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Calcium Urolithiasis, Blood Pressure and Salt Intake

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Objectives: To determine whether stone-formers have higher BP than controls drawn from the general population and matched for age, sex and ethnic origin and to compare the relationship between sodium and calcium excretion in the two groups. *Patients and methods:* Thirty-six patients [mean (±standard deviation, SD) = 49.0 ± 11.7 years; range 27–70 years] with kidney or ureteric stones and 108 controls (mean age of 49.6 ± 6.8 years; range 39–61 years), matched for gender, ethnic origin and age group were studied. Patients and controls underwent physical measurements, a venous blood sample and they were asked to collect a 24-h urine sample for sodium, potassium, calcium and creatinine. *Results:* Stone-formers were significantly heavier and had higher BP than age-, sex- and ethnic-matched population controls. Whilst the difference in systolic BP was independent of the difference in body mass index [16.8 mmHg (7.2–26.4 mmHg), $p = 0.001$), the difference in diastolic BP was attenuated after adjustment for body mass [1.8 (−3.4 to 7.1), $p = 0.49$]. Stone-formers passed less urine than controls [−438 ml/day (95% CI −852 to −25), $p = 0.038$]. They had higher urinary calcium than controls [+3.7 mmol/day (2.8–4.6 mmol/day), $p < 0.001$], even when expressed as ratio to creatinine [+0.20 (0.11–0.29), $p < 0.001$]. Sodium excretion was positively associated with urinary calcium in both stone-formers and in controls. The slopes were comparable (0.92 vs 0.98 mmol Ca/100 mmol Na) so that for any level of sodium excretion (or salt intake), stone-formers had a higher calcium excretion than controls. *Conclusions:* In stone-formers, the BP is higher than in controls. Stone-formers excrete more calcium than controls do. In stone-formers and controls, the relationship between urinary sodium and calcium is similar. Since this relationship results from an effect of sodium on calcium, a reduction in salt intake may be a useful method of reducing urinary calcium excretion in stone-formers. However, the "relative" hypercalciuria seen in stone-formers is independent of salt intake and may well reflect an underlying genetic predisposition. *Key words: blood pressure, calcium excretion, kidney stones, salt intake, urolithiasis.*

INTRODUCTION

High blood pressure is associated with abnormalities of calcium metabolism. Examples are the higher urinary calcium that is seen in hypertensives for a given sodium intake and the associated secondary hyperparathyroidism (see [1] for review). The direct relationship between urinary calcium and blood pressure has been reported in animal experimental hypertension, in children in the upper quarter of the blood pressure distribution for their age and in normotensive children of hypertensive parents [1]. In population studies, hypertension is associated with a higher prevalence of kidney stones [2, 3]. The results of prospective studies, however, whilst confirming the association, shed little light on the sequence of event [4–7]. Although several case–control studies comparing hypertensives with normotensives have consistently shown that hypertensives are more likely to have renal stones, studies comparing stone-formers with controls obtained from the general population are few. The mechanisms underlying the association between high blood pressure and alterations of calcium metabolism are as yet unknown. Two main hypotheses have been put forward [1]. The "renal calcium leak" hypothesis postulates a widespread abnormality of transmembrane calcium transport, whilst the "central blood volume" hypothesis suggests the expansion of central blood volume seen in hypertension as the pathophysiological link. Either hypothesis would explain the calcium abnormalities in hypertension.

One of the major determinants of urinary calcium excretion is salt intake or urinary sodium excretion (see [1] for review), and it has been estimated that a dietary increase of 100 mmol of sodium (approximately 6 g of salt) produces an increase in urinary calcium of 1 mmol [8–10]. A high salt intake, therefore, by increasing urinary

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Table I. *Characteristics of the stone-formers*

No.	Sex	Ethnic group	Age	Recurrence	Intervention	Stone composition	IVU	X-ray	U/S
1	F	Black	58	✓			✓		
2	M	Black	53	✓	Ureteric stent	Ca-Ph-Ox	✓	✓	
3	M	S Asian	65	✓				✓	✓
4	M	S Asian	36	✓	ESWL	Ca-Ph-Ox	✓	✓	
5	M	S Asian	62		ESWL		✓		
6	F	White	26	✓	ESWL		✓	✓	✓
7	F	White	27	✓				✓	✓
8	F	White	34	✓	ESWL	Ca-Ph-Ox		✓	
9	F	White	42					✓	
10	F	White	44		ESWL		✓	✓	✓
11	F	White	49						✓
12	F	White	49	✓	ESWL		✓	✓	✓
13	F	White	49	✓	PCNL	Ca-Ph-Ox	✓	✓	✓
14	F	White	52	✓					✓
15	F	White	54		ESWL			✓	✓
16	F	White	64	✓	ESWL		✓	✓	
17	F	White	64		ESWL			✓	
18	M	White	29	✓					✓
19	M	White	33	✓				✓	✓
20	M	White	39	✓			✓	✓	
21	M	White	41	✓	ESWL		✓	✓	✓
22	M	White	42	✓	ESWL	Ca-Ox	✓	✓	✓
23	M	White	44	✓	Ureterolithotomy	Ca-Ph-Ox	✓	✓	✓
24	M	White	44	✓		Ca-Ph-Ox	✓	✓	
25	M	White	45	✓				✓	
26	M	White	46	✓	Ureterolithotomy		✓	✓	✓
27	M	White	48	✓			✓	✓	✓
28	M	White	48				✓	✓	✓
29	M	White	51	✓	ESWL		✓	✓	
30	M	White	52	✓				✓	✓
31	M	White	55	✓	Ureteric stent		✓	✓	
32	M	White	55	✓		Ca-Ph	✓	✓	✓
33	M	White	64	✓	ESWL	Ca-Ox	✓	✓	✓
34	M	White	65	✓	ESWL and Nephrectomy				✓
35	M	White	67	✓	Ureteric stent		✓	✓	
36	M	White	70	✓	ESWL and PCNL	Ca-Ox	✓	✓	

ESWL, extracorporeal shock-wave lithotripsy; PCNL, percutaneous nephrolithotomy; Ca, calcium; Ph, phosphate; Ox, oxalate.

calcium excretion, may facilitate the formation of calcium stones [9]. The objectives of the present study are: (i) to determine whether stone-formers have higher blood pressure than controls drawn from the general population and matched for age, sex and ethnic origin and (ii) to compare the relationship between urinary sodium and calcium in the two groups.

METHODS

Selection of cases

Thirty-six patients seen in the Medical Renal Stone Clinic at St George's Hospital between 1999 and 2001 were included in the analysis. They all had a diagnosis of kidney or ureteric stones made by intra-venous uretero-pyelography (IVU), abdominal X-ray or renal ultra-sound (U/S) (Table I). Twenty-nine of them (81%) had had one or more recurrences and 21 (58%) had undergone surgical procedures for the removal of the calculi (Table I). All contained calcium either as calcium oxalate or calcium phosphate, or a combination of the two (Table I). Parathyroid overactivity was excluded by measurements of serum immunoreactive parathyroid hormone (i-PTH). 25-Hydroxy vitamin D levels (vit D) were within the normal range in all the stone-formers. Twenty-three were men, and the majority were white (Table I). Mean ($\pm$standard deviation, SD) age was 49.0 ± 11.7 years (range 27–70 years). Fourteen (39%) gave a history of urinary tract calculi in first-degree relatives.

Selection of controls

Controls were selected from a population database of individuals participating in the Wandsworth Heart & Stroke Study, a cross-sectional survey of men and women of different ethnic groups living in Wandsworth (South

Table II. *Comparisons of stone-formers and population controls*

	Renal stones ($n = 36$)	Population controls ($n = 108$)	Difference (95% CI)	p
Body mass index (kg/m^2)	30.4 (5.5)	25.0 (4.1)	5.3 (3.1–7.5)	<0.001
Systolic blood pressure (mmHg)	142.4 (20.0)	124.4 (17.2)	18.0 (11.2–24.8)	<0.001
Diastolic blood pressure (mmHg)	84.0 (10.5)	79.7 (10.0)	4.3 (0.5–8.2)	0.028
Anti-hypertensive treatment (n)	19	0		
Serum				
Sodium (mM)	138.7 (2.1)	139.4 (2.7)	−0.6 (−1.6 to 0.3)	0.193
Potassium (mM)	4.2 (0.4)	4.2 (0.2)	0 (−0.1 to −0.1)	0.461
Creatinine (μM)	87.5 (14.4)	86.3 (13.0)	1.1 (−4.0 to 6.2)	0.657
Uric acid (μM)	311 (82)	286 (85)	25 (−19 to 69)	0.264
Glucose (mM)	5.54 (1.13)	5.20 (1.60)	0.37 (−0.25 to 0.98)	0.240
Urine				
Volume (ml/day)	2139 (812)	2578 (1164)	−438 (−852 to −25)	0.038
Sodium (mmol/day)	156.0 (69.1)	165.0 (72.0)	−8.7 (−35.7 to 18.3)	0.526
Potassium (mmol/day)	82.5 (31.0)	70.6 (24.4)	11.9 (2.0–22.0)	0.019
Creatinine (mmol/day)	14.7 (4.2)	12.6 (4.2)	2.1 (0.5–3.8)	0.010
Calcium (mmol/day)	8.0 (3.0)	4.3 (2.2)	3.7 (2.8–4.6)	<0.001
Calcium/creatinine	0.57 (0.24)	0.37 (0.23)	0.20 (0.11–0.29)	<0.001

Results are mean (SD), differences (95% CI).

London) [10–12]. After exclusion of people with a past history of myocardial infarction, stroke and renal stones, three controls were selected for each case, matching for gender, ethnic origin and age group. The 108 controls so obtained had a mean age of 49.6 ± 6.8 years (range 39–61 years).

Procedures

Patients and controls underwent measurements using standard methods [12]. Height (without shoes) was measured to the nearest centimetre using a wall-mounted ruler. Weight (light clothing and no shoes) was measured to the nearest 0.1 kg using electronic scales. The body mass index (BMI) was calculated as weight/height^2 (kg/m^2). After the subjects had been resting for 5–10 min in the supine position, systolic and diastolic blood pressures were taken three times 2 min apart using an automatic sphygmomanometer and an appropriate cuff size. The average of the last two readings was used for the analysis.

A venous blood sample was taken for measurement of serum electrolytes, creatinine, glucose and uric acid in both patients and controls [12]. In the patients, i-PTH and vit D were also measured. Both patients and controls were also asked to collect a 24-h urine sample. They were given written instructions as to how to undertake the collection and supplied with a 2.5-l plastic container. Complete urine collections were either returned by the participants or collected from their home. Time and volume of collections were carefully recorded. Sodium, potassium, creatinine and calcium were measured by standard methods [10, 12]. The procedures were approved by the local ethics committee.

Statistical analysis

Comparisons of means between groups were carried out using unpaired t-tests. Analysis of covariance was used to adjust for confounders. Regression analysis was used to assess the degree of change of urinary calcium excretion over sodium excretion. Slopes were compared by an interaction test. The analysis was carried out using SPSS v10.0.

RESULTS

Patients with renal stones were significantly heavier than age-, sex- and race-matched population controls (Table II). Furthermore, they had significantly higher blood pressures than controls. Whilst the difference in systolic blood pressure was independent of the difference in body mass index [adjusted systolic blood pressure: 141.9 vs 125.1 mmHg; difference 16.8 mmHg (7.2–26.4 mmHg); $p = 0.001$], the difference in diastolic blood pressure was attenuated after adjustment for body mass [adjusted diastolic blood pressure: 82.1 vs 80.2 mmHg; difference 1.8 mmHg (−3.4 to 7.1 mmHg); $p = 0.49$]. The two groups had comparable electrolytes, glucose, uric acid and creatinine (Table II). Patients with renal stones passed less urine than the controls (−438 ml/day; 95% confidence interval, CI −852 to −25 ml/day) (Table II). Whilst both urinary sodium and potassium excretion were comparable, patients with renal stones had significantly higher urinary calcium excretion than the controls

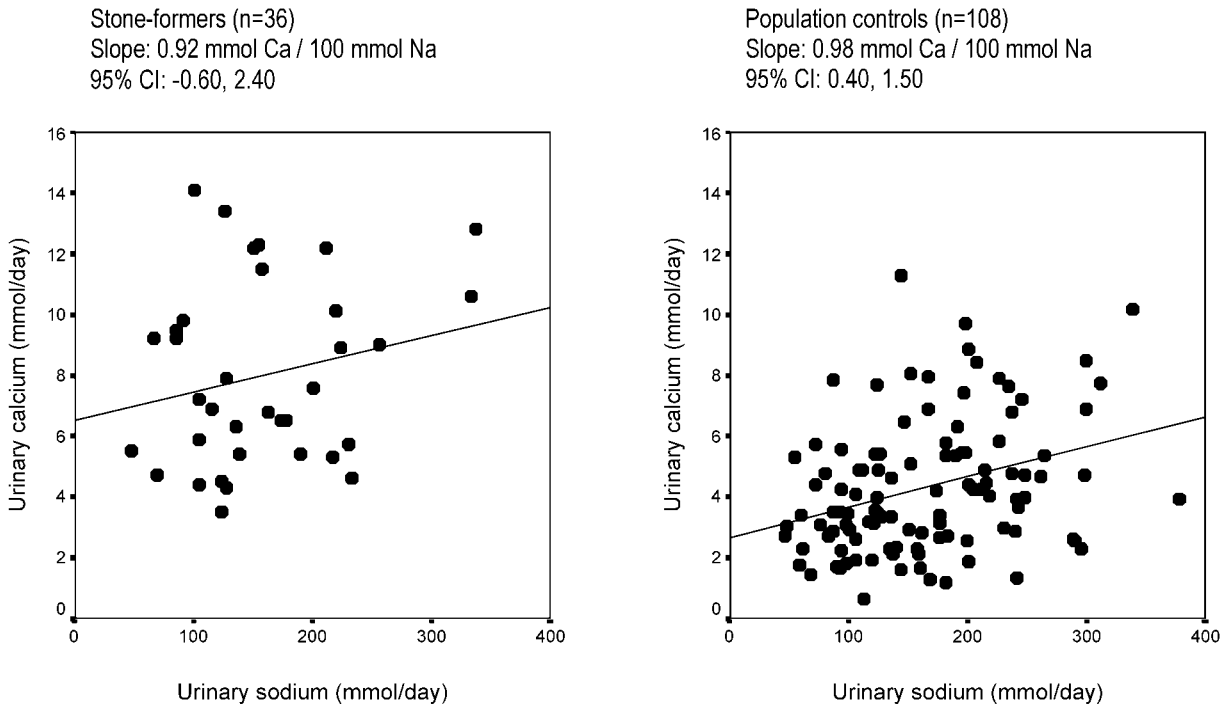

Fig. 1. Relationships between urinary sodium and calcium excretions in stone formers (left) and population controls (right).

(+3.7 mmol/day; 2.8–4.6 mmol/day), even when adjusted for differences in urinary creatinine excretion (+0.20; 0.11–0.29). Urinary sodium excretion was positively associated with urinary calcium excretion in both patients with renal stones ($r = 0.22$) and in the controls ($r = 0.32$), even when expressed as creatinine ratio ($r = 0.21$ and $r = 0.28$, respectively) (Fig. 1). Furthermore, the slopes of the regression lines were comparable in patients and controls; indeed, it can be seen that in both groups a change in urinary sodium (salt intake) of 100 mmol is accompanied by a change in urinary calcium of almost 1 mmol. For any given level of sodium excretion (or salt intake), however, patients with renal stones have a higher urinary calcium excretion compared to age-, sex- and race-matched population controls [intercept at urinary sodium excretion =0: cases 6.5 (95% CI 4.0–9.1) vs controls 2.7 (1.7–3.7)]. Amongst the cases, 15 (42%) had undergone extracorporeal shock wave lithotripsy (ESWL). They did not differ from those who did not (Table III).

DISCUSSION

Our study shows that in patients with known urinary tract calculi, the blood pressure is higher than in age-, sex- and race-matched controls drawn from the same population from which the cases were obtained. The stone-formers also had a much higher urinary calcium excretion (almost double) than controls. The study suggests that stone-formers are more likely to have hypertension than the general population and that the causal link between hypertension and urolithiasis may be a high urinary calcium excretion.

The study suggests that in stone-formers and controls the relationship between urinary sodium and urinary calcium is similar. Indeed, the slopes of the two

Table III. *Comparisons of stone-formers who had extracorporeal shock wave lithotripsy (ESWL) and those who did not*

	ESWL – Yes ($n = 15$)	ESWL – No ($n = 21$)	Difference (95% CI)	*p*
Age (years)	51.1 (13.5)	47.6 (10.2)	3.4 (−4.6 to 11.5)	0.39
Systolic blood pressure (mmHg)	140.3 (16.8)	143.8 (22.3)	−3.5 (−17.4 to 10.4)	0.61
Diastolic blood pressure (mmHg)	79.1 (7.5)	87.6 (11.0)	−8.4 (−15.1 to −1.7)	0.015
Urinary sodium (mmol/day)	149 (76)	161 (65)	−12 (−60 to 36)	0.61
Urinary calcium (mmol/day)	7.7 (3.1)	8.2 (3.0)	−0.44 (−2.55 to 1.67)	0.67

regression lines are almost identical. We would expect that for a 100-mmol change in urinary sodium (i.e. ~6 g of salt intake) there would be a 1-mmol change in urinary calcium in both stone-formers and in controls. Since this relationship results from an effect of sodium on calcium [1], a reduction in salt intake is potentially a useful method for controlling hypercalciuria in stone-formers. Muldowney *et al*. [13] demonstrated clearly in the early 1980s how closely urinary calcium followed salt intake and urinary sodium excretion, so that the definition of "idiopathic" hypercalciuria would be meaningless without allowing for the concurrent sodium intake. More recently, clinical anecdotes have strongly supported the view that a moderate reduction in salt intake could play a very important clinical role in reducing urinary calcium excretion, blood pressure and the recurrence of kidney stones in hypertensive patients suffering from recurrent urolithiasis [14]. A significant and long-term reduction in salt intake can be achieved in patients, and contrasts with the difficulty of reducing calcium intake which is much more commonly advised for this condition [15], without much evidence that it has a major effect on calcium excretion. Indeed there is convincing evidence that it can increase recurrence due to the increase in oxalate absorption [16, 17]. Finally, a recent randomized trial in men has shown that unlike dietary calcium restriction a moderate reduction in dietary protein and salt (as far as it is possible in day-to-day life) reduced the recurrence of stones in patients with "idiopathic" hypercalciuria by half over 5 years [18].

The development and introduction of ESWL in the early 1980s has dramatically changed the management of upper urinary tract calculi. Concern has been expressed about possible short- and long-term consequences of ESWL on kidney structure and function. In particular, a number of uncontrolled and/or retrospective early reports suggested that ESWL might cause hypertension [19–21]. On the other hand, these postulated deleterious effects have not been confirmed by others [22–25] and two recent independent randomized controlled trials in the USA [26] and in the UK [27] have shown that there is no detectable increase in the incidence of hypertension following ESWL. In our study, patients who had received ESWL did not have higher blood pressure than those who had not received it, so any difference in blood pressure between stone-formers and controls cannot be ascribed to ESWL treatment.

The "relative" hypercalciuria seen in stone-formers compared to population controls appears to be independent of salt intake and may well reflect an underlying renal calcium leak. We were surprised by the number of patients who had family members with stones. Genetic influences may be much more important than previously thought, and gaining an understanding of the underlying mechanisms may help to reveal the causes of the so-called "idiopathic" hypercalciuria of stone-formers [28, 29].

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