

# SODIUM-CALCIUM INTER-RELATIONSHIPS WITH SPECIFIC REFERENCE TO OSTEOPOROSIS

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## INTRODUCTION

Dietary sodium intake has long been known to influence urinary calcium excretion in man (Aub *et al.* 1937; Hills *et al.* 1959) and animals (Walser, 1961; Massry *et al.* 1967). However, up to the early 1980s Na was not included among dietary factors believed to influence Ca requirements or the pathogenesis of osteoporosis (Draper & Bell, 1979; Heaney *et al.* 1982; Spencer *et al.* 1982). Recently, there has been a renewal of interest in the calciuric effect of Na ingestion and it has been suggested that Na intake may be a contributory risk factor in the development of osteoporosis in certain individuals (Schaafsma *et al.* 1987; Heaney, 1988; Lindsay, 1988).

The present review examines the effect of dietary Na on Ca metabolism in man and animals and assesses the evidence for an association of high Na intakes with increased Ca requirements and increased bone resorption. It also attempts to identify areas in which further investigation would help to clarify the possible significance of this relationship in the development of osteoporosis.

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Table 1. *Reabsorption sites for calcium and sodium in the rat kidney\**

Site	Percentage reabsorbed	
	Ca	Na
Proximal convoluted tubule	40	45
Loop of Henle	45	43
Distal convoluted tubule	9	6
Collecting ducts	5	5

\* Adapted from Suki (1979).

### PHYSIOLOGICAL BASIS FOR THE RELATIONSHIP BETWEEN URINARY SODIUM AND CALCIUM

Most studies on the physiological basis for the relationship between urinary Na and Ca have been carried out on experimental animals, including the rat and dog, with few studies on humans.

Since there is no evidence for tubular secretion of either Ca or Na in the nephron (Sutton & Dirks, 1977), the primary determinant of renal excretion is glomerular filtration of the ions. The major proportion of both plasma Na and Ca appears to be filtered and urinary excretion of Na and Ca is controlled by the extent of reabsorption of these ions from the nephron. Normally, > 99% of filtered Na and > 95% of filtered Ca is reabsorbed (Suki, 1979). In quantitative terms, the location of the reabsorption sites is similar for both ions (Table 1).

The dependence of urinary Ca excretion on urinary Na excretion has been attributed to the existence of linked or common reabsorption pathways for the ions in the convoluted portion of the proximal tubule and in the loop of Henle (Antoniou *et al.* 1969; McCarron *et al.* 1981). In contrast, there is no evidence for a similar relationship in the distal tubule or collecting ducts (Antoniou *et al.* 1969). Such conclusions are derived from studies using stop-flow and micropuncture techniques (Howard *et al.* 1959; Edwards *et al.* 1973; Agus *et al.* 1977) and from experimental observations into the effects of diuretics acting at different sites on the nephron (Parfitt, 1969; Costanzo & Weiner, 1976; Sutton & Dirks, 1977). For example, the loop diuretic, frusemide, which inhibits Na reabsorption in the thick ascending limb of the loop of Henle also inhibits the reabsorption of Ca, suggesting a common reabsorption mechanism at this site (Sutton & Dirks, 1977). In contrast, thiazide diuretics such as chlorothiazide, which inhibit distal tubular Na reabsorption actually lead to an increase in Ca transport at this site (Costanzo & Windhager, 1978; Goulding & Campbell, 1984*b*). Consequently, it has been concluded that Na and Ca are transported independently in the distal tubule (Suki, 1979). However, the actual mechanism by which Na influences Ca reabsorption in the proximal tubule is unknown (Suki, 1979).

### EFFECT OF SALT SUPPLEMENTATION ON CALCIUM METABOLISM IN THE RAT

Numerous reports indicate that salt supplementation (80 g/kg diet) significantly increases urinary Ca excretion in both intact and parathyroidectomized young rats (Goulding, 1980*a, b*; Goulding & Campbell, 1984*a*; Shortt *et al.* 1987) and in adult intact rats (Goulding & Campbell, 1983; Goulding & Gold, 1986, 1988; Goulding & McIntosh, 1986). Greger *et al.* (1987) also demonstrated that Na intake at a level (8.4 g Na/kg diet equivalent

to 21 g NaCl) lower than that used by Goulding and co-workers led to a significant increase in urinary Ca excretion in young rats (from 0.13 to 0.32 mg/d). They found that the magnitude of calciuria was similar on days 8 and 20. The calciuric effect of salt supplementation (80 g/kg diet) has been demonstrated to be sustained over 84 d in adult rats consuming a diet deficient in Ca (1 g/kg; Goulding & Gold, 1986). However, Goulding & Campbell (1983) found that the magnitude of the increment in urinary Ca excretion, induced by increased Na intake, decreased from 8.55 mg/d to 5.64 mg/d over an 8-week period in rats fed on a diet which was very low in Ca (0.1 g/kg), suggesting that the animals may adapt to the salt loads with time.

The literature is conflicting with regard to changes in Ca absorption during NaCl supplementation in rats. Goulding & Campbell (1983) reported that adult oophorectomized rats consuming a low-Ca diet (0.1 g/kg) for an 8-week period exhibited no increase in net Ca absorption due to salt supplementation. Similarly, Goulding & Campbell (1984*a*) demonstrated that net Ca absorption was not affected by salt supplementation in weanling rats receiving adequate dietary Ca with either a moderate (250 g/kg)- or a high (600 g/kg)-protein diet. Goulding & McIntosh (1986) found no change in net Ca-absorption during salt loading over a 10 d period in adult male rats fed on a low (1 g/kg) Ca diet. In contrast, Goulding & Gold (1986) reported increased net Ca absorption (68.7 v. 43.5% intake) in adult female rats consuming a low Ca diet (1 g/kg) and salt supplement (80 g/kg diet) over a 3-month period compared to rats fed on the same diet without salt supplement. Salt supplementation reduced endogenous Ca loss but true Ca absorption was not reported. However, the increase in net Ca absorption was not sufficient to offset the increase in urinary Ca excretion induced by the salt supplements and Ca balance was lower in the salt-supplemented animals.

There is evidence that urinary hydroxyproline, an indicator of bone resorption, is significantly increased in rats given salt-supplemented diets (Goulding & Campbell, 1983; Goulding & Gold, 1986, 1988). Goulding & Gold (1988) suggested that such increases in urinary hydroxyproline during salt supplementation were mediated by parathyroid hormone (PTH), since PTH is the major determinant of bone resorption rate. This is supported by the finding that parathyroidectomy abolishes the ability of salt to elevate urinary hydroxyproline (Goulding, 1980*b*).

Since PTH increases excretion of urinary cAMP in the process of stimulating adenylate cyclase (*EC* 4.6.1.1) in the renal tubules (Garel, 1987), urinary cAMP is considered to be a sensitive index of parathyroid function. Urinary cAMP has been shown to be significantly elevated in animals given salt supplements (80 g/kg diet) compared with control animals (Goulding, 1980*b*; Goulding & Campbell, 1983, 1984*a*; Goulding & McIntosh, 1986; Goulding & Gold, 1986, 1988). Thus, Goulding & Gold (1988) have suggested that the rise in urinary cAMP excretion observed during salt supplementation is indicative of increased PTH activity. This is supported by the finding that salt supplementation does not lead to an increase in urinary cAMP excretion in parathyroidectomized rats (Goulding, 1980*b*).

Goulding (1980*b*) reported that urinary cAMP failed to increase in young rats fed on a diet containing 0.1 g Ca/kg and salt supplements (80 g/kg diet) for 84 d and suggested that maximal stimulation of PTH-mediated cAMP excretion had possibly already been caused by the low-Ca diet. Similarly, urinary cAMP was not increased by salt supplements (80 g/kg diet) in young rats given a high-protein diet (600 g/kg) containing 6 g Ca/kg diet and salt for 14 d (Goulding & Campbell, 1984*a*). The lack of an effect of salt supplementation on urinary cAMP in this study may be due to the high urinary cAMP excretion in the control group, which obscured any further increase that occurred due to salt supplementation.

Short-term (10-84 d) administration of dietary salt supplements (80 g/kg diet) have been

reported to reduce significantly bone mass and bone Ca and phosphorus content in rats consuming diets containing dietary Ca at concentrations of 0.1 g/kg (Goulding, 1980*b*; Goulding & Campbell, 1982, 1983), 1 g/kg (Goulding, 1980*a*; Goulding & Gold, 1986) or 6 g/kg (Goulding & Campbell, 1984*a*; Shortt *et al.* 1987). However, Goulding (1980*b*) failed to show a significant effect of salt supplementation (80 g/kg diet) on bone variables in young rats given diets containing 1 g Ca/kg for 16 or 84 d. Similarly, Goulding & Gold (1988) found that femur composition was similar in control and salt-supplemented (80 g/kg diet) adult female rats who were fed on a diet containing 1 g Ca/kg for 10 d. They suggested that the absence of an effect of salt supplements was due to the short duration of the study. Greger *et al.* (1987) reported a significant reduction in tibia magnesium concentration, but not in tibia Ca or P concentrations (expressed per g) in rats given a high-Na diet (8.4 g Na/kg diet equivalent to 21 g NaCl) containing adequate dietary Ca (5 g/kg), compared with controls. However, as values per bone were not reported, it is not clear whether or not bone loss occurred.

The reduced bone mass of rats fed on salt-supplemented diets has been attributed to an increase in bone resorption rather than to a decrease in bone accretion. This has been demonstrated in studies examining the release of <sup>45</sup>Ca from labelled skeletons (Goulding & Gold, 1986) and the uptake of [<sup>3</sup>H]hydroxyproline and <sup>45</sup>Ca into bone (Goulding & Gold, 1988).

Thus, there is considerable evidence that salt supplementation reduces bone mass, Ca and P in young and adult rats. This appears to be due to Na-induced calciuria which is not compensated for by increased Ca absorption or reduced endogenous loss and leads to PTH-mediated bone resorption.

However, most of the studies on the effects of salt on Ca metabolism in rats have been of relatively short duration (10–84 d) and the level of salt loading used (usually 80 g/kg) has been extremely high compared with the levels of dietary Na (0.5 g/kg diet) and chloride (0.5 g/kg diet) recommended for the rat (National Research Council, 1978). Thus, there is a need for longer-term studies on the effect of dietary salt on bone employing lower dietary concentrations of salt.

While studies with rats have been useful in illustrating a number of aspects of the Na–Ca relationship it is important to note that there are considerable differences in bone metabolism between rodents and humans. Draper (1985*a*) reported that rodents and humans differ with respect to the pattern of bone loss due to aging. In addition, rodents lack lamellar bone and consequently have a limited capacity for bone remodelling. Rodents also appear to be more susceptible than humans to the influence of dietary factors which increase the rate of bone resorption, e.g. protein and phosphorus (Draper, 1985*b*). Since a much lower percentage of ingested Ca is excreted in urine in rats (approximately 1%, Bar, 1987) than in man (approximately 16%, Schaafsma, 1983) and as Na exerts its effect on Ca primarily at the renal level, the rat may not be the most appropriate animal model for the study of Na–Ca interactions. Furthermore, the renal concentrating capacity of the rat is about twice that of humans when expressed on a body-weight basis. Thus, studies on rats must be interpreted carefully, especially when extrapolating the results to human subjects.

## RELATIONSHIP BETWEEN URINARY SODIUM AND CALCIUM EXCRETION IN MAN

### STUDIES ON FREE-LIVING INDIVIDUALS

There is considerable evidence supporting a strong positive association between urinary Na and Ca excretion in both young and adult free-living individuals of both sexes consuming

Table 2. Estimates of the incremental increase in urinary calcium excretion observed with 100 mmol increment in urinary sodium excretion in free-living individuals consuming their usual diets

Reference	Subjects			Estimated increase in urinary Ca (mg)/100 mmol rise in urinary Na
	Sex	n	Age (years)	
Modlin (1967)	M/F	46	Adult (Whites)	96
	M/F	50	Adult (Bantu)	12
McCarron <i>et al.</i> (1980)	M/F	34	43-47	54
Madden <i>et al.</i> (1983)	M	25	19-21	63
	F	26	19-21	106
Goulding <i>et al.</i> (1986)	M	484	20-69	60
	F	491	20-69	52
Nordin & Polley (1987)	F	467	Post-menopausal	52
Shortt <i>et al.</i> (1988)	M	46	19-60	91
	F	48	19-60	61

their usual diet (Modlin, 1967; Dale, 1968; Goulding, 1981; Madden *et al.* 1983; Goulding *et al.* 1986; Nordin & Polley, 1987; Law *et al.* 1988; Shortt *et al.* 1988). Goulding (1981) found that the urinary Ca:creatinine ratio was positively correlated with the urinary Na:creatinine ratio in fasting spot urine samples obtained from a group of 580 women (aged 16-82 years) during a health survey in New Zealand. Similarly, Law *et al.* (1988) found a significant positive correlation between the Ca:creatinine and Na:creatinine ratios in fasting spot urine samples of 99 male and 105 female Chinese. Furthermore, 24 h urinary Ca and Na excretion were positively correlated in every decade age-group studied during a health survey of 975 individuals in New Zealand (Goulding *et al.* 1986) and in 467 post-menopausal women in Australia (Nordin & Polley, 1987).

Results from studies on free-living individuals suggest that the average increase in urinary Ca excretion per 100 mmol increment in urinary Na in healthy individuals consuming their usual diet is in the range 12-106 mg (Table 2), indicating considerable variation between groups examined. For example, in the study of Modlin (1967), white South Africans excreted, on average, 96 mg Ca/100 mmol Na while Bantu excreted only 12 mg Ca/100 mmol Na. Such variation may indicate genetic differences in Na sensitivity but could also be due to dietary differences.

Few studies have controlled for the known calciuric effects of factors such as dietary Ca, protein, caffeine or P, or acid-base status (Lemann *et al.* 1979; Heaney & Recker, 1982; Massey & Wise, 1984) or for the possible calciuric effects of non-dietary factors such as diuretics, antacids or antibiotics (Spencer & Kramer, 1986). Madden *et al.* (1983), who observed a significant positive relationship between 24 h urinary excretion of Na and Ca in fifty-one young adults consuming their usual diet, found that 24 h urinary Ca or Na excretion were not significantly correlated with dietary Ca, protein, P or fibre intakes. Nordin & Polley (1987) found a significant positive association between urinary Na and Ca excretion for a group of post-menopausal women (*n* 445), but no significant association was observed for those individuals (*n* 174) who consumed diets containing > 1000 mg Ca/d. Future studies which examine the relationship between urinary Na and Ca excretion in free-living individuals should attempt to control for such confounding variables.

## STUDIES WITH CONTROLLED SODIUM INTAKE

In an early study it was noted that NaCl supplementation of two subjects with 30 g NaCl/d for 3 d increased urinary Ca excretion (Aub *et al.* 1937). Since then, a number of short-term studies have shown that acute increases in dietary Na intake generally cause an increase in urinary Ca excretion in healthy subjects. King *et al.* (1964) increased the dietary Na intake of eleven young adults from 20 to 160 mmol/d while maintaining a constant Ca intake (2.0 g/d). They observed that the increase in Na intake was accompanied by an increase in urinary Ca excretion in some individuals. Similarly, Kleeman *et al.* (1964) varied the Na intake of six adults, who were consuming a near-constant Ca diet, from 20 to 425 mmol/d, and found that Ca excretion increased as dietary Na intake was increased. Goulding *et al.* (1986) increased the NaCl intake of six young women, who were consuming a low-Na diet (70 mmol/d), by 50, 100 and 150 mmol/d and reported that urinary Ca excretion, measured after 4 d on the supplements, increased by an average of 32, 60, and 72 mg/d respectively. Recently, McParland *et al.* (1989) reported that urinary Ca increased by an average of 23 mg/d in ten healthy post-menopausal women when given salt supplements (100 mmol/d) with a low-Na diet.

McCarron *et al.* (1981) varied the dietary Na intake of six adult males, who were consuming a fixed diet containing 400 mg calcium/d, from 10 to 1500 mmol/d. They found that mean urinary Ca excretion increased with progressive Na loading and attained an average maximum of 262 mg/d at 1500 mmol Na/d. Within the normal physiological range of Na intake (10–300 mmol/d) a linear relationship was observed between urinary Na and Ca excretion. Urinary Ca increased by 28 mg/d, on average, for each 100 mmol increment in dietary Na intake. However, a non-linear relationship was observed over the entire range of Na intakes examined (10–1500 mmol/d). Urinary Ca excretion ( $U_{Ca}$ ) increased in proportion to increases in the natural logarithm of urinary Na ( $U_{Na}$ ):

$$U_{Ca} \text{ (mg/d)} = -69 + 40 \ln U_{Na} \text{ (mmol/d)}.$$

This study defined the limits of Ca excretion at extremes of Na intake and indicated that the linear relationship between urinary Na and Ca excretion, which is evident within the normal physiological range of Na intakes, is not maintained when Na intake is increased beyond the normal physiological limits.

Na-induced increases in urinary Ca excretion have been demonstrated in individuals on daily Ca intakes of 400 mg (Breslau *et al.* 1982; Sabto *et al.* 1984), 700–900 mg (Meyer *et al.* 1976; Shortt *et al.* 1988; McParland *et al.* 1989) and > 1000 mg (King *et al.* 1964; Castenmiller *et al.* 1985; Goulding *et al.* 1986; Nordin & Polley, 1987).

The slopes of the relationship between urinary Ca and Na excretion obtained in different studies on healthy subjects are summarized in Table 3. Urinary Ca increased by an average of 22 to 107 mg for a 100 mmol increase in urinary Na excretion.

Few investigators have considered it important to allow adequate time for adaptation to the change in dietary salt intake. While changes in Na intake may not be fully reflected in urinary Na for up to 5 d, with an average lag of 3–5 d (Hollenberg, 1980), many studies have been of very short duration (3–5 d). Furthermore, dietary Ca has been changed from the usual intake in many studies. This issue was addressed by Castenmiller *et al.* (1985) who found that increasing dietary Na intake by 150 mmol/d significantly increased urinary Ca excretion in twelve young male adults who were consuming diets with a Ca content similar to their usual diet (approximately 1.5–2.0 g/d).

Several workers have demonstrated that hypercalciuric individuals may maintain Ca excretion in the normocalciuric range by simply restricting Na intake (Phillips & Cooke 1967; Muldowney *et al.* 1982; Silver *et al.* 1983). Muldowney *et al.* (1982) reported that

Table 3. Estimates of the incremental increase in urinary calcium observed in healthy individuals with a direct increase in urinary sodium excretion of 100 mmol/d during experimental studies

Reference	Subjects			Estimated increase in urinary Ca (mg)/100 mmol rise in urinary Na	Dietary Ca (mg)
	Sex	n	Age (years)		
Phillips & Cooke (1967)	M	10	25-38	107	750
Phillips & Cooke (1967)	M	10	25-38	55	< 200
Meyer <i>et al.</i> (1976)	M/F	2	Adult	24	786
McCarron <i>et al.</i> (1981)	M	6	18-40	28	400
Breslau <i>et al.</i> (1982)	M	6	22-36	26	400
	F	5			
Sabto <i>et al.</i> (1984)	M	18	25-39	60	400
	F	20			
Castenmiller <i>et al.</i> (1985)	M	12	19-26	22	1800
Goulding <i>et al.</i> (1986)	F	6	19-23	63	—
Shortt <i>et al.</i> (1988)	M	6	21-25	35	700
	F	6	21-25	28	700
Law <i>et al.</i> (1988)	M	4	30	60	—
McParland <i>et al.</i> (1989)	F	10	67	23	850

when the Na intake of eighteen hypercalciuric subjects was reduced to approximately 80 mmol/d, urinary Ca was reduced to 278 mg/d on average. Subsequently, when the Na intake of these subjects was increased to 200 mmol/d for a further 7 d, urinary Ca excretion increased to 384 mg/d. Similarly, Silver *et al.* (1983) reported that moderate Na restriction (to less than 150 mmol/d) corrected hypercalciuria in four patients. Muldowney *et al.* (1982) suggested that idiopathic hypercalciuria may be provoked by a high Na intake and that Na restriction may be a valuable mode of therapy. Phillips & Cooke (1967) reported that hypercalciuric patients, as a group, excreted 140 mg Ca/100 mmol Na increment, while normocalciuric patients excreted, on average, 107 mg Ca/100 mmol Na increment on similar, fixed diets.

### MAGNITUDE OF SODIUM-INDUCED CALCIURIA

The magnitude of the calciuria elicited by increases in dietary Na intake is comparable with the calciuric effects of dietary constituents such as protein and caffeine (Heaney & Recker, 1982; Heaney, 1988; Lindsay, 1988). Schaafsma *et al.* (1987) calculated that increasing the protein content of the diet from natural sources by 20 g/d results in an increase in urinary Ca of 20 mg/d and that an increase of 150 mg caffeine/d (equivalent to two cups of coffee) increases urinary Ca by 5 mg/d. In comparison, studies on free-living subjects consuming their usual diet (Table 2) indicate that an increase in dietary Na intake of 100 mmol results in an average increase in urinary Ca excretion of 12-106 mg. Similarly, direct increases in urinary Na excretion have been shown to increase urinary Ca excretion on average by 22-107 mg/100 mmol Na in healthy subjects (Table 3). Considering the reported range of urinary Na excretion (and hence Na intake) in human populations (0.2-242 mmol/d, Intersalt Cooperative Research Group, 1988), the possible influence of dietary Na intake on urinary Ca loss may be considerable.

Thus, Na intake appears to be a major determinant of urinary Ca excretion. However, no studies have systematically investigated whether the calciuric effect of dietary Na intake

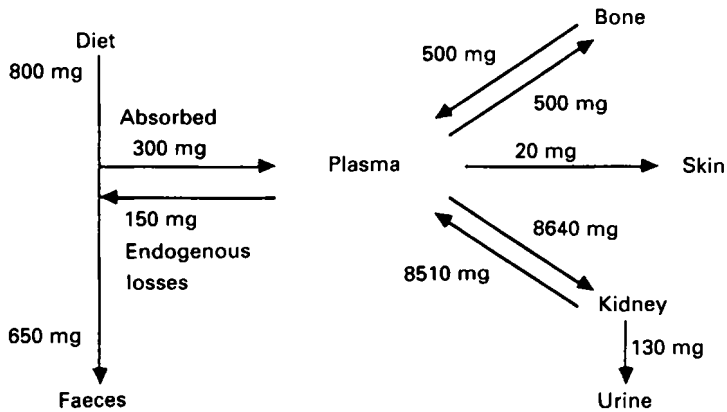


Fig. 1. Schematic representation of daily calcium turnover under balance conditions. Adapted from Schaafsma (1983).

is influenced by other dietary factors (e.g. protein, Ca, P) which are known also to affect urinary Ca excretion.

#### INDIVIDUAL VARIABILITY IN URINARY CALCIUM RESPONSE TO DIETARY SODIUM INTAKE

King *et al.* (1964) reported that, of eleven subjects given diets supplemented with 130 mmol Na/d, urinary Ca excretion increased in five, remained unchanged in four and decreased in two subjects. Since then many studies have demonstrated that there is considerable variation between healthy individuals in their calciuric response to increasing NaCl intake (Kleeman *et al.* 1964; Meyer *et al.* 1976; McCarron *et al.* 1981; Castenmiller *et al.* 1985; Shortt *et al.* 1988). Meyer *et al.* (1976) observed that, following an increase in Na intake (from 10 to 250 mmol/d) by ten subjects, urinary Ca excretion increased in five, decreased in three and showed no significant change in two subjects. Similarly, Castenmiller *et al.* (1985) reported that individual responses to an increase in dietary Na intake varied considerably among free-living young males. The urinary Ca:creatinine ratio increased for nine, remained virtually unchanged for two and decreased for one subject. Shortt *et al.* (1988) were unable to detect a relationship between Na intake (varied from 40 to 220 mmol/day) and urinary Ca excretion in seven of twelve young adults studied. For subjects in whom a positive correlation was found, the slopes of the regression lines ranged from 30 to 113 mg Ca/100 mmol Na. This suggests that, while some individuals show a strong relationship between Na intake and urinary Ca excretion, the relationship may be more difficult to detect or may not exist in others. The basis for this inter-individual variability in Na sensitivity has not been investigated.

#### EFFECT OF SODIUM INTAKE ON SERUM PARATHYROID HORMONE, CALCIUM ABSORPTION AND BALANCE

While there is little doubt that increasing salt intake increases urinary Ca excretion in many, although not all, humans this phenomenon is of little significance if there is complete adaptation, i.e. if net Ca absorption is increased by an amount sufficient to offset the increased urinary loss (see Fig. 1).



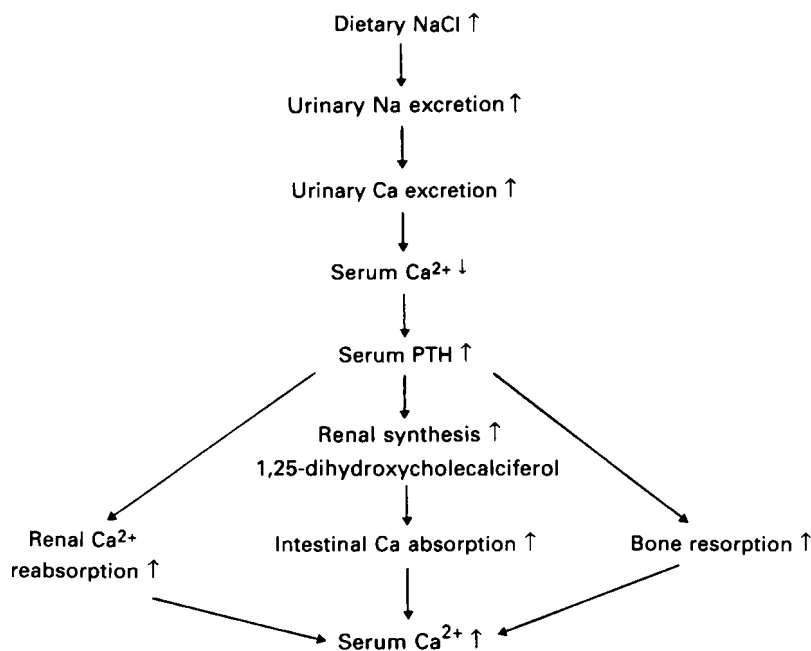


Fig. 2. Effects of increasing dietary sodium chloride on calcium metabolism. Adapted from Goulding *et al.* (1986). PTH, parathyroid hormone.

Under normal conditions, an equilibrium exists between ionized Ca and PTH in serum. It has been suggested that Na-induced calciuria temporarily depresses serum ionized Ca concentration which, in turn, stimulates the release of PTH (Fig. 2). PTH then acts on the kidney, intestine (via renal 1,25-dihydroxycholecalciferol synthesis) and bone to restore serum ionized Ca to normal levels (Goulding *et al.* 1986).

Serum PTH has been found to be significantly increased in association with Na-induced calciuria when the level of Na supplementation was within the normal physiological range (10–300 mmol/d) of Na intakes (Coe *et al.* 1975; McCarron *et al.* 1981; Breslau *et al.* 1982; Zemel *et al.* 1986). However, despite similarity in study design (subjects and Na loads), the observed increment in serum PTH with the imposition of the high-Na diets differed considerably among studies (Coe *et al.* 1975; McCarron *et al.* 1981; Breslau *et al.* 1982). Interpretation of studies which examine PTH changes are made difficult by differences in sensitivity of the radioimmunoassays used, the pulsatile nature of serum PTH concentrations, and the possible haemodilution effect of Na loading (Slatopolsky *et al.* 1982; Garel, 1987; Jubiz *et al.* 1972; Magliaro, 1983).

Ca absorption has been reported to increase in response to dietary Na intake (Meyer *et al.* 1976; Breslau *et al.* 1982). Meyer *et al.* (1976) observed that Ca absorption, as measured by <sup>47</sup>Ca uptake from calcium chloride increased by 8% on average in ten patients, including eight with normal parathyroid function and two with post-surgical hypoparathyroid function who were changed from a low-Na (10 mmol/d) to a high-Na diet (250 mmol/d) for 12 d. On an individual basis, Ca absorption increased in six of the eight subjects with normal parathyroid function and in the two with hypoparathyroid function. Using a similar study design, Breslau *et al.* (1982) increased the Na intake (10–250 mmol/d) of eleven healthy subjects (six male, five female, average age 27 years) for 10 d and found a

significant increase in fractional intestinal Ca absorption from 0.39 to 0.49 as well as in serum 1,25-dihydroxycholecalciferol (from 38 to 51 pg/ml). However, in contrast to the findings of Meyer *et al.* (1976), two patients with post-surgical hypoparathyroidism did not show similar increases. Breslau *et al.* (1982) explained the difference by suggesting that the patients in the earlier study were incorrectly diagnosed as having hypoparathyroidism, since the subjects were normocalcaemic during the study due to vitamin D treatment. It was concluded that Na-induced increases in Ca absorption were mediated by PTH.

However, Breslau *et al.* (1985) found no increase in intestinal Ca absorption in seven osteoporotic post-menopausal women maintained on a constant diet containing 10 mmol Na and 400 mg Ca/d for 10 d when Na intake was increased to 250 mmol/d for a further 10 d. Serum concentrations of 1,25-dihydroxycholecalciferol and PTH were also unchanged in response to the increase in Na intake. The authors concluded that post-menopausal women with osteoporosis have impaired adaptation of the parathyroid-vitamin D axis and of intestinal Ca absorption to salt-induced urinary Ca loss which may result in negative Ca balance and contribute to the development of osteoporosis in these women.

McParland *et al.* (1989) reported that there was no increase in mean strontium absorption (an index of Ca absorption) in nine healthy post-menopausal women (mean age, 67 years) consuming low-salt diets when they were supplemented with 100 mmol Na daily for 10 d. Urinary cAMP increased significantly for the group and also in each subject, indicating an increase in serum PTH. However, serum 1,25-dihydroxycholecalciferol showed a definite increase in only three subjects, remained largely unchanged in the other six and did not increase significantly for the group overall.

The effect of salt on Ca balance has received little study. While Goulding *et al.* (1986) have suggested that the daily Ca requirement to maintain Ca balance is higher in individuals consuming a high-Na diet than in individuals consuming a low-Na diet this has not been established in balance studies. Fujita *et al.* (1984) found that, despite a marked increase in urinary Ca excretion, Ca balance was not significantly affected in eight healthy subjects in response to oral salt loading (100 mmol/d) together with frusemide administration (80 mg/d) for an 8 d period. They observed significant increases in mean serum PTH, and in mean nephrogenous and total cAMP excretion and a significant decrease in faecal Ca excretion (365 v. 294 mg Ca/d). These results suggest that calciuria was compensated for by increased Ca absorption mediated by increased serum PTH but reduced endogenous Ca loss could also have contributed. Indeed, the effect of salt loading on endogenous Ca secretion into the gastrointestinal tract (approximately 150 mg/d in human adults; Schaafsma, 1983) has not been studied.

Thus, the available evidence suggests that healthy individuals adapt to Na-induced calciuria by a PTH-mediated increase in intestinal Ca absorption. However, this adaptive mechanism does not appear to function in all individuals (e.g. those with impaired parathyroid function, post-menopausal women with osteoporosis, as well as some healthy post-menopausal women) and even in those individuals who appear to adapt, the increase in net Ca absorption may not be sufficient to offset the increase in urinary Ca losses (Breslau *et al.* 1982). Furthermore, the capacity for such adaptation may be limited by low dietary Ca intakes, poor vitamin D status, impaired renal function or poor intestinal Ca absorption.

Thus, there is a need for further studies to clarify whether and in what circumstances Na-induced calciuria may lead to negative calcium balance.

## EFFECT OF SODIUM INTAKE ON BONE METABOLISM AND OSTEOPOROSIS IN MAN

The possible effects of a high dietary Na intake on bone metabolism have received little attention. To date, only two studies have investigated the effect of high Na intakes on bone mass in man.

Nordin & Polley (1987) reported that forearm mineral density, corrected for age and years since menopause, was significantly and negatively correlated with 24 h urinary Na excretion in a cross-sectional study of 440 healthy post-menopausal women.

A 9-month intervention study examining the effect of moderate salt restriction (to 85 mmol/d) on bone metabolism was carried out on thirty-four post-menopausal women consuming high-Ca (> 1000 mg/d) diets (Nordin & Polley, 1987). Salt restriction did not reduce the rate of bone loss, as assessed by the rate of change of forearm mineral density, which continued at a similar rate to that in matched controls (*n* 60) on an unrestricted diet. The authors suggested that salt restriction might have been more effective in decreasing bone loss in women consuming a low-Ca diet. However, the salt restriction achieved in this study was less than intended, i.e. while a reduction in 24 h urinary Na excretion did occur in the salt-restricted group, mean 24 h urinary Na remained higher than 100 mmol and the difference between the salt-restricted group and controls was only of the order of 20–30 mmol. Furthermore, compliance with salt restriction was assessed by only two 24 h urine samples over the entire 9-month intervention period.

There is considerable evidence that urinary hydroxyproline, which is a marker for bone resorption (Klein *et al.* 1964) is significantly and positively associated with Na intake. Goulding (1981) reported that the Na:creatinine ratio was positively correlated with the Ca:creatinine ratio and with the hydroxyproline:creatinine ratio in fasting urine samples obtained from 574 women aged 16–82 years. Urinary Na:creatinine ratio was also positively correlated with urinary Ca:creatinine ratio and urinary hydroxyproline:creatinine ratio in a cross-sectional study of 546 healthy post-menopausal women (Nordin & Polley, 1987). Similarly, positive associations have been found between urinary Na and urinary Ca and hydroxyproline excretion when dietary Na intake has been directly increased by 100 mmol/d in young women (Goulding & Lim, 1983; Goulding *et al.* 1986). Moreover, the Na-induced increase in Ca and hydroxyproline excretion was apparent irrespective of dietary Ca intake (200 mg or 1500 mg Ca/d; Goulding *et al.* 1986).

One reservation about the previously described studies is that dietary hydroxyproline was not controlled and dietary hydroxyproline may affect urinary hydroxyproline excretion (Sjoerdsma *et al.* 1965; Kivirikko, 1970). However, Goulding & MacDonald (1986) found that 81% of the variation in urinary hydroxyproline was explained by the variation in urinary Na in a healthy 35-year-old woman during one menstrual cycle while consuming a hydroxyproline-free diet, suggesting that increases in salt intake may increase bone resorption. Furthermore, McParland *et al.* (1989) reported increased urinary hydroxyproline excretion in nine healthy post-menopausal women consuming a low-salt diet when they were supplemented with 100 mmol Na for 10 d and gelatin was excluded from the diet.

In contrast, Castenmiller *et al.* (1985) reported that the Na-induced increase in urinary Ca excretion observed in young males while consuming diets containing 1.5–2.0 g Ca/d was not associated with an increase in urinary hydroxyproline excretion. They suggested that the extra Ca excreted was not derived from bone but may have been derived from increased absorption or by a decrease in endogenous loss. However, these variables were not measured. Goulding *et al.* (1986) have suggested that the lack of effect of Na on urinary hydroxyproline in the study of Castenmiller *et al.* (1985) may be due to the high passive

absorption of dietary Ca which may have depressed the PTH–vitamin D axis. However, Goulding *et al.* (1986) found that urinary hydroxyproline was increased in young women despite a high Ca intake (1.5 g/d).

In order to monitor the effects of dietary change on bone remodelling and to provide a more accurate assessment of bone status, future studies should measure a range of bone-turnover markers. Several markers, in addition to urinary hydroxyproline, provide an indication of bone-turnover status, e.g. serum osteocalcin and alkaline phosphatase (EC 3.1.3.1) bone isoenzyme (indices of bone formation) and urinary hydroxylysine (index of bone resorption; Delmas, 1988; Taylor *et al.* 1988). For example, (McParland *et al.* 1989) reported that serum osteocalcin concentration was increased in healthy post-menopausal women supplemented with 100 mmol Na/d, indicating increased formation of bone.

### CONCLUSIONS

Studies on rats have clearly shown that Na-induced calciuria which is not compensated for by increased Ca absorption or reduced endogenous Ca loss leads to PTH-mediated bone resorption. However, very high levels of salt loading were used in these studies and the relevance of such studies to humans is unclear, particularly given the known differences in Ca metabolism between rodents and humans.

In man, Na-induced calciuria has been clearly demonstrated in many studies and the magnitude of this effect within the usual range of Na intakes is significant in relation to overall Ca metabolism. There is also evidence of considerable inter-individual variation in the hypercalciuric effect of Na and the basis of this variation has not been investigated.

The available evidence suggests that healthy individuals adapt to Na-induced calciuria by a PTH-mediated increase in intestinal Ca absorption. However, this adaptive mechanism does not appear to function in all individuals (e.g. those with impaired parathyroid function, post-menopausal women with osteoporosis, as well as some healthy post-menopausal women) and even in those individuals who appear to adapt, the increase in net Ca absorption may not be sufficient to offset the increase in urinary Ca losses. Furthermore, the capacity for such adaptation may be limited by low dietary Ca intakes, poor vitamin D status, impaired renal function or poor intestinal Ca absorption. The effect of salt loading on endogenous Ca secretion into the gastrointestinal tract or on overall Ca balance has not been investigated and there is a need for studies to clarify whether and in what circumstances Na-induced calciuria may lead to negative Ca balance.

The possible effects of a high dietary Na intake on bone metabolism have received little attention. While there is evidence of an association between high salt intakes and increased bone resorption (as indicated by increased urinary hydroxyproline) it has not been established if this results in net bone loss. In the only longitudinal study of salt restriction on bone mass reported to date there was no evidence of an association of Na intake with bone mass.

Thus, the evidence for an association between Na intake and osteoporosis in man is not clear or strong enough at present to justify intervention at an individual or population level. However, there are still many unresolved questions regarding the Na–Ca relationship and there is a need for more studies on the effect of salt on bone metabolism, particularly in post-menopausal women.

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