# Unravelling the links between calcium excretion, salt intake, hypertension, kidney stones and bone metabolism

*Francesco P. Cappuccio[1,2], Rigas Kalaitzidis[1], Stuart Duneclift[1], John B. Eastwood[2]*

[1] Departments of Medicine and [2] Renal Medicine
St George's Hospital Medical School, London - UK

ABSTRACT: Evidence from animal, clinical and epidemiological studies suggests that high blood pressure is associated with abnormalities of calcium metabolism, leading to increased calcium loss, secondary activation of the parathyroid gland, increased movement of calcium from bone and increased risk of urinary tract stones. Some of these abnormalities are detectable in children and young people and continue throughout adult life. The cluster of abnormalities may be due either to a primary renal tubular defect ('renal calcium leak' hypothesis) or to the effect of central volume expansion seen in hypertension ('central blood volume' hypothesis). A high salt intake is known to aggravate these abnormalities and their consequences. If substantial calcium loss related to high blood pressure is sustained over many decades, increased excretion of calcium in the urine may result in an increased risk of urinary tract stones, and the increased movement of calcium from bone may result in higher rates of bone mineral loss, thereby increasing the risk of osteoporosis. The present review summarises the evidence, suggests a unifying hypothesis and discusses clinical and public health implications.

Key words: *Calcium, Sodium, Hypertension, Blood pressure, Kidney stones, Bone demineralisation, Osteoporosis*

## URINARY CALCIUM AND BLOOD PRESSURE

In 1980 McCarron et al (1) published the first report of increased urinary calcium excretion in patients with essential hypertension. The differences in urinary calcium excretion that they found were maintained when adjusted for urinary sodium excretion and associated with metabolic indices of secondary activation of parathyroid function. It is now clear that high blood pressure is associated with a number of abnormalities in calcium metabolism, including an increase in urinary calcium excretion for a given sodium intake (1), evidence of secondary increase in parathyroid gland activity (1), increase in urinary cyclic AMP (1,2), tendency to low serum ionized calcium (1-7), raised vitamin D levels (5,8-10) and increased intestinal calcium absorption (11). The association of hypertension with hypercalciuria has since been confirmed in several other studies (2) and has been reported consistently in case-control and cross-sectional studies (12). However, the underlying mechanism has not been elucidated. This increased urinary calcium loss as a function of blood pressure has been seen in animals with hypertension (13-15), in normotensive children in the upper part of the age distribution (16,17), and in normotensive children of hypertensive adults (12,17,18).

## URINARY CALCIUM AND SALT INTAKE

Sodium intake is one of the major dietary determinants of urinary calcium excretion (19-24), the other being calcium intake. There can be quite large changes in calcium excretion even within the normal inter-day variation in sodium intake (25,26), which are independent of intestinal calcium absorption (25). Within a population, calcium excretion is directly related to sodium excretion, i.e. sodium intake (23-25,27). It has been estimated that a dietary increase of 100 mmol of sodium produces an increase in urinary calcium of 1 mmol (27). Recently, this association has been confirmed in a multi-ethnic population in London (28). In this study, despite the overall lower total urinary calcium excretion in blacks compared with whites, the relationship between sodium and calcium remained. These associations are also directly comparable to the results of intervention studies in which in-

dividuals' dietary sodium intake was altered (20,23, 24,29,30). In particular, in a study of salt restriction in hypertensive patients, where sodium intake was reduced from 200 to 50 mmol per day (31), calcium excretion decreased by approximately 45%, from 4.8 to 3.4 mmol per day. Likewise, in a study of salt reduction in people over the age of 60, where sodium intake was reduced from 180 to 90 mmol per day (32), the urinary calcium excretion decreased significantly with the decrease in sodium intake by an estimated 1 mmol of calcium for every 100 mmol of sodium (Fig. 1). In a separate study on calcium supplementation in hypertensive patients in whom calcium intake was increased from 800 to 1,800 mg per day while on a constant sodium intake of 170 mmol per day (33), urinary calcium excretion increased by only 20%.

The importance of salt intake in revealing the abnormality in hypertensives is supported by experiments in spontaneously hypertensive rats, whose calcium excretion is higher than that of Wistar-Kyoto rats on a high but not on a low sodium intake (34). Furthermore, normotensive children of hypertensive parents show a greater increase in urinary calcium excretion when given a high salt diet compared with children from normotensive parents (18). This indicates that sodium intake is an important determinant of calcium excretion. Also, hypertensives excrete more calcium for a given salt intake than normotensives, suggesting a difference in the degree of sensitivity to salt intake. This is supported by studies in normotensive subjects, in which a large increase in salt intake not only causes an increase in calcium excretion, but also causes increased levels of parathyroid hormone, 1,25-dihydroxy-vitamin D and serum osteocalcin (a marker of bone formation), as well as urinary cyclic AMP and urinary hydroxyproline (a marker of bone resorption) (35-37).

## THE 'RENAL CALCIUM LEAK' HYPOTHESIS

This hypothesis states that in patients with essential hypertension renal calcium handling is altered in such a way that urinary calcium excretion is increased at each level of sodium output (12,38). The frequent association of reduced plasma ionised calcium levels (6) and increased parathyroid gland activity (1,2,4) suggests that an abnormality in the renal tubule is responsible for the enhanced urinary calcium loss (12,38). It has been proposed that this renal abnormality may be one expression of a widespread cell membrane defect involving the cellular handling of sodium and calcium at a number of sites (38). Certainly, abnormalities of ion transport have been detected in patients with so-called 'idiopathic' hypercalciuria (39) and calcium nephrolithiasis (40). Several animal models of genetic hypertension share with human hypertension both the membrane defects and the altered renal calcium metabolism (14,15,41-43). Thus, enhanced urinary calcium loss has been reported in Okamoto-Aoki spontaneously hypertensive rats (41,42), in Dahl salt-sensitive rats (15) and in the Milan hypertensive rat (14,43). Spontaneously hypertensive rats are also prone to urolithiasis (42) and Milan hypertensive rats are often in negative calcium balance and develop bone demineralisation (14,43).

## THE 'CENTRAL BLOOD VOLUME' HYPOTHESIS

Some of the evidence suggests that the increase in calcium excretion rather than as a consequence of increasing salt intake, caused by a direct effect of the increase in urinary sodium on tubular calcium excretion, may actually be secondary to the increase in extracellular volume that occurs (29,44). If either animals (45) or normal subjects (46,47) are given mineralocorticoids, they retain sodium for a few days before returning into balance. That is, sodium intake equals output, but at an expanded extracellular volume. Under these circumstances, calcium excretion increases even though sodium excretion is the same as before the mineralocorticoid was given (47). This is unlikely to be due to a direct effect of mineralocorticoids on calcium excretion, since if animals are given a very low sodium diet, little volume expansion occurs and no increase in calcium excretion is seen (45). In patients with primary aldosteronism urinary calcium excretion is higher for a given salt intake compared with normotensive controls, and there is a greater increase in calcium excretion in response to an increase in sodium intake (48).

During head-out water immersion and head-down tilting there is a shift of blood to the chest, with an increase in central blood volume and venous pressure but no change in total blood volume (49,50). This is associated with an increase in both sodium and calcium excretion and also in parathyroid hormone (49-52). During weightlessness, astronauts have a large shift of blood to the centre. This initially causes a marked loss of sodium, but within a few days they return into sodium balance with a reduced total extracellular volume but still having an elevated central blood volume (53,54). Calcium excretion remains raised throughout the time they spend in space and there is a profound negative calcium balance with ensuing bone demineralisation despite activation of compensatory mechanisms.

In rat models of inherited hypertension as well as in human hypertension there is a diminution in venous compliance and a shift of blood from the periphery to the centre, causing an increase in central blood volume

but not in total blood volume (55,56). Central venous pressure and right atrial pressure also go up (57). An underlying genetic abnormality in the kidney for the development of both inherited hypertension in rats and essential hypertension in man may be expressed as a relative defect in the ability of the kidney to excrete sodium (44). On a high salt intake there would be a tendency to sodium retention, but compensatory mechanisms attempt to overcome the underlying defect. The suggestion is that these compensatory mechanisms are responsible for an increase in arteriolar tone (rise in blood pressure) and in venous compliance (shift of blood from the periphery to the centre). It is clear that expansion of central blood volume without an increase in total blood volume could cause the increase in urinary calcium excretion leading to a chain of compensatory mechanisms including secondary hyperparathyroidism with its effects on kidney, gut and bone (44).

### URINARY CALCIUM AND KIDNEY STONES

Calcium is the main component of most urinary stones, and urinary calcium concentration plays a pivotal role in crystal precipitation and stone growth (58). It is not surprising that individuals with urinary tract calculi tend to be those with the highest calcium excretion (59). In particular, hypercalciuria is the most common risk factor for urolithiasis in adults, being present in up to 80% of patients with kidney stones (58,60,61).

### BLOOD PRESSURE AND KIDNEY STONES

In general, urolithiasis is rare in mammals, including rats. However, spontaneously hypertensive rats are prone to develop kidney stones to a degree that correlates with the severity of the hypertension (42). In humans the first report of an association between hypertension and kidney stones was in 1761 when Giovan Battista Morgagni described a patient with clinical and anatomical evidence of long-standing hypertension and stones in his kidneys (62). More recently, cross-sectional epidemiological surveys have confirmed the presence of an independent association between hypertension and a history of kidney stone disease (63-67). These studies, however, have been unable to establish which comes first, the hypertension or the urinary tract stones. It is possible that the finding of hypercalciuria at an early age in association with a predisposition to higher blood pressure explains and predicts the greater incidence of kidney stones in hypertensive adults. On the other hand, it has been suggested that kidney damage caused by the stones themselves predisposes to the development of hypertension. Recent prospective studies, however, have failed to shed light on the pathway of causality (Tab. I). Cappuccio et al (68) and Borghi et al (69) have reported an enhanced risk of developing kidney stone disease amongst hypertensive compared with normotensive individuals over 5-8 years of follow-up. The risk of developing kidney stones was almost twice as high in hypertensive men as in normotensive men, even when

**TABLE I -** PROSPECTIVE STUDIES OF HYPERTENSION AND KIDNEY STONES

| Relative risk of kidney stones in hypertensive people | | | | | |
|---|---|---|---|---|---|
| Author | Sex | Cases (%) Hypertensive | Controls (%) Normotensive | Relative Risk | 95% CI |
| Cappuccio (1999) | Men | | | | |
| all | | 19/114 (16.7) | 33/389 (8.5) | 1.89¶ | 1.12-3.18 |
| untreated only | | 14/82 (17.1) | 33/389 (8.5) | 1.94¶ | 1.10-3.43 |
| Borghi (1999) | Men & Women | 19/132 (14.3) | 4/135 (2.9) | 5.5 | 1.82-16.7 |
| Madore (1999) | Men | ?/10428 | ?/36990 | 0.99§ | 0.82-1.21 |
| Madore (1999) | Women | n/a | n/a | 1.01§ | 0.85-1.20 |

*¶ age-adjusted; § multiple adjustments.*

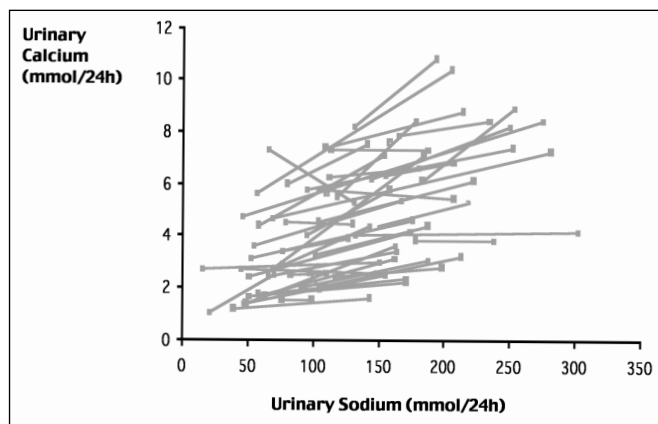| Relative risk of hypertension in stone formers | | | | | |
|---|---|---|---|---|---|
| Author | Sex | Cases (%) Stone-formers | Controls (%) Non stone-formers | Relative Risk | 95% CI |
| Strazzullo (unpub.) | Men | 19/58 (32.7) | 45/323 (13.9) | 1.96¶ | 1.25-3.07 |
| Madore (1999) | Men | 466/2676 (17.4) | 4613/35133 (13.1) | 1.30¶ | 1.16-1.45 |
| Madore (1999) | Women | 499/2109 (23.7) | 12041/65636 (18.3) | 1.36¶ | 1.20-1.43 |

*¶ age-adjusted.*

**Fig. 1 - Relationship between urinary sodium and calcium excretions during changes in salt intake in 47 men and women over the age of 60 years during a randomised double-blind cross-over trial (32). An average reduction in sodium intake of 83 mmol/day caused an average reduction in urinary calcium excretion of 1.13 mmol/day (p<0.001). The association between sodium and calcium was strong both on the low (r=0.47; p<0.001) and the high (r=0.59; p<0.001) sodium intake. It was estimated that a change in 100 mmol/day of sodium excretion would predict a 1.19 (0.28 SD) mmol/day change in urinary calcium excretion.**

the effect of age and body weight was taken into account (68). These studies in which kidney stones were sought assiduously and blood pressure carefully measured seem to suggest that hypertension may be considered a risk factor for kidney stones (68,69). On the other hand, two studies conducted in very large American cohorts of men (66) and women (67) showed that participants with a previous history of kidney stone disease and no hypertension were more likely than individuals without stones to develop hypertension over the subsequent years (Tab. I). The authors conclude that kidney stones are a risk factor for hypertension (66,67). Although we do not have a clear explanation for the discrepancy, it is possible that the studies by Madore et al (66,67) may have underestimated the relationship between hypertension and incidence of kidney stones. Indeed, both the measurement of exposure (history of kidney stone disease) and that of outcome (blood pressure) were based on participants' self-completed biennially mailed questionnaires rather than on direct examination, as in the other two studies (68,69). Finally there was no measure of renal function in the studies by Madore et al (66,67). Thus, the possibility that hypertension could be secondary to renal damage caused by stones could not be ruled out. More recently a re-analysis of the Olivetti Heart Study (Strazzullo P & Cappuccio FP, personal communication) also finds a significant association between previous kidney stones and incidence of hypertension, in keeping with the US cohorts (Tab. I). It also shows, however, that this association is not explained by re-

nal damage, as no differences in serum creatinine and creatinine clearance were detected. These results, taken together, support the view that there is a common antecedent for both hypertension and urolithiasis, i.e. alterations in calcium metabolism and hypercalciuria, that might explain the association between the two conditions.

## Salt intake and kidney stones

A high salt intake is associated with kidney stone disease in the general population. Compared with non-stone formers, stone formers have higher urinary sodium excretion (70). Also, in both men and women, the prevalence of urolithiasis in the uppermost quartile of urinary sodium excretion is nearly 3 times higher than in the lowermost quartile (70).

## Blood pressure, hypercalciuria and bone mineral loss

Metabolic studies in hypertensive rats show that hypercalciuria and ensuing hyperparathyroidism lead to reduced growth and a detectable decrease in total bone-mineral content later in life (13,14). However, until recently, there was no direct evidence of a similar phenomenon in human beings. Sustained hypercalciuria in people with high blood pressure may lead to an increased risk of bone-mineral loss. Cross-sectional studies have shown a significant negative association between blood pressure and bone-mineral density (71,72). Furthermore, the temporal sequence whereby high blood pressure precedes and predicts the loss of bone-mineral has now been established in a large prospective study in white postmenopausal women (73). In brief, 3,676 white women, aged 66-91 years who were not taking thiazide diuretics, were studied. Body weight, blood pressure and bone-mineral density at the femoral neck were measured at baseline and bone densitometry was repeated after 3.5 years by dual-energy X-ray absorptiometry (73). After adjustment for age, initial bone-mineral density, weight, weight change, smoking and use of hormone replacement therapy, the rate of bone loss at the femoral neck increased with the level of blood pressure at baseline (Fig. 2). The exclusion of anti-hypertensive medication did not alter the results. It is not known, however, whether the greater bone loss in women with higher blood pressure is associated with, or directly contributes to, increased susceptibility to fractures. These results are also consistent with the inverse association between bone-mineral density, stroke incidence (74) and cardiovascular mortality (75) (Fig. 3).
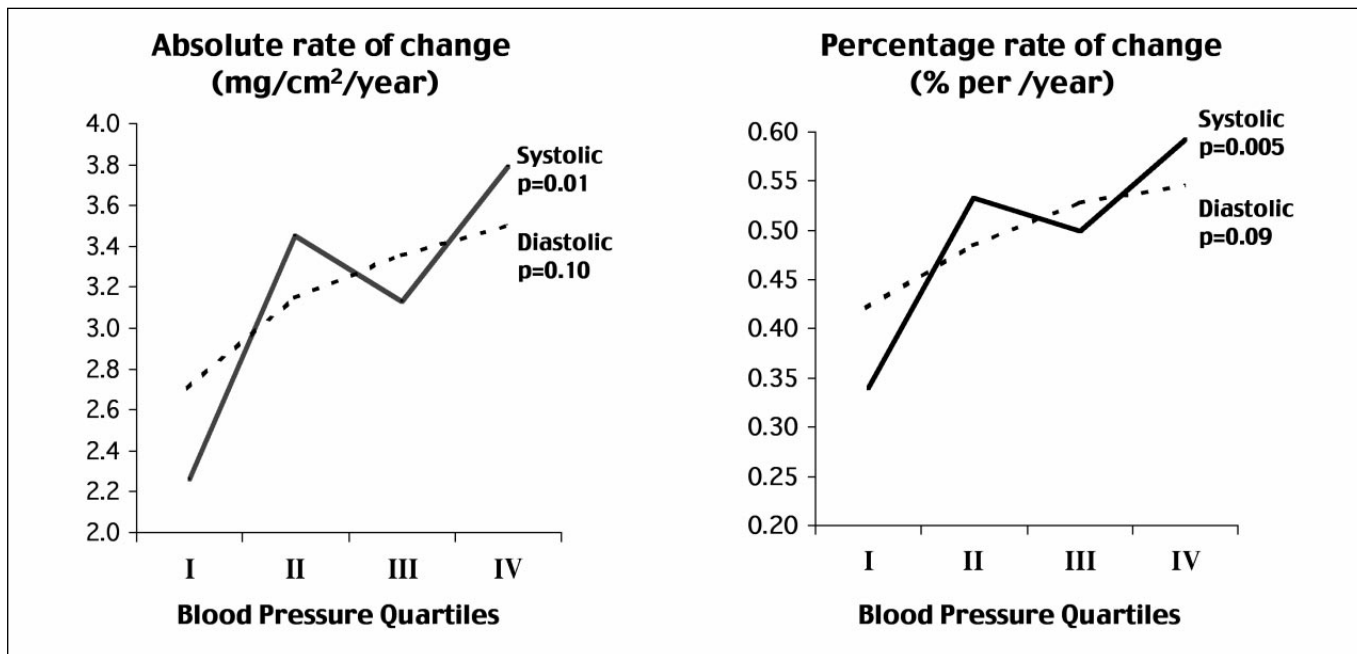
## Absolute rate of change (mg/cm²/year)

Systolic
p=0.01

Diastolic
p=0.10

**Blood Pressure Quartiles**

## Percentage rate of change (% per /year)

Systolic
p=0.005

Diastolic
p=0.09

**Blood Pressure Quartiles**

**Fig. 2** - Rate of change in femoral-neck bone-mineral density over 3.5 years in 3,676 white women aged 66-91 years not taking thiazide diuretics. Results are adjusted for age, initial bone-mineral density, body weight, weight change, smoking and use of hormone-replacement therapy. Re-drawn from reference (73).
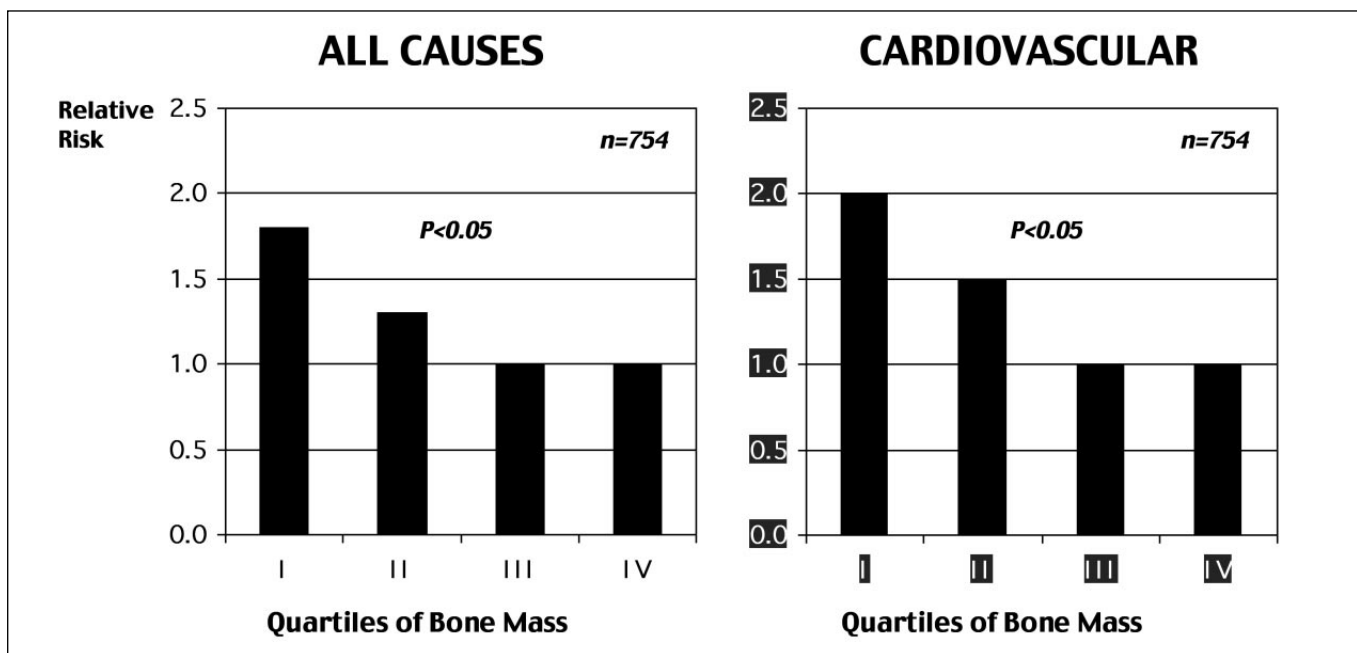
## ALL CAUSES

Relative Risk

n=754

P<0.05

**Quartiles of Bone Mass**

## CARDIOVASCULAR

n=754

P<0.05

**Quartiles of Bone Mass**

**Fig. 3** - Associations between age-adjusted mortality (all causes and cardiovascular) and quartiles of bone mass (bone mineral content of the distal forearm) in postmenopausal women, over the age of 60 years. Re-drawn from reference (75).

### SALT INTAKE, HYPERCALCIURIA AND BONE MINERAL LOSS

An association between the urinary excretion of sodium and that of hydroxyproline (marker of bone resorption) has been reported in observational studies (76-79). A high salt intake in humans induces, at least in the short-term, a reduction in the activity of biomarkers of bone formation and a significant increase in biomarkers of bone resorption (26,37). High salt intake is also associated with reduced peak bone mass in young girls aged 8-13 years (77) and with a higher rate of bone mineral loss in postmenopausal women
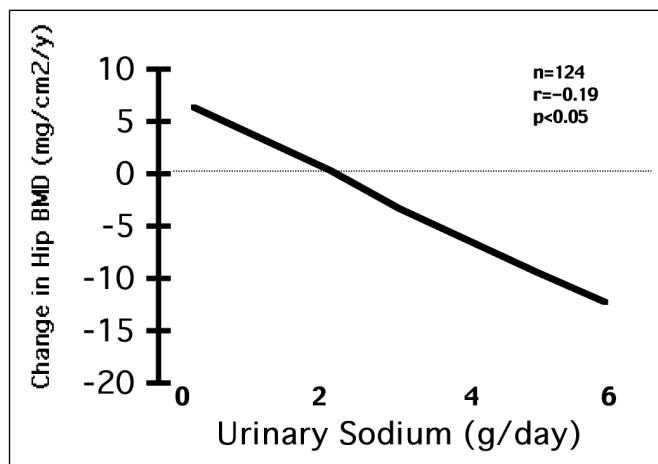
173

**Fig. 4 - Negative association between urinary sodium excretion and changes in bone mineral density (BMD) at the hip in a 2-year follow-up study of postmenopausal women. Redrawn from reference (80).**
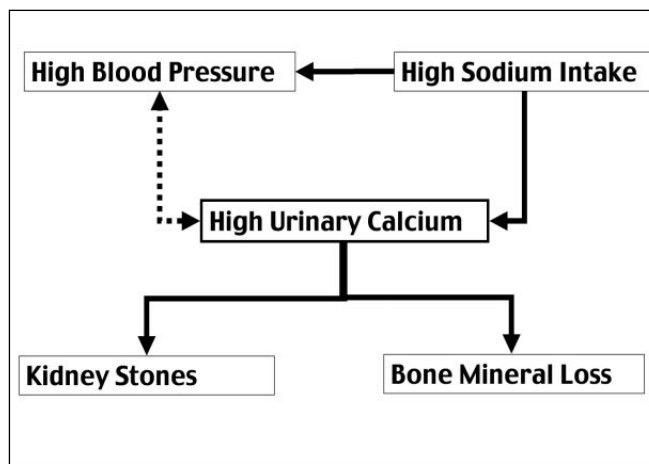


**Fig. 5 - The 'Four Cornerstones' Hypothesis: the links between high calcium excretion, hypertension, salt intake, kidney stones and bone metabolism.**

(80) (Fig. 4). Finally, whilst Nordin et al (81) found a negative correlation between forearm mineral density and urinary sodium excretion in postmenopausal women, Greendale et al (82) failed to detect any relationship between dietary sodium and bone mineral density in a 16-year prospective study. In the latter study, however, dietary sodium at the start of the study was assessed by food frequency questionnaire, an inadequate nutritional tool for the assessment of individuals' habitual sodium intake.

### THE 'FOUR CORNERSTONES' HYPOTHESIS

Our hypothesis (Fig. 5) suggests that high blood pressure (or hypertension) is associated with high urinary calcium losses (or hypercalciuria) for reasons that are not, as yet, fully understood. Furthermore, a high intake of sodium, although not directly implicated in the association between high blood pressure and high urinary calcium, has the effect of increasing both blood pressure and urinary calcium output. It, therefore, behaves as an aggravating factor in the above association. As the association holds at all ages, i.e. for one person's life span, it is conceivable that long-term consequences would be a tendency to kidney stone disease and bone mineral loss. Reduction in sodium intake on the other hand, by reducing urinary calcium and blood pressure, could play an important role in preventing both the formation of kidney stones and loss of bone mineral.

### IMPLICATIONS

The incidence of kidney stones is increasing worldwide (83, 88). It is estimated that 12-15% of the population will develop kidney stones at some time during their lives and many will have more than one episode (83, 84). Indeed, stone-formers have up to an 80% risk of recurrence (83). Although kidney stone disease is seldom fatal, it does lead to substantial morbidity from pain, urinary tract infections and obstructive uropathy, and effective treatments (most usually percutaneous nephrolithotomy, extracorporeal shock-wave lithotripsy or ESWL and open surgery) place a considerable burden on the healthcare budget (89).

Nephrolithiasis is a chronic condition requiring an integrated combination of medical and surgical management. Medical management is concerned mainly with the prevention of recurrence whereas surgical care is concerned with the removal of existing calculi. In Sweden, approximately 10% of stone formers will require hospitalization and approximately 5% will require surgical intervention (87). The incidence of urinary tract calculi in the US varies geographically from 19.3 per 10,000 in South Carolina to 4.3 per 10,000 in Missouri (83). The number of people admitted for renal stone disease in the UK in 1969 was almost double that in 1958 (90).

Prevention of kidney stones has been estimated to result in an average saving of US$ 2,158 per patient per year, which is the difference between the expenditure on tests and drugs (US$ 1,068 per patient per year) and the reduction in medical costs per patient per year (US$ 3,226). The cost of outpatient ESWL varies considerably around the world. However, in most industrialised countries (US, Europe and Japan) it exceeds US$ 2,000 per procedure (91). Unfortunately, the suggestion that a reduction in salt intake might be recommended as an additional dietary manoeuvre to control hypercalciuria and to prevent kidney stones and their recurrence (92) is still widely ignored (58).

In post-menopausal women and the elderly, osteo-porosis is associated with pain, deformity, and loss of independence (93). There are about 1.5 million fractures in the USA every year at an estimated cost of US$10 billion; in the UK there are just under 100,000 fractures costing at least £600 million. Fractures are also an important element of the work of all general hospitals. In England in 1985, there were around 180,000 admissions for treatment of fractures (94). So, the need for new preventive strategies has become a public health priority. Such strategies, would include removing any of the risk factors that are modifiable such as smoking, oestrogen deficiency and lack of exercise(95), since both the number of elderly people and the prevalence of osteoporosis continue to increase substantially. Thiazide diuretics can reduce the rate of bone mineral loss (96-98), and importantly reduce the number of hip fractures (98,99).

The two crucial factors that influence the development of osteoporosis are (a) peak bone mass attained in the first 20-30 years of life and (b) the rate at which bone is lost later in life. Osteoporosis and fractures, therefore, are preventable across the population as a whole (95). High salt intake, with its effects on urinary calcium excretion, is also related to reduced peak bone mass in adolescence (77) and accelerated bone mineral loss in post-menopausal women (80). It is clear, therefore, that if one can cut down salt intake, the ensuing fall in urinary calcium should encourage a positive calcium balance. However, despite evidence suggesting that a moderate reduction in salt intake might contribute to the prevention of bone demineralisation, national recommendations for the prevention of osteoporosis in both the United States (100-102) and the United Kingdom (95) continue to ignore salt completely (103-105).

Reprint requests to:
*F.P. Cappuccio, M.D. MSc FRCP*
*Department of Medicine*
*St George's Hospital Medical School*
*Cranmer Terrace*
*London SW17 0RE*
*UK*
*f.cappuccio@sghms.ac.uk*

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