated parathyroid hormone levels have been observed in the face of normal serum calcium and hypercalciuria, suggesting an end organ defect in calcium reabsorption in the kidney.[11,12,31] This potential ''renal leak'' has been linked to structural abnormalities of the proximal renal epithelium and to functional disturbances in active transport of calcium.[32,33] Whereas several studies have provided supportive evidence for a primary defect in renal handling of calcium in individuals with hypertension,[10–12,26,31] much controversy remains as to whether these disturbances are causally related to the development of high blood pressure.

The sodium and potassium content of the diet may play an important role in the pathogenesis of both nephrolithiasis and hypertension. High dietary intake of sodium and low intake of potassium have been associated with higher risk of hypertension[13,14] and also may increase the risk of nephrolithiasis,[15,21,34–36] possibly through an increase in urinary calcium excretion. As discussed above, the calcium content of the diet may also play an important role in the pathogenesis of both nephrolithiasis and hypertension.[15,21,23–25] Low dietary intake of calcium has been associated with higher risk of hypertension in both animal models of hypertension and epidemiological studies.[23–25] Low dietary intake of calcium has also been associated with nephrolithiasis.[15,21] In the present study, differences in dietary intake were observed between men with and without a history of nephrolithiasis. To examine the association between nephrolithiasis and hypertension, independent of dietary factors, we used multiple logistic regression analysis. After adjusting for differences in dietary intake of sodium, potassium, calcium, and magnesium, there was no substantial change in the odds ratio, suggesting that these factors may not explain the observed association.

These observations, however, do not undermine the importance of diet in terms of hypertension prevention and treatment. In a recently published, randomized controlled, trial of dietary manipulation, a diet pattern rich in calcium, potassium, magnesium, and fiber was found to be associated with a substantial reduction in blood pressure when compared with a control diet (reduction in systolic and diastolic blood pressure >11 mm Hg and >5 mm Hg, respectively).[37]

The possibility that renal damage caused by stones might contribute to hypertension has also been suggested.[9] This mechanism may be operative in rare cases, but is unlikely to be the main pathogenic factor, as even substantial damage, such as that inflicted by extracorporeal shock wave lithotripsy may only minimally affect blood pressure.[38]

The present study was based on self-reported information and we recognize that these variables were not perfectly assessed. However, incident diagnosis of nephrolithiasis has been shown to be reported accurately in this cohort.[15] Thus, the baseline history of

nephrolithiasis is likely to be reliable. The validity of self-reported diagnosis of hypertension and blood pressure levels is also supported by the results of a subsample study that confirm established associations of age and weight with incidence of hypertension and blood pressure. In particular, there was a strong association between systolic blood pressure levels and risk of future cardiovascular disease.[16] In addition, in multivariate models with diagnosis of hypertension as the dependent variable, random error in reporting of blood pressure would increase the standard error of the regression coefficients, but would not likely bias the point estimates.

Our findings are most directly generalizable to men aged 40 years and older. Whether these findings apply to women or to younger men is not known. We have no reason to believe, however, that the relationships that we observed would be different in the other groups. In addition, the intake of minerals in this cohort may not be representative of the intake of the general population.

Hypertension and nephrolithiasis are important public health problems with substantial financial and social cost to the individual and the community. Further studies are warranted to elucidate the mechanism(s) of the observed association. A better understanding is needed not only to bring new insights into the pathogenesis and prevention of hypertension and nephrolithiasis but also to design and implement preventive and therapeutic measures.

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