

# A prospective study of hypertension and the incidence of kidney stones in men

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**Objective** To examine whether hypertension predicts the incidence of kidney stone disease.

**Design** Prospective cohort study (the Olivetti Prospective Heart Study).

**Setting** The Olivetti factory in Southern Italy.

**Subjects** Five hundred and three male workers, aged 21–68 years, with no evidence of kidney stone disease at baseline.

**Follow-up** 8 years.

**Main outcome measures** Anthropometry, blood pressure, biochemistry and history of kidney stone disease were evaluated at the baseline examination in 1987. Occurrence of kidney stone disease was evaluated again in 1994–1995. Hypertension was defined as systolic blood pressure  $\geq 160$  or diastolic blood pressure,  $\geq 95$  mmHg or both, or being on drug therapy for hypertension. Occurrence of kidney stone disease was defined as radiological or echographic evidence of calculi or documented passage of one or more stones.

**Results** At baseline, 114/503 men (22.7%) had hypertension and 32 were on drug treatment. After 8 years, 52 (10.3%) incident cases of kidney stone disease were detected. The majority ( $n = 45$ ) had a documented passage of one or more stones. The incidence of kidney stone disease was higher in hypertensive than in

normotensive men (19/114 (16.7%) versus 33/389 (8.5%);  $P = 0.011$ ). Hypertensive men had a greater risk of developing kidney stones than normotensive ones (RR 1.96; 95% confidence interval 1.16–3.32). The risk was unaffected by the exclusion of treated hypertensives (2.01; 1.13–3.59) and after adjustment for age (1.89; 1.12–3.18), body weight (1.78; 1.05–3.00) or height (2.00; 1.19–3.38).

**Conclusions** Hypertension in middle-aged men is a significant predictor of kidney stone disease rather than a consequence of renal damage caused by the kidney stones. *J Hypertens* 1999, 17:1017–1022 © Lippincott Williams & Wilkins.

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## Introduction

Although naturally occurring urolithiasis is rare in animals, spontaneously hypertensive rats are prone to develop kidney stones [1]. In humans, the first report of an association between hypertension and kidney stones can be traced back to 1761 [2] when Giovan Battista Morgagni described a patient with clinical and anatomical findings suggestive of long-standing hypertension and the presence of kidney stones. More recently, cross-sectional epidemiological surveys have described an independent association between hypertension and a history of kidney stone disease [3–6].

However, given the retrospective nature of the assessment of urolithiasis, the time sequence of events is unclear, and, in particular, the possibility that hypertension may result from renal damage caused by kidney stones could not be ruled out. Prospective investigations are therefore needed to establish whether hypertension precedes the development of kidney stones and may therefore be considered as a possible cause of this condition.

Madore *et al.* [6] have recently reported prospective analyses of the Health Professionals Follow-up Study

suggesting that prior occurrence of kidney stones increases the risk of subsequent hypertension. We report the results of a prospective study of middle-aged men without evidence of urolithiasis at the baseline and followed-up for 8 years to establish the incidence of kidney stone disease and its relation to hypertension. The present study assesses both exposure and outcome by direct measurement and verification and is based on the 'a priori' hypothesis that hypertension would precede the development of kidney stones. It also provides measures of renal function and other potential confounders.

## Population and methods

### Study population

The Olivetti Prospective Heart Study is a longitudinal study of risk factors for cardiovascular disease in middle-aged working men in southern Italy [5,7,8]. The study was carried out at the two Olivetti factories in Pozzuoli and Marcianise, near Naples. In 1987, 688 men were seen and 112 of them had a positive history of kidney stone disease [5]. Of the 576 men who had no history of kidney stones in 1987, 503 (87%) were re-examined in 1994–1995 (average period of follow-up 8 years). The examinations were carried out in the morning, with the participants fasted, in a quiet, comfortable room at the factory. Participants were discouraged from vigorous exercise and were asked to refrain from smoking and not to drink alcohol, coffee or other beverages containing caffeine in the morning of the study. This included a physical examination, a blood test, the administration of a detailed questionnaire and a fasting timed urine collection [7].

### Measurement of exposure

Blood pressure was measured between 0800 and 1100 h after the subject had been sitting upright for at least 10 min. Systolic and diastolic (phase V) blood pressures were taken three times 2 min apart with a random zero sphygmomanometer (Gelman Hawksley Ltd, Sussex, UK) by trained observers who had attended blood pressure measurement training sessions for standardization of the reading procedure. The first reading was discarded and the average of the last two readings recorded and used in the analysis. Participants were defined as hypertensive if they had a systolic blood pressure  $\geq 160$  or diastolic blood pressure  $\geq 95$  mmHg, or both, or if they were receiving regular drug treatment for high blood pressure.

### Measurement of outcome

A detailed and fixed sequence of questions were asked, aimed at detecting a history of upper urinary tract stones. As we could not always distinguish between kidney and ureteric stones we use the term 'kidney stones' as synonymous with upper urinary tract stones. Indeed, most urinary stones in patients in most coun-

tries are renal stones [9]. Men were classified as incident cases of kidney stones if, within the period of follow-up, they experienced any of the following: spontaneous passage of one or more stones, X-ray or echographic evidence of one or more stones in the upper urinary tract, lithotripsy or surgical removal of stones from kidney or ureter. The self-reported occurrence of kidney stones was checked against available medical records.

### Measurements of other variables

Age was recorded as that at the last birthday. Body weight and height were taken on a standard beam balance scale with an attached ruler, participants wearing indoor clothing and no shoes. The body mass index was calculated as the weight (kg) divided by the square of the height in metres ( $\text{kg}/\text{m}^2$ ). Venous blood was taken (after the blood pressure measurements) with the subject seated and without stasis between 0800 and 1100 h for determination of serum electrolytes and creatinine concentrations by standard methods. A questionnaire was administered both in 1987 and in 1994–1995 by trained observers unaware of the man's blood pressure. After an overnight fast, a timed urine collection was obtained from each participant on the morning of the examination after ingestion of 400 ml of tap water at the beginning of the collection. Volume (in ml) and duration of the collection (in min) were recorded and specimens were taken for creatinine determinations [7]. The average collection time was  $207 \pm 40$  min (mean  $\pm$  SD) and the average volume was  $294 \pm 175$  ml. Creatinine clearance was taken as an index of glomerular filtration rate.

### Statistical methods

Results are expressed as mean, SD and 95% confidence intervals. Differences between means were tested by a two-sample *t* test and  $\chi^2$  cross-tabulation statistics were used to test differences between frequencies. Risk ratio (95% confidence intervals) was taken as an estimate of the relative risk of disease (kidney stones) associated with the exposure (hypertension). The Mantel–Haenszel pooled estimate of the risk ratio (95% confidence intervals) was also used in stratified analysis to control for the potential confounding effect of age, body weight or height. Two-tailed *P* values  $< 0.05$  were taken as statistically significant.

## Results

At baseline, 114/503 (22.7%) of the participants had hypertension. Thirty-two of them (28.1%) were on drug therapy for it (ten on thiazide diuretics, six on  $\beta$ -blockers, four on calcium-channel blockers, two on an ACE inhibitor and one on another drug alone; nine were on combination therapy). The baseline characteristics of the normotensive and hypertensive men are shown in Table 1. Hypertensives were older, heavier

**Table 1 Characteristics of normotensive and hypertensive men at the baseline examination in 1987. The Olivetti Prospective Heart Study**

Variables	Normotensives (n = 389)	Hypertensives (n = 114)	Difference (95% CI)	P value
Age (years)	45.1 ± 7.4	48.7 ± 7.6	3.6 (2.0, 5.2)	< 0.001
Weight (kg)	72.4 ± 9.6	79.3 ± 9.0	6.9 (5.0, 8.8)	< 0.001
Height (cm)	168.1 ± 5.8	168.9 ± 6.1	0.8 (-0.4, 2.1)	0.21
BMI (kg/m <sup>2</sup> )	25.6 ± 3.0	27.8 ± 2.6	2.2 (1.6, 2.7)	< 0.001
Systolic BP (mmHg)	120.0 ± 11.7	145.5 ± 18.1	25.4 (21.9, 27.0)	< 0.001
Diastolic BP (mmHg)	82.3 ± 7.0	100.0 ± 8.7	17.7 (15.9, 19.4)	< 0.001
On drug therapy n(%)		32 (28.1)		
Serum sodium (mmol/l)	140.1 ± 2.2	139.7 ± 2.1	-0.4 (-0.9, 0.1)	0.07
Serum potassium (mmol/l)	4.36 ± 0.38	4.26 ± 0.42	-0.10 (-0.19, -0.01)	0.023
Creatinine clearance (ml/min)	98.6 ± 21.9	96.2 ± 21.9	-2.4 (-7.1, 2.3)	0.31
FE sodium (%)	1.05 ± 0.47	0.99 ± 0.43	-0.06 (-0.16, 0.03)	0.18

Results are means ± SD. BMI, body mass index; BP, blood pressure; FE, fractional excretion.

and had a lower plasma potassium concentration than normotensives. Renal function (measured as creatinine clearance) did not differ between the two groups.

After 8 years of follow-up, 52/503 men (10.3%) had developed kidney stone disease. The majority (45; 86.5%) had a documented passage of one or more stones. In Table 2, the baseline characteristics of those men who developed kidney stones during the period of follow-up are compared with those of the men who remained free from kidney stone disease during the same period. The two groups were comparable for age, body mass, serum biochemistry and renal function. However, future stone-formers tended to show a higher blood pressure than non-stone-formers.

The incidence of kidney stone disease was higher in hypertensive than in normotensive men (16.7 versus

8.5%;  $P = 0.011$ ) (Table 3). The risk of developing kidney stones amongst the hypertensive men was nearly twofold greater than in the normotensives. The increased risk estimate was not attenuated when treated hypertensives were excluded ( $P = 0.018$ ) and after adjustment for age (Mantel-Haenszel  $\chi^2 = 4.88$ ;  $P = 0.027$ ), body weight (Mantel-Haenszel  $\chi^2 = 3.86$ ;  $P = 0.049$ ) or height (Mantel-Haenszel  $\chi^2 = 5.91$ ;  $P = 0.015$ ) (Table 3).

The baseline characteristics of the 73 men (13%) who were lost to the follow-up examination were comparable to those who were followed-up (data not shown).

## Discussion

The results of this prospective study of middle-aged men provide evidence that hypertension significantly increases the risk of developing kidney stones. This

**Table 2 Characteristics at the baseline examination in 1987 in non-stone-formers and stone-formers during follow-up. The Olivetti Prospective Heart Study**

Variables	Non-stone-formers (n = 451)	Stone-formers (n = 52)	Difference (95% CI)	P value
Age (years)	45.8 ± 7.7	47.1 ± 6.5	1.3 (-0.6, 3.3)	0.18
Weight (kg)	74.0 ± 10.0	73.4 ± 9.0	-0.6 (-3.3, 2.0)	0.64
Height (cm)	168.5 ± 5.9	166.8 ± 5.9	-1.6 (-3.3, 0.9)	0.07
BMI (kg/m <sup>2</sup> )	26.0 ± 3.1	26.3 ± 2.9	0.3 (-0.6, 1.2)	0.50
Systolic BP (mmHg)	125.6 ± 16.9	127.7 ± 19.5	2.1 (-3.5, 7.8)	0.45
Diastolic BP (mmHg)	86.0 ± 10.1	89.7 ± 12.9	3.7 (0, 7.4)	0.05
Serum sodium (mmol/l)	140.0 ± 2.2	140.4 ± 2.3	0.4 (-0.3, 1.1)	0.24
Serum potassium (mmol/l)	4.33 ± 0.39	4.31 ± 0.38	-0.02 (-0.13, 0.09)	0.69
Creatinine clearance (ml/min)	98.1 ± 22.1	97.5 ± 20.2	-0.5 (-6.7, 5.6)	0.86
FE sodium (%)	1.03 ± 0.46	1.07 ± 0.49	0.04 (-0.10, 0.11)	0.57

Results are means ± SD. BMI, body mass index; BP, blood pressure; CI, confidence interval; FE, fractional excretion.

**Table 3 Risk of kidney stone disease amongst hypertensive and normotensive men during 8 years of follow-up. The Olivetti Prospective Heart Study**

Groups	Incidence % (n)	RR (95% CI) Crude	RR (95% CI) Age-adjusted	RR (95% CI) Weight-adjusted	RR (95% CI) Height-adjusted
Normotensives (n = 389)	8.5 (33)	1.00	1.00	1.00	1.00
All hypertensives (n = 114)	16.7 (19)**	1.96 (1.16-3.32)	1.89 (1.12-3.18)	1.78 (1.05-3.00)	2.00 (1.19-3.38)
Untreated hypertensives (n = 82)	17.1 (14)*	2.01 (1.13-3.59)	1.94 (1.10-3.43)	1.82 (1.02-3.22)	2.01 (1.19-3.69)

RR, risk ratio; CI, confidence interval. \* $\chi^2 = 5.55$ ,  $P = 0.018$ ; \*\* $\chi^2 = 6.36$ ,  $P = 0.011$  versus normotensives.

increased risk does not appear to be associated with differences in age and other variables such as weight, serum electrolytes and renal function, and is not attenuated when men on drug therapy are excluded. This is in agreement with the cross-sectional evidence of an independent association between hypertension and prevalence of a positive history of kidney stones [3–6]. In addition, it provides clear evidence that hypertension precedes the occurrence of kidney stones.

Our results are at variance with the recent report by Madore *et al.* [6] based on the analysis of a large cohort of men followed up for 8 years. They suggest that whilst men with hypertension were more likely to have had prior history of kidney stones, the reverse was not true; for example, that kidney stones preceded the development of hypertension. We do not have an explanation for this discrepancy. The study by Madore *et al.* was based on a very large sample but also had a number of limitations which would bias the assessments of both hypertension and incident kidney stone disease. The use of self-reported blood pressure is a limitation that may lead to a biased assessment of hypertension, especially taking into consideration the recent JNC VI report that 32% of the hypertensives in the USA are unaware of their hypertension [10]. Proper validation by direct blood pressure was only carried out in 139 selected men (less than 0.3% of the cohort) living in the Boston area. Likewise, history of kidney stones was ascertained by self-reported questionnaire. Again, validation was attempted in a sub-sample of only 60 men (less than 0.2% of the cohort). This is important as a large proportion of patients with urolithiasis may remain asymptomatic for several years. Finally, the study was not based on an '*a priori*' hypothesis and no direct measures of renal function were reported to support the contention that renal damage by calculi may have caused hypertension.

In our study, the assessment of hypertension at baseline was based on direct measurements. The definition of incident cases of kidney stones was also based on direct evidence of pathological findings, and, in 86% of the cases, on the passage of one or more stones. Moreover, we also measured renal function both at baseline and at follow-up so as to investigate the possibility that renal damage by kidney stones could have been responsible for the development of hypertension. Our results argue against this explanation as they clearly establish the time sequence by which hypertension precedes the incidence of kidney stones. Moreover, no difference in renal function was detected between those who did and those who did not develop kidney stones.

In our study, potential biases might have resulted from loss to follow-up, ascertainment of disease, interference

by drug therapy or a 'healthy worker' effect. The proportion of men lost to follow up was 13%. However, the characteristics of those lost to follow-up were similar to those of the men who were seen 8 years later, making selection bias unlikely. Ascertainment bias could have occurred as hypertensive people are more likely to undergo radiological or ecographic investigations, thereby increasing the likelihood of detecting the presence of asymptomatic kidney or ureteric calcifications. This bias is also unlikely as the majority of incident cases of kidney stones (86.5%) had actually passed one or more stones. As for drug treatment, 32 hypertensive men (28%) were on regular drug therapy at the baseline and 10 of them were taking thiazide diuretics either alone or in combination. Thiazide diuretics are known to reduce the incidence of kidney stone formation [11], so this could only have led to an under-estimate of the true association between hypertension and kidney stone incidence in this study. Moreover, the exclusion of treated hypertensives did not attenuate the association. As to the presence of a 'healthy worker' effect, this would also lead to an under-estimate of the effect of exposure. Finally, statistical power was not an issue in our study as, despite the relatively small cohort and number of incident cases, statistical significance was attained. As we only studied white working men, caution should be used before extending these results to the general population including women and different ethnic groups.

#### Potential mechanisms

Hypertension is associated with abnormalities in calcium metabolism, including an increase in urinary calcium excretion – for a given sodium intake [12,13] – and evidence of secondary increase in parathyroid gland activity [12]. Hypercalciuria in hypertension has been consistently reported in both case-control and cross-sectional studies [14]. The reason for this enhanced urinary calcium loss is not clear. It has been suggested that it could be due to a renal tubular defect, possibly associated with altered sodium handling, leading to a sustained calcium leak and ensuing secondary hyperparathyroid activation [14,15]. Hypercalciuria has similarly been shown in several models of animal hypertension [16–18]. It has also been described in normotensive children in the upper part of the blood pressure distribution for their age [19,20] and in normotensive offspring of hypertensive parents [20,21]. This supports the view that an inherited abnormality in the kidney of those at risk of hypertension is also associated with a tubular defect in calcium handling. Alternatively, it has also been proposed that hypercalciuria could be an effect of the tendency to central volume expansion in people with hypertension [15,22]. Volume expansion independently of sodium intake causes an increase in urinary calcium excretion [23] and this effect can be

sustained, as seen in astronauts exposed to weightlessness [24], as well as during other experimental conditions of central volume expansion [25–27]. Whatever its origin, hypercalciuria is the commonest cause of the formation of upper urinary tract stones [9,28]. It is therefore conceivable that sustained hypercalciuria in hypertension may lead to a greater risk of development of kidney stones. Although biologically plausible, our interpretation remains speculative as measurements of 24 h urinary calcium excretion were not obtained in the present cohort. Furthermore, we were unable to ascertain in every case that the stones were made of calcium. However, it is unlikely that there were a substantial number of stones other than calcium given that a large proportion had been seen at X-ray and that more than 80% of kidney stones are usually of either calcium phosphate or calcium oxalate [9].

We did not measure parathyroid hormone to rule out the presence of primary hyperparathyroidism. However, serum total calcium levels were all within the normal range. Since the overall prevalence of primary hyperparathyroidism in a middle-aged population is not expected to exceed 1 per 1000, we feel it is unlikely that our results could be explained by the presence of undetected primary hyperparathyroidism.

### Implications

The incidence of kidney stones is increasing worldwide [29–33]. It is estimated that 12–15% of the population will develop kidney stones over their life-time [29,30]. Moreover, stone-formers are at a much greater risk of recurrence (as high as 80%) [29]. Although kidney stone disease is seldom fatal, it does lead to substantial morbidity from pain, urinary tract infections and obstructive uropathy, with a considerable economic burden on healthcare provision for an effective treatment (mostly removal, fragmentation or extracorporeal shock-wave lithotripsy) [34]. Primary prevention and prevention of recurrence would therefore be an important aspect of the population approach to the overall control of urolithiasis. Despite early reports of cross-sectional associations between hypertension and kidney stones [3–5], very little attention has so far been paid to consideration of hypertension as a risk factor (or a marker of risk) for urolithiasis [28,35], nor has a reduction of the intake of sodium – a major determinant of urinary calcium excretion – been seriously implemented as a dietary approach to the management of hypercalciuria [28,35]. The present prospective study highlights the importance of hypertension as a marker of kidney stone risk.

Measurements of urinary calcium excretion (along with sodium) and investigations for the detection of stones in asymptomatic hypertensives may help identify kidney stones at a pre-symptomatic or pre-morbid state

with the opportunity of early management and potential cost savings for emergency care and prolonged hospitalization. Moreover, a general preventive strategy of reduction in sodium intake [36] and balanced electrolyte composition of the diet for the control of hypercalciuria is in agreement with the beneficial effect of such measures on blood pressure levels [37]. To endorse these preventive strategies, however, we need to confirm the cost-effectiveness of such early diagnosis and the beneficial effect of sodium restriction not only on the reduction of urinary calcium excretion [36] but on the overall reduction of the incidence of kidney stones or their recurrence rate using a randomized controlled clinical trial.

In conclusion, hypertension in middle-aged white men is a significant predictor of kidney stone disease. It is possible, though as yet unproven, that greater and sustained urinary calcium losses in people with high blood pressure are the pathophysiological link. These findings may have important implications for the early detection and prevention of kidney stone disease amongst hypertensives.

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