PNL best wishes AJC

Food and Chemical Toxicology 38 (2000) 237–253

PERGAMON OSTEOPOROSIS 18B

COHEN2000

www.elsevier.com/locate/foodchemtox

Review

Review of Risk Factors for Osteoporosis with Particular Reference to a Possible Aetiological Role of Dietary Salt

A. J. COHEN[1]* and F. J. C. ROE[2]

[1]Toxicology Advisory Services, Hamilton House, 17 Cedar Road, Sutton, Surrey SM2 5DA and [2]11B Raymond Road, Wimbledon, London SW19 4AD, UK

(Accepted 30 July 1999)

Summary—Laboratory animal, clinical and epidemiological studies in the published literature have been reviewed in order to establish whether excessive salt intake is an important risk factor for the development of osteoporosis and whether an intervention strategy based on salt restriction would be beneficial in the prevention of osteoporosis. Genetic factors appear to be far more important than the combination of nutritional, hormonal, environmental and lifestyle factors in the pathogenesis of osteoporosis. The most important single non-genetic factor is oestrogen deficiency in postmenopausal women. Preventive measures should be aimed at maximizing peak bone mass at skeletal maturity and retarding bone loss thereafter. Apart from postmenopausal oestrogen deficiency, various factors have been incriminated as risk factors for osteoporosis, and these include age at menarche, age at and years since menopause, insufficient physical exercise, alcohol, smoking, low calcium intake, low or high protein intake and high intake of phosphorus, sodium or caffeine. Many of the risk factors are considered to be weak, although when combined they could impact significantly on bone health. Increased intakes of various nutritional factors (potassium, magnesium, zinc, vitamin C), fibre and alkaline-producing fruit and vegetables favour adult bone health. Calcium homeostasis is normally well regulated such that increased calcium loss via the urine leads to increased calcium absorption from the gut. However, the duration of this adaptive process may be greater than that of many of the studies demonstrating that increased salt intake leads to both increased sodium and calcium in the urine. In any case, higher urinary calcium output appears to be seen only in a minority of humans in response to increased salt intake. As numerous factors—genetic, nutritional, hormonal and lifestyle—are involved in the maintenance of calcium homeostasis, it is difficult to devise human studies which adequately take into account all the important factors. Another difficulty is that many past studies have relied on imprecise methods for the measurement of bone resorption. Nor have studies based on the use of the laboratory rat produced clear answers to the problem because the rat, as a species, is uniquely deficient in its ability to handle the relevant minerals. Limited studies to date indicate that increased sodium intake neither exerts a consistent effect on various biomarkers of bone health nor leads to irreversible changes in the bone modelling process in men or in pre- or postmenopausal women. We conclude from the available evidence that increased sodium (or salt) intake is not an important risk factor for osteoporosis and that a reduction of salt intake from 9 to 6 g/day in the diet would not be beneficial as an intervention measure in the prevention of osteoporosis. More research is needed to (i) assess the effects (especially long-term) of various nutrients including sodium on bone health, (ii) assess the long-term value of any intervention strategy involving reduced intake of a particular nutrient such as sodium; and (iii) determine whether subpopulations exist particularly in the elderly (e.g. sodium-responsive subjects) in which adaptation to sodium-induced hypercalciuria may be compromised. General prudence dictates that excessively high levels of dietary salt should be eschewed by those persons with raised blood pressure or a limited range of genetic disorders. However, for the generally healthy person there is no sound evidence that the consumption of salt at the present average level of 9 g/day constitutes a risk factor for osteoporosis.

Keywords: salt; osteoporosis; sodium chloride; bone health; calcium homeostasis; bone resorption.

Abbreviations: AMP = adenosine monophosphate; BMD = bone mineral density; HP = hydroxyproline; hPTH = human parathyroid hormone (recombinant); HRT = hormone replacement therapy; IGF = insulin growth factor; PTH = parathyroid hormone; SD = standard deviation.

*Corresponding author. Tel: (0)20 8642 8265; Fax: (0)20 8642 2135.

0278-6915/00/$ - see front matter
PII S0278-6915(99)00145-3

Introduction

General considerations on osteoporosis

Osteoporosis is a skeletal disease characterized by low bone mass and disruption of bone architecture, resulting in reduced bone strength and increased risk of fracture (Waine, 1997). Diagnosis is typically based on bone mineral density measurements or a history of fracture following minimal trauma (Compston, 1997; Cooper and Dennison, 1997).

Osteoporosis is a major public health problem, especially in elderly Caucasian women. Osteoporotic fractures are claimed to affect 50% of women and 30% of men aged over 50 years (Prince, 1997). In the UK and USA, respectively 150,000 and 1.2 million fractures relating to osteoporosis occur each year (Cooper and Dennison, 1997; Lyles, 1989; Ralston, 1997). In the USA, by age 90 one in every three women and one in every six men will have suffered a hip fracture (Lyles, 1989). In the UK, about 5 million people suffer from osteoporosis (Waine, 1997). The incidence of osteoporosis is lower in Japan and other Asian countries than in Europe and the USA (Draper, 1994; Lau and Woo, 1994). However, the incidence of osteoporosis is rising in all these regions in association with increasing longevity.

The main clinical manifestations are back pain, loss of height, spinal deformity and fractures of the vertebrae, hips, wrists and, to a lesser extent, other bones (Riggs, 1988). Assessment of bone density by dual-energy X-ray absorptiometry provides the best non-invasive measure of future fracture risk (Cooper and Dennison, 1997); peripheral quantitative computed tomography can also be used (New *et al.*, 1996b). The broadband ultrasound attenuation technique for measuring bone mass has recently been developed (New *et al.*, 1997b).

Biochemical markers of bone formation include serum osteocalcin and serum bone-specific alkaline phosphatase and of bone resorption urinary type I collagen C-telopeptide and urinary pyridinoline and deoxypyridinoline (pyridinium crosslinks of collagen) (Adachi *et al.*, 1997; Delmas, 1992; Delmas *et al.*, 1997; Ginty *et al.*, 1998; Lietz *et al.*, 1997; New *et al.*, 1996b; Robins and New, 1997). Rapid bone loss is associated with changes in these biomarkers (Ross and Knowlton, 1998). Urinary hydroxyproline excretion is currently less used since it is no longer considered to be a reliable marker of bone resorption (Delmas, 1992; Drüeke, 1997; Evans and Eastell, 1995; Ginty *et al.*, 1998; Lietz *et al.*, 1997; Robins and New, 1997). Strontium absorption tests are used to assess the intestinal absorption of calcium (Milsom *et al.*, 1987; Reid *et al.*, 1986).

Conditions associated with osteoporosis

Type I or postmenopausal osteoporosis occurs usually 10–15 years after the menopause with fractures of the trabecular-rich bones such as the vertebrae and distal forearm. Type 2 or senile osteoporosis, which occurs mainly after 70 years of age, is two to three times more prevalent in women than in men, and affects both trabecular and cortical bones. Idiopathic osteoporosis is rare and occurs in children/young adults of both sexes with normal gonadal function (Berkow *et al.*, 1992; Lyles, 1989; Riggs, 1988).

Conditions associated with primary and secondary osteoporosis are shown in Table 1. Genetic fac-

Table 1. Conditions associated with osteoporosis[a]

Primary osteoporosis is associated with	Secondary osteoporosis may be associated with
· ageing	· amenorrhoea
· menopause	· long-term or high-dose oral corticosteroid use
· impaired adult peak bone density	· hyperthyroidism
	· immobilization
	· rheumatoid arthritis
	· anorexia nervosa
	· malignant disease, especially myeloma
	· excessive alcohol intake
	· smoking
	· malabsorption
	· female hypogonadism
	· male hypogonadism
	· hyperprolactinaemia
	· Cushing's syndrome
	· thyroxine treatment
	· increasing age, especially if associated with being institutionalized or housebound
	· chronic liver disease
	· chronic inflammatory bowel disease
	· multiple sclerosis/chronic inflammatory arthritis
	· treatments for endometriosis

[a]Data from Waine (1997).

tors are highly relevant in the pathogenesis of osteoporosis and are considered to be one of the most important determinants of bone mass and risk of osteoporotic fracture (Ralston, 1997). Data obtained from twins and families indicate that as much as 80% variance in bone mass within a population is genetically determined (Heaney and Burckhardt, 1991; Ralston, 1997; Seeman *et al.*, 1998). Bone density in later life depends on the peak achieved at skeletal maturity and on subsequent age-related bone loss, peak bone density being strongly determined by genetic factors (Cooper and Dennison, 1997). In addition, nutritional, hormonal, lifestyle and environmental factors play contributory roles in the development of this multifactorial disease, accounting for 20% of variance in bone mass within a population (Heaney and Burckhardt, 1991); the most important single aetiological factor is oestrogen deficiency in postmenopausal women (Nordin *et al.*, 1995).

Mineral homeostasis and hormonal control

The apparent solidity and characteristic shape of the bony skeleton is deceptive, and the fact that bone is a living tissue which is constantly undergoing renewal and remoulding under the influence of numerous factors including several hormones, minerals and vitamins can be overlooked. About one-third of the skeleton is composed of minerals (mainly calcium and phosphorus) with protein and collagen making up the remainder. The pharmacokinetics of these minerals is mainly regulated by parathyroid hormone (PTH), calcitonin and vitamin D (Lyles, 1989).

PTH maintains serum calcium levels by enhancing bone resorption and renal calcium reabsorption and activating vitamin D leading to increased intestinal calcium absorption. PTH also decreases renal reabsorption of phosphorus, resulting in increased phosphate excretion, lowered serum phosphate and maintenance of serum calcium. Serum PTH increases with age, possibly in response to decreased intestinal calcium absorption. Increased PTH could thus account for the age-related increase in bone loss. PTH binds to cell-membrane receptors in target organs (kidneys and bone) to activate adenylate cyclase resulting in the increased production of cyclic AMP. Enhanced urinary excretion of cyclic AMP is thus a marker of PTH action on the kidney (Lyles, 1989).

The hormone calcitonin is secreted by the C-cells of the thyroid and reduces serum calcium by inhibiting osteoclastic-mediated bone resorption. Calcitonin release is suppressed by hypocalcaemia and stimulated by hypercalcaemia (Lyles, 1989; Waine, 1997). The major effect of calcitriol, the active metabolite of vitamin D, is the enhancement of the intestinal absorption of calcium and phosphorus to satisfy bone mineralization. Serum calcitriol declines with age (Lyles, 1989). Certain abnormal hormonal states (e.g. hypogonadism, hyperthyroidism) stimulate bone resorption. Glucocorticoids can suppress bone growth and promote bone resorption and also decrease intestinal calcium absorption. These actions account for the commonly-seen corticosteroid-induced osteoporosis (Lyles, 1989).

Other hormones and humoral substances including prostaglandins, osteoclast activating factor, interleukin-1, lymphotoxin, tumour necrosis factor α and other cytokines have been found to increase bone resorption, although their contributory role in the pathogenesis of osteoporosis remains to be established (Lyles, 1989). More recently, the insulin-like growth factor IGF-1 has been implicated as an important determinant of bone mineral density (Rosen *et al.*, 1998).

Dr Alexander L. Macnair, an independent consultant in preventive medicine, has recently summarized the position with regard to sodium and calcium homeostasis as follows (A.L. Macnair, personal communication, 1998):

"The physiology of calcium homeostatis is complex but well established. Although about 99% of the kilogram or more of calcium in the average human body is in the bones, the calcium that is important is the 0.5% or so that exists as free ions in the plasma at a concentration of 1.01 to 1.26 mmol/l (about half of the calcium in plasma is bound to albumin or complexed with citrate and phosphate giving total plasma calcium concentration of 2.2 to 2.6 mmol/l or 8.5 to 10.5 mg/100 ml). Ionic calcium is maintained at its level by the interaction of processes, largely under the control of the parathyroid hormone, that constantly feed calcium into and withdraw calcium from the extracellular fluid. Calcium enters the plasma by absorption from the small intestine or by resorption from bone. It leaves the extracellular fluid in large amounts in secretions entering the intestine, in lesser amounts by deposition in bone, or in the urine and there are small losses in sweat. The parathyroid hormone has as its principal function the maintenance within close limits of the plasma concentration of ionic calcium. Free calcium ions are as important as sodium and potassium ions in cell regulation. The parathyroid hormone acts directly on bone (increasing dissolution of bone mineral) and kidney (reducing renal clearance of calcium) and indirectly on intestinal absorption of calcium by regulating synthesis in the kidney of a second hormone 1-alpha 25 dihydroxycholecalciferol [$1,25(OH)_2CC$] from a vitamin D derivative produced in the liver. This latter hormone stimulates synthesis of calcium binding protein in the intestine and thereby enhances the absorption of calcium. Parathyroid hormone production is itself closely regulated by the concentration of free calcium ions in the plasma and this feedback system is probably the fundamental homeostatic mechanism although other hormones (growth hormone,

cortisol, oestrogens and prolactin) have effects on the rate of production of $1,25(OH)_2CC$. Thus, with such a highly regulated system for calcium homeostasis, it seems inherently unlikely that the amount of sodium in the urine will significantly alter calcium homeostasis."

Diagnosis and assessment of osteoporosis

Where evidence of established osteoporosis exists (e.g. history of fracture fragility or radiological evidence of osteopenia), assessment of bone mass by non-invasive bone densitometry is used to confirm the diagnosis. The response to treatment can also be assessed using bone densitometry and radiology (Compston, 1997). In order to provide a more consistent approach to the assessment of osteoporosis, especially in investigative studies, WHO, in 1994, introduced a classification scheme based on three levels of bone mineral density (BMD) measured relative to the population mean in young adults: (i) normal—BMD values at a threshold set at 1 SD below the mean; (ii) osteopenia—BMD values at 1–2.5 SDs below the mean; and (iii) osteoporosis—BMD values at >2.5 SDs below the mean (Cooper and Dennison, 1997).

Osteoporosis is the most common metabolic bone disease; others include osteomalacia, Paget's disease and various malignancies. Osteomalacia (a disorder in which newly-formed osteoid tissue fails to mineralize normally) may be confused with osteoporosis on radiology but can be distinguished by abnormal serum chemistry and bone biopsy (Berkow *et al.*, 1992; Lyles, 1989).

Treatment of osteoporosis

Treatment of established osteoporosis includes not only surgery and supportive measures but also therapeutic agents which prevent further bone loss and reduce the risk of new fractures. Antiresorptive agents act by decreasing bone resorption and, although they do not increase bone mass, they can decrease the fracture risk even in elderly patients with a low bone mass (Berkow *et al.*, 1992; Compston, 1997; Cooper and Dennison, 1997; Lyles, 1989; Riggs, 1988). Oestrogen, calcitonin and supplements of calcium/vitamin D (including calcitriol) have been used in the treatment of established osteoporosis, with calcium/vitamin D serving more as adjuvants to other treatments.

During bone resorption, osteoclasts remove a specific amount of bone before undergoing programmed cell death (apoptosis). The bisphosphonates etidronate and aledronate are thought to block bone resorption by promoting osteoclast apoptosis (Berkow *et al.*, 1992; Ralston, 1997; Rosen, 1997). Etidronate has also been found to prevent bone loss and fractures in patients treated with corticosteroids, drugs known to induce osteoporosis (Adachi *et al.*, 1997). There is evidence to indicate that the bisphosphonates not only suppress bone loss but also stimulate bone formation, leading to increased bone mass (Bonn, 1996; Rosen, 1997). Other so-called formation-stimulating agents include recombinant human parathyroid hormone (hPTH) (Bonn, 1996), sodium fluoride (Berkow *et al.*, 1992; Bonn, 1996; Riggs, 1988) and the non-steroidal benzothiophene, raloxifene (Delmas *et al.*, 1997).

Data from the oophorectomized rat, the standard animal model for postmenopausal osteoporosis, indicate that hPTH can activate two signalling pathways in osteoblasts: adenylate cyclase (a trigger for osteogenesis) and protein kinase C (which stimulates osteoblast proliferation but not bone growth) (Bonn, 1996). Interestingly, hPTH stimulates bone-building osteoblasts when present at physiological concentrations but stimulates bone-resorbing osteoclasts when present at supraphysiological concentrations. Apart from the bisphosphonates, the formation-stimulating agents are still in the developmental stage and unpleasant side-effects are associated with sodium fluoride treatment (Bonn, 1996).

Prevention of osteoporosis

Bone density peaks at around age 35 years and thereafter declines in both men and women with bone loss being particularly marked in postmenopausal women. Hence, measures to prevent osteoporosis should be aimed at both maximizing peak bone density at skeletal maturity and at retarding the subsequent bone loss.

Genetic, nutritional, hormonal, environmental and lifestyle factors are all known to influence bone health. One obvious approach is the promotion of beneficial factors (e.g. adequate calcium and vitamin D nutrition and physical activity) and discouragement of risk factors (e.g. heavy alcohol consumption and cigarette smoking) in the general population. Another approach is the identification of high-risk individuals. In the future, genetic testing may enable prophylactic treatment to be implemented (Ralston, 1997). Thus, future identification of polymorphisms of genes [e.g. those for vitamin D receptor (Eisman, 1998; Wood and Fleet, 1998), oestrogen receptor, transforming growth factor β, collagen type I and interleukin 6, known to relate to bone mass or osteoporotic fracture], which can consistently predict low bone density or fracture, might serve as a means of screening for high risk individuals (Ralston, 1997).

Currently, hormone replacement therapy (HRT) in postmenopausal women is an important intervention strategy in the primary prevention of bone loss and hence osteoporotic risk. However, possible increased risks of some forms of cancer and of thromboembolism contra-indicate the use of HRT, certainly in some women. Apart from HRT, various therapeutic agents known to retard bone loss are used in the treatment of established osteo-

porosis, but their value in the primary prevention of bone loss is less certain (Cooper and Dennison, 1997).

Evaluation of various risk factors in osteoporosis

Risk factors considered in the review by Nordin et al.(1995)

Oestrogen deficiency is the most important single cause of osteoporosis, as evidenced by the high incidence of postmenopausal osteoporosis. However, individual variations in peak bone density at skeletal maturity and the rate of bone loss thereafter can be influenced by other contributory risk factors.

Nordin *et al.* (1995) reviewed the relative importance of various risk factors based on data from the published literature as well as data generated by themselves in pre- and postmenopausal women. The genetic, nutritional and lifestyle factors considered and the conclusions reached are shown in Table 2. The following risk factors were considered weak or non-significant: exercise (except at extremes), age at menarche, age and type of menopause, length of reproductive life and parity. Low dietary calcium is deemed to be a weak risk factor, being overshadowed by poor calcium absorption and increased calcium excretion. Smoking is a less important risk factor than excessive alcohol consumption but the combination of smoking and alcohol may be of more significance. Although many of the risk factors are considered to be weak, when taken together they could, between them, account for nearly 40% of the variance on bone status in terms of severity on the osteoporosis scale. It is noteworthy that sodium was not specifically considered to be a risk factor by Nordin *et al.* (1995), although reference was made to its urinary calcium-enhancing property. Certain variables, such as plasma albumin, serum dehydroepiandrosterone and skin thickness, showed reduction in postmenopausal osteoporosis and were included in the review by Nordin *et al.* (1995) since they were deemed to be of possible relevance in the pathogenesis of the disease.

Risk factors considered by other workers

Studies of risk factors considered by other authors are summarized in Table 3. We have not attempted to review extensively the various risk factors, other than salt, that have been implicated in osteoporosis. High intakes of protein and caffeine as well as smoking and a low-protein diet have been reported to be associated with adverse effects on calcium balance and/or bone health. Remarkably, one study (Cumming *et al.*, 1997) observed an increased bone fracture risk with the current use of a calcium supplement, but this finding was dismissed on the grounds of inadequate control of confounding by potential differences in

Table 2. Risk factors for osteoporosis reviewed by Nordin *et al.* (1995)

Risk factor	Comments on significance as risk factor
Genetic make-up	Strong genetic component in peak bone mass but less apparent after menopause
Exercise	Bone formation from vigorous exercise and bone loss from immobilization; bone health not significantly affected by variations in moderate, regular exercise
Age at menarche	Higher peak bone mass associated with early menarche unconfirmed; late menarche may have adverse effect on postmenopausal bone status
Age at menopause	Bone density reduction in postmenopausal women significantly correlated with years since menopause but not with age at menopause
Years since menopause	Both age and years since menopause both determinants of bone loss becoming more apparent with passage of time
Type of menopause	Generally-held view that oophorectomy increases osteoporotic risk not confirmed; type of menopause does not affect subsequent bone status
Length of reproductive life	Duration of period between menarche and menopause minimal effect on subsequent bone density
Parity	Child-bearing has no apparent long-term effect on bone density
Alcohol	Conflicting data on effect on bone density; social drinking may have modest adverse effect; drinkers showed higher 24-hour urinary Ca excretion and lower plasma alkaline phosphatase than non-drinkers; alcohol may act by depressing bone formation and increasing urinary Ca; alcohol effect greater than that of smoking
Smoking	Marginal adverse effect on bone density - possibly by reduction in Ca absorption; lesser effect than with alcohol but combination of alcohol and smoking probably the most significant
Body weight	Related to bone mass by common factor of bone size; relationship between body weight and bone density evident in post- but not premenopausal women; more due to effect on bone loss than on peak bone density
Ca intake	Ca deficiency causes osteoporosis in animals and Ca supplementation can retard bone loss in postmenopausal women; yet no relationship demonstrated between Ca intake (from diet histories) and bone status in postmenopausal women
Ca absorption	Ca absorption inversely related to Ca intake in normal but not in osteoporotic subjects; increasing decline in Ca absorption with increasing severity of osteoporosis
Urinary Ca excretion	Increase in morning urinary Ca/creatinine ratio (marker of obligatory Ca loss) with increasing severity of osteoporosis; Ca excretion major risk factor especially for vertebral compression
Plasma albumin	Age-related decline, most marked in postmenopausal osteoporosis
Serum dehydro-epiandrosterone sulfate (DHAS)	Age-related decline, most marked in postmenopausal osteoporosis
Skin thickness	Weak reduction in postmenopausal osteoporosis

use pattern in patients with varying degrees of osteoporosis.

Possible aetiological role of dietary salt in osteoporosis

Effect of dietary sodium on urinary calcium excretion

An increase in dietary sodium is associated with high urinary calcium excretion in men and women of all ages (Evans and Eastell, 1995). Although this relationship is unlikely to be linear, within the range 70–250 mmol sodium/day (spanning the UK dietary sodium intake), various studies have shown that an increase of 100 mmol sodium/day (equivalent to 5.8 g NaCl/day) causes an additional urinary excretion of about 0.6 mmol calcium/day in young men and women and in postmenopausal women (Evans and Eastell, 1995) (Table 4). In an analysis of 17 salt loading studies and 18 population surveys, the median ratios of urinary calcium/urinary sodium (mmol/100 mmol) were 0.69 and 1.15, respectively (Massey and Whiting, 1996) (Table 4). These data support the conclusion (Nordin *et al.*, 1993, 1994b) that a 100 mmol/day increase in dietary sodium intake would increase urinary calcium by 1 mmol/day. However, it should be realized that in a group of people, only a minority of subjects show a significant response in terms of sodium-induced hypercalciuria (sodium responsive) while the majority show little or no response (sodium-non-responsive) (Ginty *et al.*, 1998; Shortt and Flynn, 1990; Shortt *et al.*, 1988).

Biological significance of increased urinary calcium excretion

Increased urinary calcium excretion can result from increases in bone resorption or intestinal absorption or a reduction in renal reabsorption of the mineral. Data from various studies of the effects of dietary sodium on factors involved in calcium homeostasis are summarized in Table 5. In one important study (Breslau *et al.*, 1982), young adults responded to increased sodium intake with increases in urinary calcium, serum PTH and calcitriol and intestinal calcium absorption. Similar changes have been observed in patients with hypercalciuria and these have been reversed by treatment with a thiazide diuretic (Zerwekh and Pak, 1980). In contrast, the increased urinary calcium excretion following an increase in sodium intake in postmenopausal women was not accompanied by increases in serum

Table 3. Risk factors for osteoporosis considered by other workers

Risk factor	Principal findings	Reference
High protein intake	Causes hypercalciuria probably due to multiple factors including changes in acid-base balance; whether excess protein adversely affects bone health outside experimental setting remains controversial; ability to adapt to protein-induced hypercalciuria if Ca intake is adequate is a possibility	Anderson and Metz, 1995; Barzel and Massey, 1998; Heaney, 1998; Heaney and Burckhardt, 1995; Kerstetter and Allen, 1994; Massey, 1998; Metz *et al.*, 1993; Reid and New, 1997; Rizzoli *et al.*, 1998
Low protein intake	Associated with reduction in bone mineral density and osteoporotic hip fracture; protein supplementation may be beneficial	Bonjour and Rizzoli, 1995; Heaney and Burckhardt, 1995; Reid and New, 1997; Rizzoli *et al.*, 1998
Caffeine	High intake enhances urinary Ca excretion & bone loss in postmenopausal women on low Ca intake	Matkovic *et al.*, 1995[a]
Caffeine	Negative association with Ca balance in 168 women (aged 36–45 years)	Heaney and Recker, 1982
Caffeine	Review of published data concludes that 4 cups of coffee/day associated with decreased bone density although effect reduced or eliminated by adequate Ca intake	Harris, 1998
Ca intake	Cohort study in 9704 postmenopausal women; no association between dietary Ca intake & bone fracture risk; current Ca supplement use associated with increased risk, finding probably due to inadequately-controlled confounding by indication for use of Ca supplements	Cumming *et al.*, 1997
Physical activity	Regular exercise an important determinant of bone mineral density	Department of Health, 1998; Lamberg-Allardt *et al.*, 1995; Uusi-Rasi *et al.*, 1998
Smoking	Review of 13 studies of bone mineral density in smokers & non-smokers; smoking not important influence on peak bone density but associated with increased rate of subsequent bone loss; lower body weight, earlier menopause and oestrogen synthesis inhibition in smokers deemed of little or no importance; effect on androstenedione & cortisol may be important factors	Law, 1990
Smoking	Meta-analysis of 48 cross-sectional, cohort or case-control studies of differences in bone density & hip fracture rates in smokers & non-smokers; bone density reduced after but not before menopause in smokers versus non-smokers (about 2% for every 10-yr increase in age); hip fracture rate after age 50 higher in smokers; associations not explained by thinness, younger age at menopause, physical activity or oestrogenic status	Law and Hackshaw, 1997
Environmental contaminants	Lead and cadmium potential risk factors; relationship between aluminium and osteoporosis unclear	Goyer *et al.*, 1994

[a]Cited data.

Table 4. Effect of dietary Na on urinary Ca excretion

Study subjects	Na diet/ supplement (mmol)	Dietary Ca (mg)	Urinary Ca/urinary Na ratio (mmol/100 mmol)[a]	Reference
		Data compiled by Evans and Eastell (1995)		
Postmenopausal women (52–70 years old)	Usual diet + 51 or 102	Usual diet	0.6	Zarkadas *et al.*, 1989
Young men	122-278	1558)	0.6)	Castenmiller *et al.*, 1985
		1880)	0.5)	
Young women	10-250	400	0.6	Breslau *et al.*, 1985
Postmenopausal osteoporotic women	10-250	400	0.5	Breslau *et al.*, 1985
Young women	43-217	452-937	0.7	Shortt *et al.*, 1988
Postmenopausal women	70-170	850	0.6	McParland *et al.*, 1989
Study type		**Adult subjects**		**Urinary Ca/urinary Na ratio (mmol/100 mol)[a]**
		Data compiled by Massey and Whiting (1996)		
Salt loading (17 studies)	"Normal" males & females; hypertensive males & females; osteoporotic and post-menopausal females			range 0.30–2.3; median 0.69
Population survey	"Normal" males & females; pre- and post-menopausal women; elderly "normal" males			range 0.7–3.04 median 1.15

[a]100 mmol Na ≡ 2.3 g Na ≡ 5.8 g NaCl.

PTH or calcitriol or in intestinal calcium absorption (Breslau *et al.*, 1985). This lack of response is not unexpected, since serum calcitriol and intestinal calcium absorption decline with age, this being particularly marked in women with postmenopausal osteoporosis; moreover, in elderly individuals with/without osteoporosis, these age-related changes are not reversed by reduced dietary calcium intake (Breslau *et al.*, 1985). It would thus appear (Evans and Eastell, 1995) that young adults adapt to a high sodium diet by increased serum PTH, leading in turn to increased calcitriol production and to increased intestinal calcium absorption. While an increase in intestinal calcium absorption appears to be the adaptive mechanism in young adults, in the elderly enhanced urinary calcium excretion in response to increased sodium intake may be a consequence of increased bone resorption (Breslau *et al.*, 1985) (see Fig. 1). Based on an increase of urinary calcium by 0.6 mmol/day in response to an additional sodium intake of 100 mmol/day, it has been estimated that, for a woman with a total body calcium content of 900 g, this would be equivalent to an additional annual rate of bone loss of 1%, assuming the increased urinary excretion entirely emanates from increased bone resorption (Evans and Eastell, 1995; Zarkadas *et al.*, 1989).

The higher urinary calcium (after overnight fasting) in osteoporotic than normal postmenopausal women was not due to an increase in the filtered load of calcium but to a reduction in renal tubular reabsorption. This indicates that the calcium loss in the urine is more likely to be the cause rather than the effect of the bone resorption state (Nordin *et al.*, 1994a).

Evaluation of evidence implicating dietary sodium as an important risk factor in osteoporosis

The influence of nutrients on bone mineral density is still poorly understood and uncertain. Calcium intake is an important determinant in peak bone mass development and in retarding bone loss in postmenopausal women. The effects of other nutrients on bone mass have received less attention. Many studies of dietary influences on bone health have suffered from older and less reliable bone mineral density measuring techniques, weaknesses in dietary assessment methodology and failure to adjust for total energy intake and other confounding variables such as weight, height, smoking, socioeconomic status and physical activity. Moreover, the recent findings of higher bone mass and lower bone resorption in women consuming high intakes of potassium, magnesium, zinc, vitamin C and fibre as well as fruit emphasize the importance of taking into account the impact of variations in other nutrients when focusing on a particular nutrient (New *et al.*, 1995, 1996a,b, 1997a,b, 1998, 1999; Reid and New, 1997).

It can be seen from the studies summarized in Table 6 that dietary sodium has no consistent effect on various biomarkers of bone health.

It has been argued (Antonios and MacGregor, 1996; MacGregor, 1996) that a high salt intake is a major risk factor for osteoporosis, based on the following reported observations: dietary salt claimed to be the main determinant of urinary calcium excretion (McCarron *et al.*, 1981), negative correlation between urinary sodium excretion and bone density in postmenopausal women (Devine *et al.*, 1995), increased serum PTH and urinary hydroxyproline in postmenopausal women with increased salt intake (McParland *et al.*, 1989), suggestive evidence that increased urinary calcium caused by high salt intake may adversely affect bone health in young girls (Matkovic *et al.*, 1995), claim that patients with hypercalciuria have a reduction in bone mass, the magnitude of which is dependent on salt intake (Silver *et al.*, 1983), reduced salt intake is as effective as a thiazide diuretic in reducing urinary cal-

Table 5. Effect of dietary Na on Ca homeostasis

Study subjects	Diet/supplement treatment	Principal findings	Reference
Community-based; 4055 subjects		Poor correlation between dietary Na & 24-hour urinary Ca	Kesteloot and Joossens, 1990
38 healthy men and women, wide age range	Fixed Ca diet, 400 mg/day for 7 days	Highly significant correlation between 24-hour urinary Na & 24-hour urinary Ca	Sabto *et al.*, 1984
Postmenopausal women, 52–70 years old	Usual Na diet supplemented with 51 or 102 mmol/day of NaCl, 4 days/week for 3 weeks	Urinary Ca excretion increased by 0.5-0.6 mmol/day at both dose levels of NaCl	Zarkadas *et al.*, 1989
6 young men	Dietary supplementation 10-1500 mmol Na/day	Increased urinary Ca but no effect on serum PTH	McCarron *et al.*, 1981
11 young healthy subjects, 22–36 years old	Low Na (10 mmol/day) or high Na (250 mmol/day) diet plus fixed Ca diet (10 mmol/day) for 10 days	Increased dietary Na resulted in increases in urinary Na & Ca excretion, serum PTH & calcitriol & intestinal Ca absorption	Breslau *et al.*, 1982
7 healthy men	High Na intake/low Ca intake	Increases in urinary Na & Ca; no effect on serum PTH	Chan *et al.*, 1992
10 elderly women (mean 70 years old)	Low salt diet alone or with 100 mmol/day supplement, each for 10 days	Increases in urinary cyclic AMP & serum calcitriol; no increase in Ca absorption	McParland *et al.*, 1989
7 women with untreated postmenopausal osteoporosis	10 or 250 mmol/day Na for 10 days	No change in serum Ca, PTH or calcitriol or in Ca absorption	Breslau *et al.*, 1985
Postmenopausal women		Increasing Na intake by 50 mmol increases urinary Ca by 0.5 mmol	Nordin *et al.*, 1994b
Survey of 410 male and 476 female Japanese, aged 20-79 years	–	Positive correlations between urinary Na & Ca after allowance for sex, age, body weight & protein, Ca & P intakes; urinary Ca/Na ratios were 0.6 & 1.0 mmol Ca/100 mmol Na in under 50 and over 50 age groups respectively	Ito and Suyama, 1996
Two groups of 8 Na-sensitive & 8 Na-non-sensitive healthy young women	80 or 180 mmol Na/day for 14 days (Ca fixed at 12.5 mmol/ day)	Na-sensitive but not Na-non-sensitive women showed increased urinary Ca excretion; only 8/29 women found to be Na-sensitive to 40-200 mmol/day of Na for 7 days	Ginty *et al.*, 1998
Pre- and postmenopausal women	50 or 300 mmol Na/day for 7 days	Increase in dietary Na enhanced 24-hour urinary Na and Ca relative to creatinine in both age groups; urinary Ca increased by 0.5 & 0.7 mmol/100 mmole Na in pre- and postmenopausal women, respectively	Evans *et al.*, 1997
249 healthy men and 665 healthy women aged over 65 years	24-hour urinary Na & Ca measured at different Ca intakes	24-hour urinary Na & Ca significant correlation at Ca intakes of 12.2-29.1 mmol/day (greater in men than women) but not at 6.7 mmol Ca/day; highest serum PTH at lowest Ca intake	Dawson-Hughes *et al.*, 1996

cium in patients with hypercalciuria (Pak *et al.*, 1984), evidence in hypertensive patients that increased urinary calcium is compensated not by increased intestinal absorption but by bone resorption, and that hypertensive patients are more prone to bone demineralization (MacGregor and Cappuccio, 1993), severe bone demineralization in spontaneously-hypertensive rats (Izawa *et al.*, 1985), and thiazide diuretics decrease urinary calcium, increase bone density and reduce the risk of hip fracture (LaCroix *et al.*, 1990). Based on these various observations, it was considered that a reduction of salt intake from about 10 to 5 g/day in the general population could have a major beneficial effect on bone density and the subsequent development of osteoporosis (Antonios and MacGregor, 1996; MacGregor, 1996). The actual experimental findings obtained in these studies (Devine *et al.*, 1995; Izawa *et al.*, 1985; LaCroix *et al.*, 1990; McCarron *et al.*, 1981; MacGregor and Cappuccio, 1993; McParland *et al.*, 1989; Matkovic *et al.*, 1995; Pak *et al.*, 1984; Silver *et al.*, 1983) are summarized in Table 7, so that the effects directly attributable to changes in sodium (or salt) intake can be more clearly seen. It is apparent that in only three of the above studies was the effect of sodium (or salt) on indices of bone health actually investigated (Devine *et al.*, 1995; McParland *et al.*, 1989; Matkovic *et al.*, 1995). For reasons given below, we consider that none of these three studies provides evidence of an adverse effect on bone health.

As to the study showing increased urinary hydroxyproline in response to NaCl supplementation (McParland *et al.*, 1989), this biomarker is no longer considered to be a reliable indicator of enhanced bone resorption (Delmas, 1992; Drüeke, 1997; Evans and Eastell, 1995; Ginty *et al.*, 1998; Lietz *et al.*, 1997; Robins and New, 1997). Also, some evidence of bone formation (increased serum osteocalcin), albeit slight, was seen in the study by McParland *et al.* (1989), thus confounding the hydroxyproline response. Although other studies have shown a relationship between increased sodium intake and increased urinary hydroxypro-

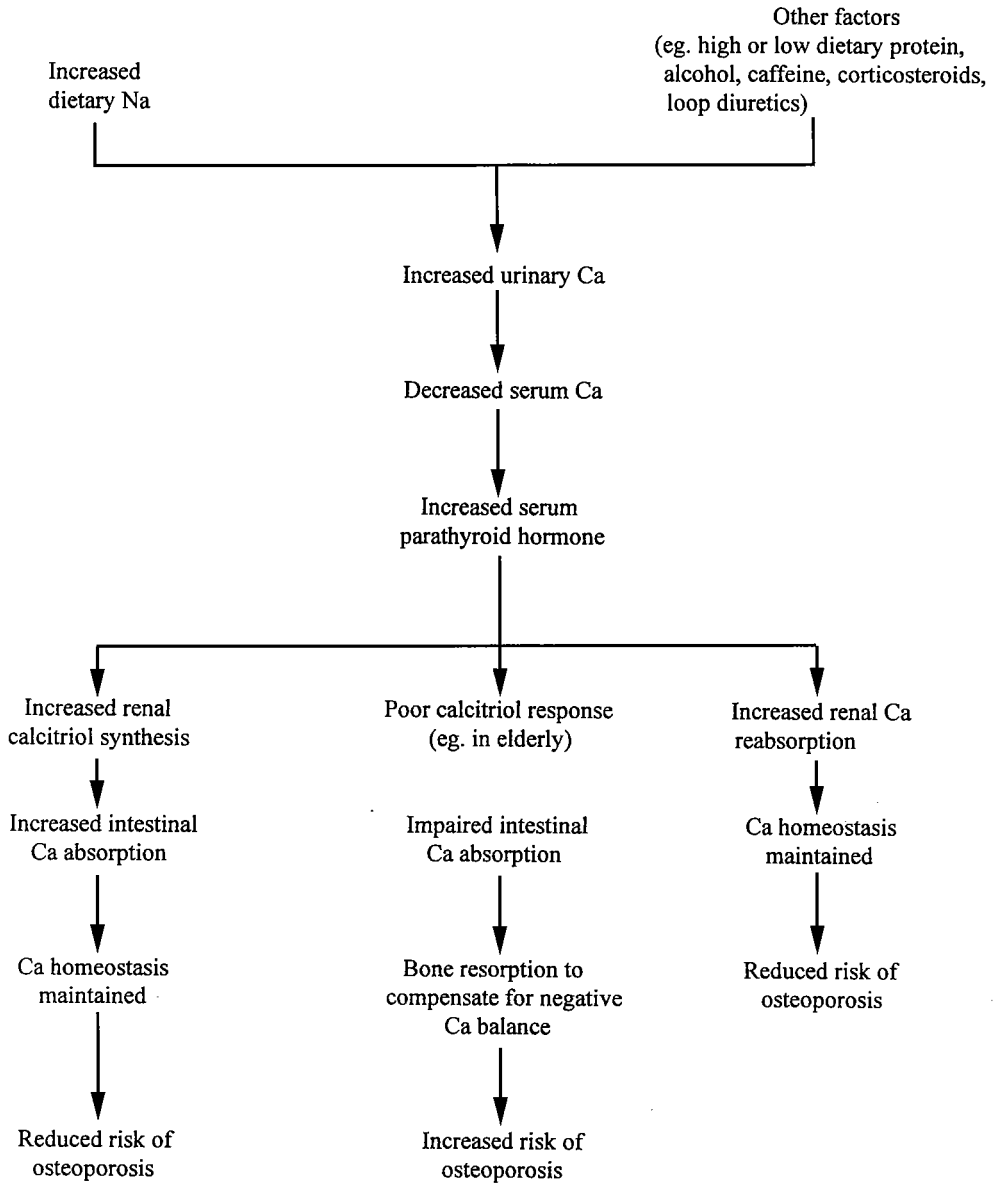

Fig. 1. Possible pathogenetic pathways leading to osteoporosis [adapted from Evans and Eastell (1995)].

line, no consistent effect has been seen with respect to the more reliable biomarkers of bone resorption (urinary pyridinoline and deoxypyridinoline) (Table 6).

As to the negative correlation between urinary sodium and bone density in postmenopausal women (Devine *et al.*, 1995), the correlation was weak ($r = 0.19$) and the study was only controlled for a limited number of confounding variables (calcium intake, body weight, physical activity). Allowance for further confounding variables (total energy intake, age, height, smoking, socioeconomic status) has been made in other studies (New *et al.*, 1996a, 1997a). Moreover, conflicting data have been obtained in other studies investigating a possible relationship between increased sodium intake and bone loss (Table 6).

With respect to the cross-sectional study in young girls (Matkovic *et al.*, 1995), Antonios and MacGregor (1996) regarded the findings obtained as providing suggestive evidence of a negative association between increased urinary calcium excretion and bone mass indices; however, this study failed to show a direct association between urinary sodium and any of the bone mass indices studied, despite urinary sodium ranging from 25 to 362 mmol/day in the group of 370 females. Indeed, the mean urinary calcium/sodium ratio was 1.93 mmol calcium/100 mmol sodium, almost twice the median ratio of the adult population (see Table 4). The authors of this study considered that

Table 6. Effect of dietary Na on various biomarkers of bone health in humans

Bone health biomarker	Na status	Effect on biomarker	Reference
Urinary hydroxyproline	Na loading	No effect	Castenmiller *et al.*, 1985
	Na loading/increased urinary Na	Increase	Chan *et al.*, 1992; Goulding, 1981; Goulding *et al.*, 1986; Goulding and Lim, 1983; Goulding and McDonald, 1986; Itoh and Suyama, 1996; McParland *et al.*, 1989
	Na restriction	Decrease	Need *et al.*, 1991; Goulding *et al.*, 1986
Urinary pyridinoline	Na loading	No effect	Ginty *et al.*, 1998
	Dietary Na	No correlation	New, 1998
Urinary deoxypyridinoline	Na loading	No effect	Evans *et al.*, 1997[a]; Ginty *et al.*, 1998; Lietz *et al.*, 1997
	Dietary Na	No correlation	New 1998
	Na loading	Increase	Evans *et al.*, 1997[a]
Serum osteocalcin	Na loading	No effect	Evans *et al.*, 1997[b]; Ginty *et al.*, 1998
	Dietary Na	No effect	New, 1998
	Na loading	Increase	McParland *et al.*, 1989
	Na loading	Decrease	Evans *et al.*, 1997[b]
Serum bone-specific alkaline phosphatase	Na loading	No effect	Ginty *et al.*, 1998
Bone mineral density	Na restriction	No effect	Nordin and Polley, 1987
	Dietary Na	No correlation	New, 1998
	Dietary Na	Slight increase	Greendale *et al.*, 1994
	Urinary Na	No correlation	Dawson-Hughes *et al.*, 1996; Matkovic *et al.*, 1995
	Urinary Na	Negative correlation	Devine *et al.*, 1995

[a]No effect in premenopausal but increase in postmenopausal women. [b]Decrease in premenopausal but no effect in postmenopausal women.

the intakes of protein, caffeine and phosphorus were not high enough to have had any enhancing effect on urinary calcium excretion and it was presumed, therefore, that the main determinant of increased urinary calcium excretion in this study was increased urinary sodium.

It would appear from major works (Draper, 1994) and proceedings of international symposia on nutritional aspects of osteoporosis held in 1990 (Burckhardt and Heaney, 1991), 1993 (Wahlqvist *et al.*, 1994), 1994 (Burckhardt and Heaney, 1995) and 1997 (Burckhardt *et al.*, 1998), that there has been a significant shift of opinion regarding the importance of dietary sodium intake as a risk factor for osteoporosis. Thus, while Nordin *et al.* (1991) concluded that sodium must be an important risk factor, scant attention was given to this possibility by the same group in major contributions by Nordin and Need (1994) and Nordin *et al.* (1995). Moreover, reference was made to the absence of direct evidence that high sodium intake is an important risk factor for osteoporosis (Lau and Woo, 1994) and also to the low incidence of osteoporosis in south-east Asia, where high salt intake is common, indicating that sodium is not a major risk factor (Draper, 1994). In a major review of nutritional factors in osteoporosis, no reference was made to dietary sodium as a risk factor for the disease (Heaney, 1993). Finally, a UK advisory group on nutrition and bone health (Department of Health, 1998) did not make any reference to increased salt or sodium being a risk factor for osteoporosis.

Although recognizing that young adults, but not postmenopausal women, may adapt to a high sodium intake by a mechanism avoiding bone resorption (Evans and Eastell, 1995), it was felt that before sodium reduction could even be considered as a preventive measure, it was necessary to see whether (i) older subjects consistently show evidence of increased bone resorption in response to increased sodium intake, and (ii) any beneficial effects of sodium restriction on bone density in the short-term can persist over several years in many subjects.

As clearly stated in the context of sodium intake and hypertension, public health recommendations must be based on proof of safety and benefit (Alderman, 1997). It is argued that this should apply not only to the primary aim of the intervention but also to any secondary changes resulting therefrom. Nevertheless, MacGregor's group (Antonios and MacGregor, 1995; Antonios and MacGregor, 1996; Cappuccio, 1996; Cappuccio and MacGregor, 1997; MacGregor, 1996, 1997; MacGregor and Cappuccio, 1993; MacGregor and de Wardener, 1998) and others (Devine and Prince, 1996) continue to campaign for dietary salt reduction, essentially on the outcome of a limited number of studies (Devine *et al.*, 1995; McParland *et al.*, 1989; Matkovic *et al.*, 1995) purportedly reporting an adverse effect of increased salt intake on bone health. The UK advisory group on nutrition and bone health (Department of Health, 1998) considered that a previously-made recommendation for healthy living, namely reduction in dietary sodium intake from 150 to 100 mmol/day, would have no adverse effect on bone health and might be beneficial.

Calcium absorption and the need for calcium balance studies

Calcium is mainly absorbed in the upper part of the small intestine along with monosaccharides, particularly glucose, which is very efficiently absorbed in this part of the intestinal tract. The disaccharide lactose, present in milk, has to be broken down into glu-

Table 7. Studies reportedly implicating increased Na intake as a risk factor for osteoporosis

Statements by Antonios and MacGregor (1996) implicating salt as risk factor	Principal findings reported in original papers cited by Antonios and MacGregor (1996)	Reference
Dietary salt main determinant of urinary Ca excretion	6 normal men given dietary Ca (400 mg/day) & Na (10, 300, 800 mmol/day for 7, 3 & 3 days respectively & 800 mmol/day in diet for further 3 days with 700 mmol/day IV (NB. 300 mmol Na ≡ 17.4 g NaCl); dose-related increases in urinary Na and Ca; decrease in serum PTH at 2 top Na dose levels; increases in urinary cyclic AMP dose unrelated; no effect on serum Ca	McCarron *et al.*, 1981
2-yr longitudinal study in 124 postmenopausal women - significant relationship between urinary Na & reduction in hip bone density; no bone loss with urinary Na of < 90 mmol/day	Weak negative correlation (r = −0.19) between urinary Na and bone density observed for 2 of 6 bone sites after allowance for certain confounding variables (Ca intake, body weight, exercise activity); no bone loss at urinary Na of 92-114 mmol/day; weak positive correlation between dietary Ca and bone density for 4 of 6 bone sites; no correlation between urinary Na & plasma alkaline phosphatase or serum PTH or calcitriol	Devine *et al.*, 1995
Increased salt intake in postmenopausal women increases urinary Ca, PTH (serum) & hydroxyproline (urine); in separate study reduction in Na intake from 170 to 70 mmol caused large reductions in Ca excretion, 1,25-dihydroxyergocalciferol & serum osteocalcin indicating decrease in bone mobilization	Low salt diet alone or with 100 mmol/day salt supplement for 10 days each with fixed Ca intake 850 mg/day in 10 women; after 100 mmol salt, significant increases in 24-hour urinary Na, Ca, hydroxyproline and cyclic AMP and in serum calcitriol (not significant) & osteocalcin; serum PTH not studied; no increase in strontium absorption; with low salt diet 24-hour urinary Na, Ca and hydroxproline values lower than with normal diet	McParland *et al.*, 1989
Suggestion that low Ca intake plus high urinary Ca loss due to high salt intake in young girls may reduce skeletal Ca retention & peak bone mass	In cross-sectional study of 370 females (8-13 years old), positive associations between Ca intake & urinary Ca (r = 0.17), urinary Na & urinary Ca (r = 0.4) & Ca intake & bone mineral density; negative association between urinary Ca and bone mineral density; urinary Na not directly associated with bone mass indices	Matkovic *et al.*, 1995
Patients with idiopathic hypercalciuria have reduced bone mineral mass & extent of abnormality directly related to salt intake	4 patients with renal stones showed high 24-hour urinary Ca and Na levels; with dietary salt restriction, urinary Ca normalized	Silver *et al.*, 1983
Reduced salt intake in hypercalciuria as effective as a thiazide diuretic	Review of dietary management of idiopathic Ca urolithiasis; Na restriction & other dietary adjustments useful adjuncts with thiazide therapy	Pak *et al.*, 1984
Hypertensive patients show increases in urinary Ca & serum PTH and 1,25-dihydroxyergocalciferol and reduced serum Ca; data show increased urinary Ca not compensated by increased Ca absorption and that Ca mobilization from bone occurs; higher risk of bone demineralization in hypertensive than normotensive subjects with same Na intake	Review article—no original data on effect of Na on Ca homeostasis or bone health	MacGregor and Cappuccio, 1993
Severe bone demineralization in spontaneously-hypertensive & salt-sensitive rat strain with ageing	Compared with normotensive rat strain, hypertensive rats (26 weeks old) showed reductions in urinary Ca, bone cortical thickness, longitudinal bone growth and ash weight indices	Izawa *et al.*, 1985
In normotensive & hypertensive subjects, thiazide diuretics decrease urinary Ca, cause Ca retention, increase bone density & lower fracture rates; moderate salt reduction likely to have same effect as thiazide diuretic on bone health	In 9518 men and women (aged ≥65 years) followed for 4 years, hip fracture rates one-third lower among thiazide than non-thiazide users	LaCroix *et al.*, 1990

cose and fructose before it aids calcium absorption. This, being a rather slow process, has the effect of extending the length of the gut in which calcium is absorbed and results in an overall increase in calcium absorption. This is of considerable importance in growing children who need calcium for bone-building (Hodgkinson and Heaton, 1965). In laboratory animals, the feeding of excessive amounts of lactose, other disaccharides, certain polyols or chemically-modified starches can lead to excessive calcium absorption which results in manifestations of toxicity including renal stone formation. This sequence of events has not been shown to cause calcium toxicity in humans. However, there is clear evidence that the consumption of carbohydrates generally is associated with increased calcium absorption in man (Fournier, 1965).

Insofar as many factors affect both calcium absorption and calcium excretion, it is clearly not appropriate to assume that increased urinary calcium indicates a negative calcium balance. For the assessment of calcium balance, one needs to have measurements of calcium intake in food and of calcium loss in faeces as well as of loss in urine. Nor is it appropriate to rely on short-term observations in order to assess where in the longer term there is a

balance between intake and loss. For these reasons, caution is needed in the interpretation of many of the reported studies relating salt intake to urinary output of calcium.

Animal studies: effect of salt supplementation on bone health

Studies of the effects of high dietary salt supplementation on bone health in rats have provided evidence of reduced bone calcium content over 16 days of the growing period (Goulding and Campbell, 1984), bone loss due to increased bone resorption rather than decreased bone formation using a radiolabelling technique (Goulding and Gold, 1988), accelerated bone loss in the oophorectomized rat on a low calcium/high sodium diet (Goulding and Campbell, 1983), increased urinary calcium and hydroxyproline excretion with moderate sodium doses over 4 or 12 months in normal and oophorectomized rats (Chan and Swaminathan, 1993, 1998), reduction in bone density in ovariectomized rats (Gold and Goulding, 1995), increases in serum PTH and urinary cyclic AMP (Goulding, 1980; Pernot *et al.*, 1979) and increase in urinary deoxypyridinoline (Chung *et al.*, 1998). Overall, the data indicate a link between high dietary NaCl intakes and bone loss but in one study (Goulding, 1980) a diet containing 8% salt and 0.1% calcium when given to rats for 12 weeks failed to affect bone composition.

Humans, however, are far more tolerant than the laboratory rat to wide variations in intake of minerals such as calcium, magnesium and phosphorus (Roe, 1993). The high susceptibility of the rat to mineral imbalance can lead to renal, parathyroid and adrenal medullary pathological changes following exposure, for example, to increased intestinal calcium absorption or increased dietary calcium/magnesium intakes (Roe, 1993). Therefore, caution is needed in extrapolating rat data to humans, especially when toxicological manifestations resulting from mineral imbalance are at issue.

General discussion

The risk of osteoporosis is determined by peak bone mass and rate of bone loss after skeletal maturity, with genetic factors playing a far more influential role than nutritional, hormonal, environmental and lifestyle factors combined.

It should be recognized that bone is an active tissue undergoing continual renewal of defective areas through the osteoclasts and osteoblasts. About 10% of the adult skeleton is replaced each year. The osteocyte may have an important regulatory role in detecting imperfections or microfractures, and initiate a remodelling cycle. The renewal process in each remodelling unit takes several months to complete. As bone resorption and formation at a particular site are separated in time, expressing bone balance as a simple ratio between the two is only valid when the skeleton is in complete equilibrium. In many cases, changes in bone markers reflect primarily alterations in the number of remodelling sites. The risk of osteoporosis has been assessed by measuring bone mineral density and biochemical markers of bone resorption and formation but in future attention will also need to focus on the rate of bone turnover, recently identified as a risk factor in osteoporosis (Robins and New, 1997).

In any consideration of the aetiology of osteoporosis, many different factors need to be considered. The list includes genetic constitution, sex and hormonal status, age, and a range of dietary and lifestyle factors. Calcium homeostasis is tightly regulated such that serum calcium levels do not reflect calcium throughput. Nor can calcium levels in urine by themselves be taken as an indication of calcium balance. Serum levels are potentially influenced by absorption from the gut, deposition in or resorption from bones and loss in the urine or by excretion into the gut lumen. Thus, to form anything like a complete picture of calcium homeostasis, it is essential to have good information on absorption of calcium from and excretion of calcium into the gut lumen and this poses the need for the measurement of calcium both in food and in faeces. Without such data, it is not possible to be sure whether calcium uptake and output are in a positive or a negative relationship. A further point is that time needs to be given for adaptation. Thus, for example, the observation of a raised urinary level of calcium and sodium after a short period of high salt intake should not be taken to indicate that the high salt intake is a risk factor for osteoporosis. An overview of the available data shows that there is a paucity of reliable information from balance studies of sufficient duration.

Various risk factors in osteoporosis have been reported including physical activity, body mass profile, menopausal status, alcohol, smoking, corticosteroids, caffeine and high protein, salt or phosphorus intake. In addition, protective factors have been identified including calcium /vitamin D supplementation, certain trace minerals (potassium, magnesium, zinc), vitamin C, fibre as well as fruit intake (Metz *et al.*, 1993; New *et al.*, 1995, 1996a,b, 1997a,b, 1998, 1999; Reid and New, 1997; Saltman and Strause, 1993; Utiger, 1998). Thus, in focusing on the potential effect of an individual risk factor, there is need to take into account all other relevant protective and risk factors, otherwise erroneous conclusions could be drawn.

The main objective of this review is to establish from the available published literature the importance, if any, of high dietary salt intake as a risk factor in osteoporosis. Clearly, increased urinary sodium excretion is associated with increased urinary calcium excretion. Salt accounts for over 90%

of total dietary sodium intake (Cohen and Roe, 1997), which usually exceeds 100 mmol/day, equivalent to 5.8 g NaCl/day. A 1 mmol urinary calcium loss in response to an increase in dietary sodium intake of 100 mmol/day would cause a negative balance of 18,250 mmol calcium over 50 years. As this amount represents about 75% of total body calcium in an adult, adaptation to the urinary calcium loss must occur. The extent of this adaptation is unknown since techniques measuring calcium balance may not detect small but real losses in total body calcium. Some older people may be less able to adapt by increasing intestinal calcium absorption (Massey and Whiting, 1996).

Of particular importance is the individual variability in urinary calcium response to dietary sodium intake. It appears that many individuals show little or no increase in urinary calcium loss in response to increased sodium intake (i.e. sodium non-responsive subjects) while only a minority show a significant response (i.e. sodium-responsive subjects) (Ginty *et al.*, 1998; Shortt and Flynn, 1990; Shortt *et al.*, 1988). In what appears to be the first study on the influence of dietary sodium on bone metabolism in sodium-responsive subjects, no effect was seen on the more reliable biochemical markers of bone resorption (urinary pyridinoline and deoxypyridinoline) (Ginty *et al.*, 1998). If the majority of the population is indeed sodium non-responsive, this would seriously undermine the value of dietary salt reduction as an intervention strategy in the prevention of osteoporosis as recommended by two groups of workers (Antonios and MacGregor, 1995, 1996; Cappuccio, 1996; Cappuccio and MacGregor, 1997; MacGregor, 1996, 1997; MacGregor and Cappuccio, 1993; MacGregor and de Wardener, 1998; Devine and Prince, 1996; Prince and Devine, 1998).

Conflicting results have been obtained with respect to the effects of increased dietary sodium on various indices of bone health (Table 6). Relatively few such studies have been undertaken because of the need to determine sodium intake by 24-hour urinary collection and the duration required for bone changes to develop (Massey and Whiting, 1996). Current evidence suggests that young adults adapt better than postmenopausal women to the effects of high dietary sodium on urinary calcium (Evans and Eastell, 1995). To what extent sodium-induced hypercalciuria is influenced by age and gender, so that certain subpopulations may be more sensitive than others, remains to be determined. For example, some but not all studies suggest (Massey and Whiting, 1996) that postmenopausal women are more sensitive than premenopausal women to the calcium-depleting effect of salt. It is noteworthy that a UK advisory group on nutrition and bone health found the evidence linking an effect of sodium-induced hypercalciuria on bone mineral density to be inconclusive (Department of Health, 1998).

Although there is no evidence to show that the level of dietary calcium influences the magnitude of the salt-induced hypercalciuric response, it is likely that a sufficiently high dietary calcium intake can compensate for any bone resorption induced by salt (Massey and Whiting, 1996). Moreover, it has been shown recently (Dawson-Hughes *et al.*, 1996) that the effect of increased sodium intake on urinary calcium loss is not seen under conditions of low calcium intake.

It is noteworthy that other sodium salts (e.g. bicarbonate or citrate) (Lemann *et al.*, 1989) as well as potassium chloride (Massey and Whiting, 1996) have little or no ability to increase urinary calcium excretion, demonstrating the importance of retaining chloride as the anion to sodium in producing hypercalciuria (Massey and Whiting, 1996). Such importance was also demonstrated by Berkelhammer *et al.* (1988) in patients with marked hypercalciuria given total parenteral nutrition. Replacement of sodium chloride by sodium acetate led to a marked reduction in urinary calcium excretion and a positive calcium balance. It was the chloride and acetate cations that determined blood pH (being 7.37 with sodium chloride and 7.46 with sodium acetate) and the degree of urinary calcium excretion that paralleled total acid excretion. Thus acidosis should be considered a risk factor for osteoporosis (Bushinsky, 1998).

We concur with the view (Evans and Eastell, 1995; Massey and Whiting, 1996) that additional research is needed before specific recommendations can be made for the prevention of osteoporosis as far as salt restriction is concerned. In particular, studies need to focus on whether (i) short-term changes in bone health, if demonstrable, are reversible through remodelling in the longer term; (ii) intervention studies involving reduction of say 9 g to 6 g salt/day would have any impact on bone health in both the short and long term; and (iii) subpopulations exist among the elderly which may be particularly sensitive to the consequences of the hypercalciuric effect of high dietary sodium intake, especially in sodium-responsive subjects.

As poor appetite and borderline nutrition are general problems in older people, salt restriction which reduces the palatability of food may encourage a general diminution in food intake and a shortfall not only in calcium but also in the consumption of other essential nutrients. A more useful recommendation would be to increase the intake of calcium and vitamin D.

We consider that, on the weight of available evidence, the current average dietary intake of salt in the UK (i.e. 9 g/day) does not represent an important risk factor for osteoporosis.

Conclusions

Although increased dietary sodium intake appears to be associated with enhanced urinary calcium excretion in only a minority of human subjects, there is no evidence to indicate that the calcium loss leads to any consistent effects on bone health or any irreversible changes in the bone remodelling process. After consideration of the available evidence on sodium in particular, as well as on other nutritional, hormonal, environmental and lifestyle risk factors, we conclude that the current average dietary intake of 9 g/day of salt in the UK does not represent an important risk factor for osteoporosis. Moreover, the available evidence is far too weak and inconsistent to conclude that a reduction in salt intake would be beneficial in the prevention of osteoporosis. Further research, as indicated in our review, is recommended before any such preventive measure is considered.

Acknowledgements—Thanks are due to the Salt Manufacturers' Association for funding this review, to Dr Susan New and Professor Albert Flynn for their helpful comments on the manuscript, and to Mrs Diana Morris for her secretarial support in producing this manuscript.

REFERENCES

Adachi J. D., Bensen W. G., Brown J., Hanley D., Hodsman A., Josse R., Kendler D. L., Lentle B., Olszynski W., Ste-Marie L-G., Tenenhouse A. and Chines A. A. (1997) Intermittent etidronate therapy to prevent corticosteroid-induced osteoporosis. *New England Journal of Medicine* **337,** 382–387.

Alderman M. (1997) Data linking sodium intake to subsequent morbid and fatal outcomes must be studied. *British Medical Journal* **315,** 484–485.

Anderson J. J. B. and Metz J. A. (1995) Adverse association of high protein intake to bone density. In *Nutritional Aspects of Osteoporosis. Challenges of Modern Medicine*, ed. P. Burckhardt and R. P. Heaney, Vol. 7, pp. 407–412. Ares-Serono Symposia Publications, Rome.

Antonios T. F. T. and MacGregor G. A. (1995) Deleterious effects of salt intake other than effects on blood pressure. *Clinical and Experimental Pharmacology and Physiology* **22,** 180–184.

Antonios T. F. T. and MacGregor G. A. (1996) Salt—more adverse effects. *Lancet* **348,** 250–251.

Barzel U. S. and Massey L. K. (1998) Excessive dietary protein can adversely affect bone. *Journal of Nutrition* **128,** 1051–1053.

Berkelhammer C. H., Wood R. J. and Sitrin M. D. (1988) Acetate and hypercalciuria during total parenteral nutrition. *American Journal of Clinical Nutrition* **48,** 1482–1489.

Berkow R., Fletcher A. J. and Beers M. H. (Eds) (1992) Bone and cartilage disorders with articular manifestations: Osteoporosis. In *The Merck Manual of Diagnosis and Therapy*. pp. 1357–1359. Merck Research Laboratories, Rahway, NJ.

Bonjour J-P. and Rizzoli R. (1995) Inadequate protein intake and osteoporosis: possible involvement of the IGF system. In *Nutritional Aspects of Osteoporosis. Challenges of Modern Medicine*, ed. P. Burckhardt and R. P. Heaney, Vol. 7, pp. 399–406. Ares-Serono Symposia Publications, Rome.

Bonn D. (1996) Parathyroid hormone for osteoporosis. *Lancet* **347,** 50.

Breslau N. A., McGuire J. L., Zerwekh J. E. and Pak C. Y. C. (1982) The role of dietary sodium on renal excretion and intestinal absorption of calcium and on vitamin D metabolism. *Journal of Clinical and Endocrinological Metabolism* **55,** 369–373.

Breslau N. A., Sakhaee K. and Pak C. Y. C. (1985) Impaired adaptation to salt-induced urinary calcium losses in postmenopausal osteoporosis. *Transactional Association of American Physicians* **98,** 107–115.

Burkckhardt P., Dawson-Hughes B. and Heaney R. P. (Eds) (1998) *Nutritional Aspects of Osteoporosis*. pp. 336. Serono Symposia S.A. Publication. Springer-Verlag, New York.

Burckhardt P. and Heaney R. P. (Eds) (1991) *Nutritional Aspects of Osteoporosis*. Vol. 85. Serono Symposia Publications, Raven Press, New York.

Burckhardt P. and Heaney R. P. (Eds) (1995) *Nutritional Aspects of Osteoporosis '94. Challenges of Modern Medicine*. Vol. 7. pp. 217–435. Ares-Serono Symposia Publications, Rome.

Bushinsky D. A. (1998) Acid-base imbalance and the skeleton. In *Nutritional Aspects of Osteoporosis*, ed. P. Burckhardt, B. Dawson-Hughes and R. P. Heaney, pp. 208–217. Serono Symposia S.A. Publication. Springer-Verlag, New York.

Cappuccio F. P. (1996) Dietary prevention of osteoporosis: are we ignoring the evidence? *American Journal of Clinical Nutrition* **63,** 787.

Cappuccio F. P. and MacGregor A. (1997) Dietary salt restriction: benefits for cardiovascular disease and beyond. *Current Opinion in Nephrology and Hypertension* **6,** 477–482.

Castenmiller J. J. M., Mensink R. P., van der Heijden L., Kouwenhoven T., Hautvast J. G. A. J., de Leeuw P. W. and Schaafsma G. (1985) The effect of dietary sodium on urinary calcium and potassium excretion in normotensive men with different calcium intakes. *American Journal of Clinical Nutrition* **41,** 52–60.

Chan E. L. P., Ho C. S., MacDonald D., Ho S. C., Chan T. Y. K. and Swaminathan R. (1992) Interrelationships between urinary sodium, calcium, hydroxyproline and serum PTH in healthy subjects. *Acta Endocrinologica* **127,** 242–245.

Chan E. L. P. and Swaminathan R. (1993) Effect of different amounts of sodium intake for 4 months on calcium metabolism in normal and oophorectomized rats. *Journal of Bone and Mineral Research* **8,** 1185–1189.

Chan E. L. P. and Swaminathan R. (1998) Calcium metabolism and bone calcium content in normal and oophorectomized rats consuming various levels of saline for 12 months. *Journal of Nutrition* **128,** 633–639.

Chung Y. S., Lee S. K., Lee K. B., Kim B-S., Kim D., Cho J. H. and Kim H. M. (1998) The effects of high salt intake on bone mineral metabolism in growing rats. *Journal of Bone and Mineral Research* **13** (Suppl. 1), S491(abstract F340).

Cohen A. J. and Roe F. J. C. (1997) Evaluation of the aetiological role of dietary salt exposure in gastric and other cancers in humans. *Food and Chemical Toxicology* **35,** 271–293.

Compston J. E. (1997) Osteoporosis: Management of established disease. *Prescribers' Journal* **37,** 119–124.

Cooper C. and Dennison E. (1997) Osteoporosis: Prevention of osteoporotic fractures. *Prescribers' Journal* **37,** 112–119.

Cumming R. G., Cummings S. R., Nevitt M. C., Scott J., Ensrud K. E., Vogt T. M. and Fox K. (1997) Calcium intake and fracture risk: results from the study of osteoporotic fractures. *American Journal of Epidemiology* **145,** 926–934.

Dawson-Hughes B., Fowler S. E., Dalsky G. and Gallagher C. (1996) Sodium excretion influences calcium homeostasis in elderly men and women. *Journal of Nutrition* **126,** 2107–2112.

Delmas P. D. (1992) Clinical use of biochemical markers of bone remodelling in osteoporosis. *Bone* **13,** S17–S21.

Delmas P. D., Bjarnason N. H., Mitlak B. H., Ravoux A-C., Shah A. S., Huster W. J., Draper M. and Christiansen C. (1997) Effects of raloxifene on bone mineral density, serum cholesterol concentrations, and uterine endometrium in postmenopausal women. *New England Journal of Medicine* **337,** 1641–1647.

Department of Health (1998) Nutrition and Bone Health: with particular reference to calcium and vitamin D. Report of the Subgroup on Bone Health, Working Group on the Nutritional Status of the Population of the Committee on Medical Aspects of Food and Nutrition Policy. Report on Health and Social Subjects No. 49. HMSO, London. pp. xvii + 124.

Devine A., Criddle A. R., Dick I. M., Kerr D. A. and Prince R. L. (1995) A longitudinal study of the effect of sodium and calcium intakes on regional bone density in postmenopausal women. *American Journal of Clinical Nutrition* **62,** 740–745.

Devine A. and Prince R. L. (1996) Dietary prevention of osteoporosis: are we ignoring the evidence? *American Journal of Clinical Nutrition* **63,** 788.

Draper H. H. (1994) *Nutrition and Osteoporosis. Advances in Nutritional Research*, Vol. 9, pp. ix–xiv. Plenum Press, New York.

Drüeke T. B. (1997) Osteoporosis and Salt, pp. 1–10. Unpublished report.

Eisman J. A. (1998) Vitamin D polymorphisms and calcium homeostasis: A new concept of normal gene variants and physiologic variation. *Nutrition Reviews* **56** (2 Part II), S22–S29.

Evans C. E. L., Chughati A. Y., Blumsohn A., Giles M. and Eastell R. (1997) The effect of dietary sodium on calcium metabolism in premenopausal and postmenopausal women. *European Journal of Clinical Nutrition* **51,** 394–399.

Evans C. and Eastell R. (1995) Adaptation to high dietary sodium intake. In *Nutritional Aspects of Osteoporosis. Challenges of Modern Medicine*, ed. P. Burckhardt and R. P. Heaney, Vol. 7, pp. 413–418. Ares-Serono Symposia Publications, Rome.

Fournier P. (1965) Influence of lactose on calcium utilization and ossification. *Pathologie et Biologie* **13,** 143–151.

Ginty F., Flynn A. and Cashman K. D. (1998) The effect of dietary sodium intake on biochemical markers of bone metabolism in young women. *British Journal of Nutrition* **79,** 343–350.

Gold E. and Goulding A. (1995) High dietary salt intakes lower bone mineral density in ovariectomised rats: a dual X-ray absorptiometry study. *Bone* **16,** 115S (abstract).

Goulding A. (1980) Effects of dietary NaCl supplements on parathyroid function, bone turnover and bone composition in rats taking restricted amounts of calcium. *Mineral and Electrolyte Metabolism* **4,** 203–208.

Goulding A. (1981) Fasting urinary sodium/creatinine in relation to calcium/creatinine and hydroxyproline/creatinine in a general population of women. *New Zealand Medical Journal* **93,** 294–297.

Goulding A. and Campbell D. (1983) Dietary NaCl loads promote calciuria and bone loss in adult oophorectomized rats consuming a low calcium diet. *Journal of Nutrition* **113,** 1409–1414.

Goulding A. and Campbell D. R. (1984) Effects of oral loads of sodium chloride on bone composition in growing rats consuming ample dietary calcium. *Mineral and Electrolyte Metabolism* **10,** 58–62.

Goulding A., Everitt H. E., Cooney J. M. and Spears G. F. S. (1986) Sodium and osteoporosis. In *Recent Advances in Clinical Nutrition*, ed. M. L. Wahlqvist and A. S. Truswell, Vol. 2, pp. 99–108. John Libbey, London.

Goulding A. and Gold E. (1988) Effects of dietary NaCl supplementation on bone synthesis of hydroxyproline, urinary hydroxyproline excretion and bone ^{45}Ca uptake in the rat. *Hormone Metabolism Research* **20,** 743–745.

Goulding A. and Lim P. E. (1983) Effects of varying dietary salt intake on the fasting urinary excretion of sodium, calcium and hydroxyproline in young women. *New Zealand Medical Journal* **96,** 853–854.

Goulding A. and McDonald B. (1986) Intra-individual variability in fasting urinary Ca/Cr and Hp/Cr measurements. In *Recent Advances in Clinical Nutrition*, ed. M.L. Wahlqvist and A. S. Truswell, Vol. 2. pp. 312–313. John Libbey, London.

Goyer R. A., Epstein S., Bhattacharyya M., Korach K. S. and Pounds J. (1994) Environmental risks for osteoporosis. *Environmental Health Perspectives* **102,** 390–394.

Greendale G. A., Barrett-Connor E., Edelstein S., Ingles S. and Haile R. (1994) Dietary sodium and bone mineral density: Results of a 16-year follow-up study. *Journal of the American Geriatrics Society* **42,** 1050–1055.

Harris S. S. (1998) Effects of caffeine consumption on hip fracture, bone density, and calcium retention. In *Nutritional Aspects of Osteoporosis*, ed. P. Burckhardt, B. Dawson-Hughes and R. P. Heaney, pp. 163–171. Serono Symposia S.A. Publication. Springer-Verlag, New York.

Heaney R. P. (1993) Nutritional factors in osteoporosis. *Annual Reviews of Nutrition* **13,** 287–316.

Heaney R. P. (1998) Excess dietary protein may not adversely affect bone. *Journal of Nutrition* **128,** 1054–1057.

Heaney R. P. and Burckhardt P. (1991) Concluding comments: the impact of nutrition on the epidemiology, the prevention, and the treatment of osteoporosis. In *Nutritional Aspects of Osteoporosis*, ed. P. Burckhardt and R. P. Heaney, Vol. 85, pp. 371–375. Serono Symposia Publications, Raven Press, New York.

Heaney R. P. and Burckhardt P. (1995) Nutrition and bone health. In *Nutritional Aspects of Osteoporosis, Challenges of Modern Medicine*, ed. P. Burckhardt and R. P. Heaney, Vol. 7, pp. 419–424. Ares-Serono Symposia Publications, Rome.

Heaney R. P. and Recker R. R. (1982) Effects of nitrogen, phosphorus, and caffeine on calcium balance in women. *Journal of Laboratory and Clinical Medicine* **99,** 46–55.

Hodgkinson A. and Heaton F. W. (1965) The effect of food ingestion on the urinary excretion of calcium and magnesium. *Clinica Chimie Acta* **11,** 354–362.

Itoh R. and Suyama Y. (1996) Sodium excretion in relation to calcium and hydroxyproline excretion in a healthy Japanese population. *American Journal of Clinical Nutrition* **63,** 735–740.

Izawa Y., Sagara K., Kadota T. and Makita T. (1985) Bone disorders in spontaneously hypertensive rat. *Calcificied Tissue International* **37,** 605–607.

Kerstetter J. E. and Allen L. H. (1994) Protein intake and calcium homeostasis. In *Nutrition and Osteoporosis*, ed. H. H. Draper, Vol. 9, pp. 167–180. Advances in Nutritional Research, Plenum Press, New York.

Kesteloot H. and Joossens J. V. (1990) The relationship between dietary intake and urinary excretion of sodium, potassium, calcium and magnesium: Belgian interuniversity research on nutrition and health. *Journal of Human Hypertension* **4,** 527–533.

LaCroix A. Z., Wienpahl J., White L. R., Wallace R. B., Scherr P. A., George L. K., Cornoni-Huntley J. and

Ostfeld A. M. (1990) Thiazide diuretic agents and the incidence of hip fracture. *New England Journal of Medicine* **322,** 286–290.

Lamberg-Allardt C., Kärkkäinen M., Laitinen K., Palmgren J. and Välimäki M. (1995) Exercise, smoking and calcium intake during adolescence and early adulthood as determinants of peak bone mass. In *Nutritional Aspects of Osteoporosis '94. Challenges of Modern Medicine*, ed. P. Burckhardt and R. P. Heaney, Vol. 7, pp. 163–168. Ares-Serono Symposia Publications, Rome.

Lau E. M. C. and Woo J. (1994) Osteoporosis in Asia. In *Advances in Nutritional Research*, ed. H. H. Draper, Vol. 9, pp. 101–118. Plenum Press, New York.

Law M. (1990) Smoking and osteoporosis. In *Smoking and Hormone-related Disorders*, ed. N. Wald and J. Baron, pp. 83–92. Oxford University Press.

Law M. R. and Hackshaw A. K. (1997) A meta-analysis of cigarette smoking, bone mineral density and risk of hip fracture: recognition of a major effect. *British Medical Journal* **315,** 841–846.

Lemann J., Jr, Gray R. W. and Pleuss J. A. (1989) Potassium bicarbonate, but not sodium bicarbonate, reduces urinary calcium excretion and improves calcium balance in healthy men. *Kidney International* **35,** 688–695.

Lietz G., Avenell A. and Robins S. P. (1997) Short-term effects of dietary sodium intake on bone metabolism in postmenopausal women measured using urinary deoxypyridinoline excretion. *British Journal of Nutrition* **78,** 73–82.

Lyles K. W. (1989) Osteoporosis. In *Textbook of Internal Medicine*, ed. W. N. Kelley, pp. 2601–2607. J.B. Lippincott Co, Philadelphia.

McCarron D. A., Rankin L. I., Bennett W. M., Krutzik S., McClung M. R. and Luft F. C. (1981) Urinary calcium excretion at extremes of sodium intake in normal man. *American Journal of Nephrology* **1,** 84–90.

MacGregor G. A. (1996) Salt and osteoporosis. In Newsletter produced by LoSalt, Scotland. Issue no. 6 of Nutrition Issues.

MacGregor G. A. (1997) Salt—more adverse effects. *American Journal of Hypertension* **10,** 37S–41S.

MacGregor G. A. and Cappuccio F. P. (1993) The kidney and essential hypertension: a link to osteoporosis? *Journal of Hypertension* **11,** 781–785.

MacGregor G. A. and de Wardener H. E. (1998) *Salt, Diet and Health*, pp. 180–184. Cambridge University Press, Cambridge.

McParland B. E., Goulding A. and Campbell A. J. (1989) Dietary salt affects biochemical markers of resorption and formation of bone in elderly women. *British Medical Journal* **299,** 834–835.

Massey L. K. (1998) Does excess dietary protein adversely affect bone? Symposium overview. *Journal of Nutrition* **128,** 1048–1050.

Massey L. K. and Whiting S. J. (1996) Dietary salt, urinary calcium, and bone loss. *Journal of Bone and Mineral Research* **11,** 731–736.

Matkovic V., Ilich J. Z., Andon M. B., Hsieh L. C., Tzagournis M. A., Lagger B. J. and Goel P. K. (1995) Urinary calcium, sodium, and bone mass of young females. *American Journal of Clinical Nutrition* **62,** 417–425.

Metz J. A., Anderson J. J. B. and Gallagher P. N., Jr (1993) Intakes of calcium, phosphorus, and protein, and physical-activity level are related to radial bone mass in young adult women. *American Journal of Clinical Nutrition* **58,** 537–542.

Milsom S., Ibbertson K., Hannon S., Shaw D. and Pybus J. (1987) Simple test of intestinal calcium absorption measured by stable strontium. *British Medical Journal* **295,** 231–234.

Need A. G., Morris H. A., Cleghorn D. B., De Nichilo D., Horowitz M. and Nordin B. E. C. (1991) Effect of salt restriction on urine hydroxyproline excretion in postmenopausal women. *Archives of Internal Medicine* **151,** 757–759.

New S. A., Bolton-Smith C., Grubb D. A. and Reid D. M. (1995) Present and past dietary intake - effects on wintertime bone mineral density. In *Nutritional Aspects of Osteoporosis. Challenges of Modern Medicine*, ed. P. Burckhardt and R. P. Heaney, Vol. 7, pp. 61–71. Ares-Serono Symposia Publications, Rome.

New S. A., Bolton-Smith C., Grubb D. A. and Reid D. M. (1996a) Influence of current nutrient intake on bone mass: an epidemiological investigation. In *Osteoporosis '96*, ed. S. E,. Papapoudos *et al.* pp. 119–124. Elsevier Science, New York.

New S. A., Bolton-Smith C., Grubb D. A. and Reid D. M. (1997a) Nutritional influences on bone mineral density: a cross-sectional study in premenopausal women. *American Journal of Clinical Nutrition* **65,** 1831–1839.

New S. A., Robins S. P., Campbell M. K., Martin J. C., Garton M. J., Bolton-Smith C., Grubb D. A., Lee S. J. and Reid D. M. (1999) Dietary influences on bone mass and bone metabolism—further evidence of a positive link between fruit and vegetable consumption and bone health? *American Journal of Clinical Nutrition.* In press.

New S. A., Robins S. P., Garton M. J., Martin J. C., Grubb D. A., Bolton-Smith C., Lee S. J. and Reid D. M. (1996b) Effects of dietary and non-dietary factors on bone metabolism in women. *Proceedings of the Nutrition Society* **55,** 12A.

New S. A., Robins S. P. and Reid D. M. (1998) Fruit and vegetable consumption and bone health: Is there a link?. In *Nutritional Aspects of Osteoporosis*, ed. P. Burckhardt, B. Dawson-Hughes and R. P. Heaney, pp. 199–207. Serono Symposia S.A. Publication. Springer-Verlag, New York.

New S. A., Stewart A., Grubb D. A. and Reid D. M. (1997b) Relationship between present and past dietary intake and bone mass using broadband ultrasound attenuation. *Proceedings of the Nutrition Society* **56,** 142A.

Nordin B. E. C., Horowitz M., Need A. and Morris H. A. (1994a) Renal leak of calcium in post-menopausal osteoporosis. *Clinical Endocrinology* **41,** 41–45.

Nordin B. E. C., Morris H. A. and Need A. G. (1994b) Calcium and osteoporosis. The effect of menopause and dietary sodium and protein on calcium requirement. In *Nutrition in a Sustainable Environment*, ed. M,. Wahlqvist *et al.* pp. 647–650. Proc. XVth Int Congress of Nutrition: IUNS Adelaide. Smith-Gordon, London.

Nordin B. E. C. and Need A. G. (1994) The effect of sodium on calcium requirement. In *Advances in Nutritional Research: Nutrition and Osteoporosis*, ed. H. H. Draper, Vol. 9, pp. 209–230. Plenum Press, New York.

Nordin B. E. C., Need A. G., Morris H. A. and Horowitz M. (1991) Sodium, calcium and osteoporosis. In *Nutritional Aspects of Osteoporosis*, ed. P. Burckhardt and R. P. Heaney, Vol. 85, pp. 279–295. Serono Symposia Publications, Raven Press, New York.

Nordin B. E. C., Need A. G., Morris H. A. and Horowitz M. (1993) The nature and significance of the relation between urinary sodium and urinary calcium in women. *Journal of Nutrition* **123,** 1615–1622.

Nordin B. E. C., Need A. G., Morris H. A., Horowitz M., Chatterton B. E. and Sedgwick A. W. (1995) Bad habits and bad bones. In *Nutritional Aspects of Osteoporosis. Challenges of Modern Medicine*, ed. P. Burckhardt and R. P. Heaney, Vol. 7, pp. 1–25. Ares-Serono Symposia Publications, Rome.

Nordin B. E. C. and Polley K. J. (1987) Metabolic consequences of the menopause: A cross-sectional, longitudinal and intervention study on 557 normal postmenopausal women. Calcified Tissue International. 41 (Supplement No. 1) S1–S59.

Pak C. Y. C., Smith L. H., Resnick M. I. and Weinerth J. L. (1984) Dietary management of idiopathic calcium urolithiasis. *Journal of Urology* **131,** 850–852.

Pernot F., Berthelot A., Schleiffer R. and Gairard A. (1979) Ionized serum calcium, urinary cAMP and immunoreactive PTH after DOCA + NaCl treatment in the rat. *Mineral and Electrolyte Metabolism* **2,** 258.

Prince R. L. (1997) Diet and the prevention of osteoporotic fractures. *New England Journal of Medicine* **337,** 701–702.

Prince R. L. and Devine A. (1998) Salt effects on bone and calcium metabolism. In *Nutritional Aspects of Osteoporosis*, ed. P. Burckhardt, B. Dawson-Hughes and R. P. Heaney, pp. 216–218. Serono Symposia S.A. Publication. Springer-Verlag, New York.

Ralston S. H. (1997) Osteoporosis. *British Medical Journal* **315,** 469–472.

Reid D. M. and New S. A. (1997) Nutritional influences on bone mass. *Proceedings of the Nutrition Society* **56,** 977–987.

Reid I. R., Pybus J., Lim T. M. T., Hannon S. and Ibbertson H. K. (1986) The assessment of intestinal calcium absorption using stable strontium. *Calcified Tissue International* **38,** 303–305.

Riggs B. L. (1988) Osteoporosis. In *Cecil's Textbook of Medicine. XVII: Diseases of bone and bone metabolism.* pp. 1426–1431.

Rizzoli R., Schürch M-A., Chevalley T., Ammann P. and Bonjour J-P. (1998) Protein intake and osteoporosis. In *Nutritional Aspects of Osteoporosis*, ed. P. Burckhardt, B. Dawson-Hughes and R. P. Heaney, pp. 141–154. Serono Symposia S.A. Publication. Springer-Verlag, New York.

Robins S. P. and New S. A. (1997) Markers of bone turnover in relation to bone health. *Proceedings of the Nutrition Society* **56,** 903–914.

Roe F. J. C. (1993) Mineral metabolism and chemical toxicity. In *Food, Nutrition and Chemical Toxicity*, ed. D. V. Parke, C. Ioannides and R. Walker, Chapter 9, pp. 91–104. Smith-Gordon, London.

Rosen C. J. (1997) A tale of two worlds in prescribing etidronate for osteoporosis. *Lancet* **350,** 1340.

Rosen C. J., Donahue L. R., Beamer W. G., Adler R. A., Kurland E. S. and Bilezikian J. P. (1998) IGF-1 and osteoporosis: Lessons from mice and men. In *Nutritional Aspects of Osteoporosis*, ed. P. Burckhardt, B. Dawson-Hughes and R. P. Heaney, pp. 135–140. Serono Symposia S.A. Publication. Springer-Verlag, New York.

Ross P. D. and Knowlton W. (1998) Rapid bone loss is associated with increased levels of biochemical markers. *Journal of Bone and Mineral Research* **13,** 297–302.

Sabto J., Powell M. J., Breidahl M. J. and Gurr F. W. (1984) Influence of urinary sodium on calcium excretion in normal individuals: A redefinition of hypercalciuria. *Medical Journal of Australia* **140,** 354–356.

Saltman P. D. and Strause L. G. (1993) The role of trace minerals in osteoporosis. *Journal of the American College of Nutrition* **12,** 384–389.

Seeman E., Hopper J. L., Pearce G., Tabensky A. and Bradney M. (1998) Interaction between genetic and nutritional factors. In *Nutritional Aspects of Osteoporosis*, ed. P. Burckhardt, B. Dawson-Hughes and R. P. Heaney, pp. 85–98. Serono Symposia S.A. Publication. Springer-Verlag, New York.

Shortt C. and Flynn A. (1990) Sodium-calcium inter-relationships with specific reference to osteoporosis. *Nutrition Research Reviews* **3,** 101–115.

Shortt C., Madden A., Flynn A. and Morrissey P. A. (1988) Influence of dietary sodium intake on urinary calcium excretion in selected Irish individuals. *European Journal of Clinical Nutrition* **42,** 595–603.

Silver J., Rubinger D., Friedlaender M. M. and Popovtzer M. M. (1983) Sodium-dependent idiopathic hypercalciuria in renal-stone formers. *Lancet* **ii,** 484–486.

Uusi-Rasi K., Sievänen H., Vuori I., Pasanen M., Heinonen A. and Oja P. (1998) Associations of physical activity and calcium intake with bone characteristics in women. In *Nutritional Aspects of Osteoporosis*, ed. P. Burckhardt, B. Dawson-Hughes and R. P. Heaney, pp. 61–66. Serono Symposia S.A. Publication. Springer-Verlag, New York.

Utiger R. D. (1998) The need for more vitamin D. *New England Journal of Medicine* **338,** 828–829.

Wahlqvist M. et al. (1994) *Nutrition in a Sustainable Environment.* Proc. XV Int Congress on Nutrition: IUNS Adelaide. Smith-Gordon, London.

Waine C. (1997) *Osteoporosis—Prevention and Management in Primary Care.* Royal College of General Practitioners, London. pp. 24.

Wood R. J. and Fleet J. C. (1998) The genetics of osteoporosis: Vitamin D receptor polymorphisms. *Annual Review of Nutrition* **18,** 233–258.

Zarkadas M., Gougeon-Reyburn R., Marliss E. B., Block E. and Alton-Mackey M. (1989) Sodium chloride supplementation and urinary calcium excretion in postmenopausal women. *American Journal of Clinical Nutrition* **50,** 1088–1094.

Zerwekh J. E. and Pak C. Y. C. (1980) Selective effects of thiazide therapy on serum 1α,25-dihydroxyvitamin D and intestinal calcium absorption in renal and absorptive hypercalciurias. *Metabolism* **29,** 13–17.