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Nutrition Society Medal Lecture

The role of the skeleton in acid–base homeostasis

Susan A. New
Centre for Nutrition and Food Safety, School of Biomedical & Life Sciences, University of Surrey, Guildford, Surrey GU2 7XH, UK

Nutritional strategies for optimising bone health throughout the life cycle are extremely important, since a dietary approach is more popular amongst osteoporosis sufferers than drug intervention, and long-term drug treatment compliance is relatively poor. As an exogenous factor, nutrition is amenable to change and has relevant public health implications. With the growing increase in life expectancy, hip fractures are predicted to rise dramatically in the next decade, and hence there is an urgent need for the implementation of public health strategies to target prevention of poor skeletal health on a population-wide basis. The role that the skeleton plays in acid–base homeostasis has been gaining increasing prominence in the literature; with theoretical considerations of the role alkaline bone mineral may play in the defence against acidosis dating as far back as the late 19th century. Natural, pathological and experimental states of acid loading and/or acidosis have been associated with hypercalciuria and negative Ca balance and, more recently, the detrimental effects of 'acid' from the diet on bone mineral have been demonstrated. At the cellular level, a reduction in extracellular pH has been shown to have a direct enhancement on osteoclastic activity, with the result of increased resorption pit formation in bone. A number of observational, experimental, clinical and intervention studies over the last decade have suggested a positive link between fruit and vegetable consumption and the skeleton. Further research is required, particularly with regard to the influence of dietary manipulation using alkali-forming foods on fracture prevention. Should the findings prove conclusive, a 'fruit and vegetable' approach to bone health maintenance may provide a very sensible (and natural) alternative therapy for osteoporosis treatment, which is likely to have numerous additional health-related benefits.

Skeletal health: Acid–base balance: Fruit and vegetable consumption: Bone metabolism: Dietary potassium

'One farmer says to me, 'You cannot live on vegetable food solely, and it furnishes nothing to make bones with,' and so he religiously devotes a part of his day to supplying his system with the raw material of bones; walking all the while he talks behind his oxen, which, with vegetable-made bones, jerk him and his lumbering plow along in spite of every obstacle.'
H. D. Thoreau (Barzel, 1970; First International Symposium on Osteoporosis, June 1969)

Introductory comments

Defining bone health

Throughout the life cycle, the skeleton requires optimum development and maintenance of its integrity, since the resultant effect of poor bone health is osteoporotic fracture. Osteoporosis is defined as a metabolic bone disease that has two predominant characteristics; the first being low bone mass and the second being micro architectural deterioration of bone tissue, with both factors leading to enhanced bone fragility and a consequent increase in fracture risk (Royal College of Physicians, 2000). Bone 'weakness' relates to both poor structural quality and decreased bone mass, and an illustration of 'normal' and 'osteoporotic' bone can be seen in Fig. 1

Considerable alterations occur within the skeleton throughout an individual's life, and it is now well established that there are two principal mechanisms determining adult bone health: (1) the maximum attainment of peak bone mass which is achieved during growth and early adulthood;

Abbreviations: APOSS, Aberdeen Prospective Osteoporosis Screening Study; DASH, Dietary Approaches to Stopping Hypertension.
Corresponding author: Dr Susan New, fax +44 1483 576978, email s.new@surrey.ac.uk

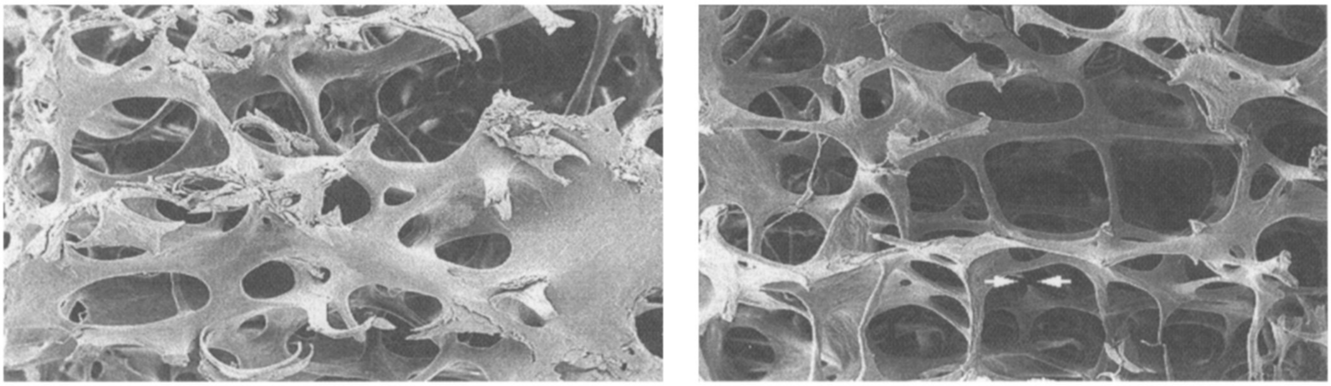

Fig. 1. Definition of osteoporosis: a progressive systemic skeletal disease characterised by low bone mass and micro-architectural deterioration of bone tissue, with consequent increase in bone fragility and susceptibility to fracture. (From World Health Organization, 1994; Royal College of Physicians, 2000.)

(2) the rate of bone loss with advancing age, with the menopausal years being a time of considerable concern for women. An example of the changes that occur in bone mass with ageing, for both men and women, can be seen in Fig. 2.

Implications of osteoporosis from a public health perspective

Current data estimate that one in three women and one in twelve men over the age of 55 years will suffer from osteoporosis in their lifetime. Approximately 200 000 osteoporotic fractures occurred in the UK alone in 2000 (National Osteoporosis Society, 2002), with financial costs to the National Health Service in excess of £1·7 billion per year (Torgerson *et al.* 2001). In the context of other conditions, as indicated in Fig. 3, osteoporosis is grossly under-funded when compared with other diseases such as cardiovascular disease and cancer. Given the projected rise in osteoporotic fracture worldwide to 6·26 million in the year 2050 (compared with 1·66 million in 1990; World Health Organization, 1994), there can be no doubt that the future economic impact of osteoporosis will be astronomical.

Determinants of bone health: modifiable v. *non-modifiable factors*

The pathogenesis of osteoporosis is multi-factorial (Cummings *et al.* 1995). Both the development of peak bone mass in the younger population and the rate of bone loss in post-menopausal women and the elderly are determined by a combination of genetic, endocrine, mechanical and nutritional factors, with evidence of extensive interactions within and between these groups (Heaney, 2000; Fig. 4). It is indeed this phenomenon that captivates bone health researchers alike, and essentially characterises the 'all-consuming' nature of the discipline of osteology.

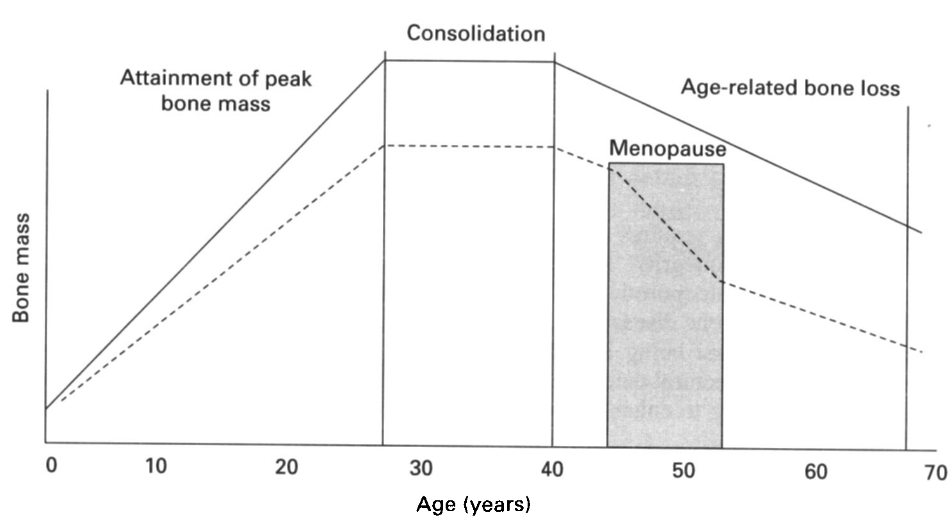

Fig. 2. Alterations in skeletal mass in men (–) and women (- - -) throughout the life cycle.

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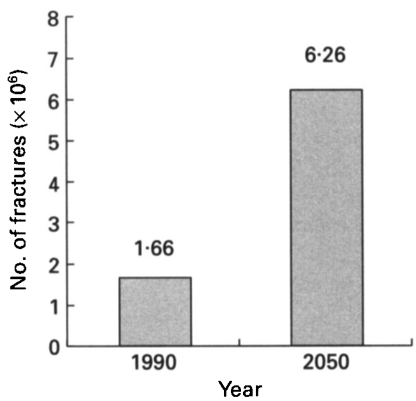

Fig. 3. Osteoporosis in context. In the UK the annual cost of osteoporosis is £1.7 billion compared with the annual cost of CHD which is £1.6 billion. Medication costs however are £527 million for CHD compared with £52 million for osteoporosis. (From Torgerson *et al.* 2001.)

There is good evidence to show that endogenous factors have a very important influence on the skeleton. Research focusing on monozygotic and dizygotic twins as well as comparisons between mother and daughter pairs indicate a genetic influence on bone health in the region of approximately 75 % (Eisman, 1999). Furthermore, a number of specific gene polymorphisms have been linked to reduced bone mass (Ralston, 1999), with the interleukin 6-promoter gene being the most recently identified receptor to be associated with skeletal health (Ferrari *et al.* 2000; Zumda *et al.* 2000).

That said, the modifiable factors (in particular, exercise and nutrition) do have a critical role to play in the development and maintenance of bone strength. Physical activity of 'weight-bearing' type has been shown to be beneficial to skeletal preservation across the age range, but the exact type, intensity and duration that is of most benefit to the skeleton remains unclarified (Marcus, 1999). It is interesting to note that an apparent 'threshold' effect exists; excessive exercise, which results in amenhorroea, is extremely detrimental to bone in the long-term, with evidence suggesting that such a deleterious impact is irreversible (New, 1998).

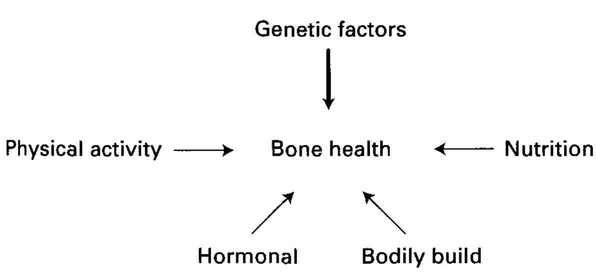

Fig. 4. Modifiable *v.* non-modifiable factors influencing bone health.

Importance of nutritional strategies for optimising bone health

Introductory remarks

Nutritional strategies for optimising bone health are important for a number of reasons: (1) nutrition is an exogenous factor and is thus amenable to change; (2) identification of the key 'bone health nutrients' has relevant public health implications; (3) a nutritional approach is far more popular with osteoporosis sufferers than drug intervention, a point of particular relevance given the poor long-term compliance rates associated with a number of currently available treatments (New, 1999).

Fundamentals of acid–base maintenance: criticality to health

'Life is a struggle, not against sin, not against the money power, not against malicious animal magnetism, but against hydrogen ions' (Mencken, 1919; cited by Kraut & Coburn, 1994). As noted by Kraut & Coburn (1994), these famous words by Mencken in the early 20th century about the meaning of life and death may also apply to the struggle of the healthy skeleton against the deleterious effects of retained acid.

Acid–base homeostasis is critical to health. The pH of extracellular fluid remains between 7·35 and 7·45 and it is a major challenge to the body's balance to keep the H^+ concentrations between 0·035 and 0·045 mmol/l (Green & Kleeman, 1991). Maintaining H^+ within such narrow limits is essential to survival, and the body's adaptive response involves three specific mechanisms: (1) buffer systems; (2) exhalation of CO_2; (3) kidney excretion.

On a daily basis, human subjects eat substances that both generate and consume protons, and as a net result adults on a normal Western diet generate approximately 1 mEq acid/d (Kurtz *et al.* 1983). The more acid precurors a diet contains, the greater the extent of systemic acidity (Bushinsky, 1998). Furthermore, as individuals age, the overall renal function declines, including the ability to excrete acid (Frassetto *et al.* 1996). Thus, with increasing age, human subjects become significantly (albeit slightly) more acidic (Frassetto & Sebastian, 1996).

A role for the skeleton in acid–base homeostasis: early work

Theoretical considerations of the role alkaline bone mineral may play in the defence against acidosis date back as far as the 1880s (Goto, 1918; Irving & Chute, 1933; Albright & Reifenstein, 1948). There are a number of studies providing evidence that in natural (e.g. starvation), pathological (e.g. diabetic acidosis) and experimental (e.g. NH_4Cl ingestion) states of acid loading and acidosis, an association exists with both hypercalciuria and negative Ca balance (Gastineau *et al.* 1960; Reidenberg *et al.* 1966). The pioneering work of Lemann (Lemann *et al.* 1966) and Barzel (1969) over three decades ago showed extensively the effects of 'acid' from the diet on bone mineral in both man and animals. Consideration of the skeleton as a source of buffer, contributing to both the preservation of the body's pH and defence of the

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system against acid–base disorders was a topic of much debate at the first ever Conference on Osteoporosis held in 1969 (Barzel, 1970; Bernstein *et al.* 1970).

In the 1960s Wachman & Bernstein (1968) put forward a hypothesis linking the daily diet to the development of osteoporosis, based on the role of bone in acid–base balance, and noted specifically that 'the increased incidence of osteoporosis with age may represent, in part, the results of a lifelong utilisation of the buffering capacity of the basic salts of bone for the constant assault against pH homeostasis' (Wachman & Bernstein 1968). The intake of 'acid' is a way of everyday life, and it is known that animal proteins and cereals are rich sources of H_3PO_4 and H_2SO_4 and are recognised as 'acid-ash' foods (Barzel & Massey, 1998; Heaney, 1998). The net production of acid is related to nutrition, and there is a gross quantitative relationship between the amount of acid produced (as reflected by urine pH) and the amount of acid-ash consumed in the diet. When one considers the extent of loss, if 2 mEq Ca/d is required to buffer about 1 mEq fixed acid/d, over 10 years (and assuming a total body Ca of approximately 1 kg), this requirement would account for a 15 % loss of inorganic bone mass in an average individual (Widdowson *et al.* 1951). Thus, consideration of a diet consisting of large quantities of fruit and vegetables (hence favouring 'alkaline-ash') may be important for bone health maintenance (Barzel, 1995).

Systemic acidosis and the skeleton: mechanisms of action?

Novel work by Arnett & Dempster (1986, 1990) and Arnett *et al.* (1994) demonstrated a direct enhancement of osteoclastic activity following a reduction in extracellular pH, an effect that was independent of parathyroid hormone (Fig. 5). Osteoclasts and osteoblasts appear to respond independently to small changes in pH in the culture media in which they are growing (Kreiger *et al.* 1992), and there is evidence that a small drop in pH, close to the physiological range, causes a tremendous burst in bone resorption (Arnett & Spowage, 1996; Bushinsky, 1996). Recent work by Arnett's group (Meghji *et al.* 2001), has shown that metabolic acidosis stimulates resorption by activating mature osteoclasts already present in calvarial bone rather than by inducing formation of new osteoclasts (Fig. 6 (a–d)). It is considered that almost all the bone mineral release that occurs in response to acidosis is due to osteoclast activation, which results in increased resorption pit formation in bone (with the organic matrix being destroyed at the same time; TR Arnett, personal communication), although there is evidence that excess H^+ directly induce physico-chemical Ca release from bone (Bushinsky *et al.* 1994).

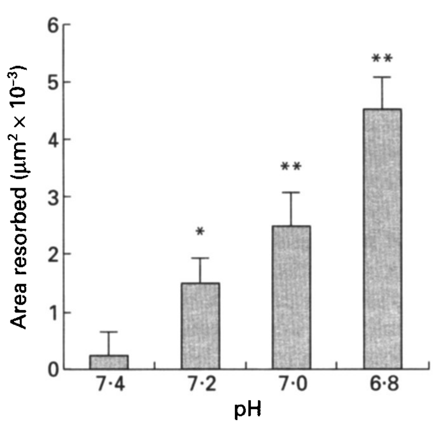

Fig. 5. Increase in osteoclastic activity with a reduction in extracellular pH. Mean values were significantly different from that at pH 7·4: **P*<0·05, ***P*<0·01. (From Arnett & Dempster, 1986.)

Vegetarianism and skeletal health

Following the recognition of the role that bone plays in acid–base balance and the hypothesis linking diet to osteoporosis, it was proposed that long-term ingestion of vegetable-based diets may have a beneficial effect on bone mineral mass. The earlier studies (published before 1990) in general appeared to support the hypothesis, i.e. bone mineral mass was found to be higher in the vegetarian group compared with their omnivorous counterparts (Table 1; Ellis *et al.* 1972; Marsh *et al.* 1980, 1983, 1988; Tylavsky & Anderson, 1988; Hunt *et al.* 1989). However, there are two important points concerning this data which require specific attention: (1) there was a fundamental error in the interpretation of the photographic density measurements in the first paper published by Ellis *et al.* (1972; i.e. their conclusions should have been the opposite of what they claimed; Meema 1973, 1996; Ellis *et al.* 1974; Barzel, 1996); (2) subjects in several of the published studies were Seventh Day Adventists with a different lifestyle from that of the omnivorous group, which is likely to have been an important confounding influence (e.g. the Seventh Day Adventist group refrained from smoking and caffeine intake and physical levels were higher).

Studies published in the last decade suggest no differences in bone mineral density between vegetarians and omnivores (Lloyd *et al.* 1991; Tesar *et al.* 1992; (Table 2). In a 5-year prospective study of changes in radial bone density of elderly white American women no differences were seen in bone loss rates between the lacto-ovo vegetarians and the omnivorous group (Reed *et al.* 1994). Furthermore, in the most recently published studies, bone mass was found to be significantly lower in the vegetable-based dietary groups (Chiu *et al.* 1997; Lau *et al.* 1998), although it is likely that protein 'undernutrition' may account for some of these differences (Rizzoli *et al.* 1998).

Very few studies have focused attention with regard to bone health on populations consuming a diet highly dependent on animal foods, particularly that of meat (Hammond & Storey, 1970). Mazess & Mather (1974) examined the bone mineral content of forearm bones in a sample (217 children, eighty-nine adults and 107 elderly) of Eskimo natives from the north coast of Alaska. After the age of 40 years, the Eskimos of both genders were found to have a deficit of bone mineral in the order of magnitude of between 10 and 15 % relative to white standards. An even greater ageing bone loss was found in Canadian Eskimos (Mazess & Mather, 1975*a*). The issue of 'dietary change' amongst the Eskimo population (particularly the utilisation of refined carbohydrates) was raised (Mann, 1975) and

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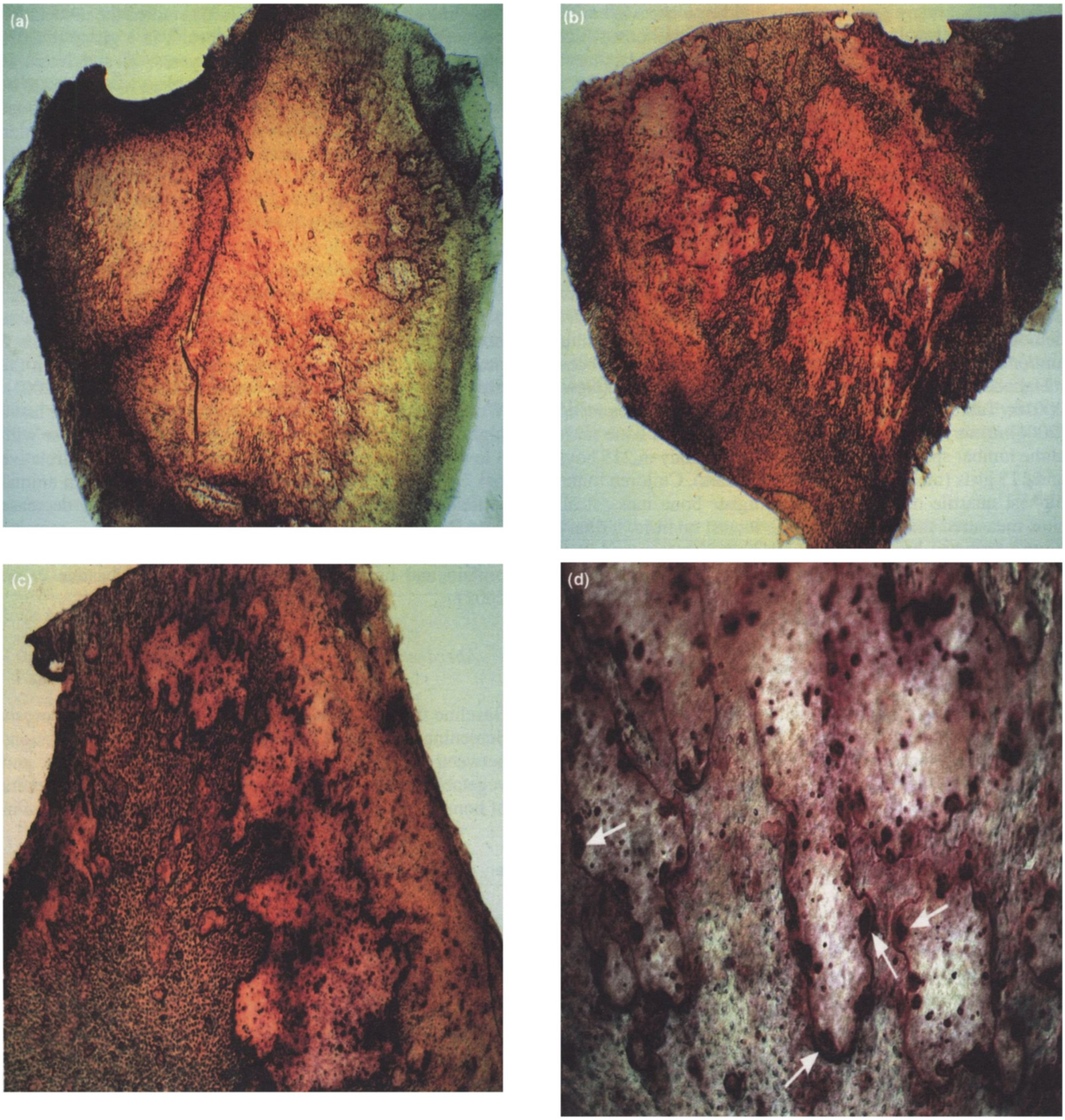

Fig. 6. Micrographs showing that metabolic acidosis stimulates resorption by activating mature osteoclasts already in mouse calvarial bone rather than by inducing formation of new osteoclasts. (a) tartrate resistant acid phosphatase-stained control bone, 3 d culture (pH 7·208) scale bar 500 μm, (b,c) resorption stimulated by bicarbonate acidosis (pH 7·01) scale bar 500 μm, (d) osteoclast activation by carbon dioxide acidosis at pH 6·8, scale bar 100 μm. (From Meghji *et al.* 2001; reproduced with kind permission of Dr T.R. Arnett.)

subsequently discussed (Mazess & Mather, 1975*b*). Clearly these findings are of considerable interest to the interaction between diet and bone in the regulation of systemic acid–base balance, and further work in this area is clearly warranted (New, 2001*a*).

Quantifying the acidity of foods: potential renal acid load

Of considerable interest is the finding that vegetable-based proteins generate a large amount of acid in the urine (Remer & Manz, 1994). Work by Remer & Manz (1995) examining the potential renal acid loads of a variety of foods has

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indicated that many grain products and some cheeses have a high potential renal acid load (Table 3). These foods, which are likely to be consumed in large quantities in lacto-ovo vegetarians, may provide an explanation for the lack of a positive effect on bone health indices in studies comparing vegetarians *v.* omnivores (Buclin *et al.* 2001). The potentially deleterious effect of specific foods on the skeleton has been a topic of recent debate (Fox, 2001; New *et al.* 2002*a*).

Fruit and vegetable intake and bone health: findings from population-based studies

A number of population-based studies published in the last decade investigating the impact of diet on bone health, have demonstrated a beneficial effect of fruit and vegetable and/or K intake on axial and peripheral bone mass and bone metabolism in men and women across the age ranges (New, 2001*b*; Table 4). In the most recent study by Jones *et al.* (2001) urinary K was positively associated with bone mass at the lumbar spine, femoral neck and total body in 215 boys and 115 girls (mean age 8·1 (SD 0·33) years). Children in the highest quartile of urinary K had higher bone mass at all sites measured than children in the lowest quartile. Urinary K was found to be correlated with both K intake and fruit and vegetable consumption.

Several important papers were also presented at the recent 2001 American Society of Bone and Mineral Research conference. Chen *et al.* (2001) examined the association between diet and bone mineral density in a group of 668 early post-menopausal Chinese women. Results showed that higher intakes of fruit were positively associated with bone mineral density at all three bone mass sites measured, and fruit intake accounted for 1·7 and 1·4 % of changes in both bone mineral density and bone mineral content respectively at the whole-body level, with similar results found for the spine and hip. Stone *et al.* (2001) studied the association between dietary intake and bone health in a group of 1075 elderly American men aged ≥65 years. K and lutein (a carotenoid found in dark-green vegetables) were found to be significantly associated with whole-body and hip bone mineral density. In a further study examining the association between diet and bone mass in American men aged 50–91 years Miller *et al.* (2001) noted that low dietary intakes of Mg (<300 mg/d) and K (<2·5 g/d) were found to be significantly associated with low femoral neck and radial bone mass.

Work recently published by Professor Anthony Sebastian's group examined the hypothesis that a high dietary animal protein:vegetable protein intake increases bone loss, and risk of fracture was investigated in a prospective cohort of 1035 women who participated in the Study of Osteoporotic Fractures (Sellmeyer *et al.* 2001). Women with a higher animal:vegetable protein intake had a higher rate of bone loss at the femoral neck than those with a low ratio, as well as a greater risk of hip fracture (relative risk 3·7). These findings suggest that a reduction in animal protein and an increase in vegetable protein may decrease bone loss and risk of hip fracture. Controversy remains concerning the relationship between animal *v.* vegetable protein and bone health (Heaney, 2001; Sebastian *et al.* 2001).

Aberdeen Prospective Osteoporosis Screening Study: baseline and longitudinal findings

Baseline findings of the Aberdeen Prospective Osteoporosis Screening Study (APOSS) have shown specific associations between nutrients found in abundance in fruit and vegetables and axial and peripheral bone mass and markers of bone resorption. In the first study of 994 women, those in

Table 1. Vegetarianism and bone health: summary of studies; earlier work (New, 2001*b*)

Reference	Findings	Summary
Ellis *et al.* (1972)	BMD ↑ in vegetarian group	✓
Ellis *et al.* (1974)	BMD ↓ in vegetarian group	×
Mazess & Mather (1974)	BMC ↓ in North Alaskan Eskimos	✓
Mazess & Mather (1975*a*)	BMC ↓ in Canadian Eskimos	✓
Marsh *et al.* (1980)	Bone loss ↑ in omnivores	✓
Marsh *et al.* (1983)	BMD ↑ in vegetarians	✓
Marsh *et al.* (1988)	BMD ↑ in elderly vegetarians	✓
Tylavsky *et al.* (1988)	No difference in BMD between groups	–
Hunt *et al.* (1989)	No difference in BMD between groups	–

BMD, bone mineral density; BMC, bone mineral content; ↑, higher; ↓, lower; ✓, positive association; ×, negative association.

Table 2. Vegetarianism and bone health: summary of studies; later work (New, 2001*b*)

Reference	Findings	Summary
Lloyd *et al.* (1991)	No difference in BMD between groups	–
Tesar *et al.* (1992)	No difference in BMD between groups	–
Reed *et al.* (1994)	Bone loss rates similar	–
Chiu *et al.* (1997)	BMD ↓ in vegan group	×
Lau *et al.* (1998)	Hip BMD lower in vegetarian group	×

BMD, bone mineral density; ↓, lower; ×, negative association.

the lowest quartile of intake of K, Mg, fibre, vitamin C and β-carotene had significantly lower lumbar spine and femoral neck bone mineral densities, findings which were independent of important confounding factors ($P<0.01$ for K in both cases; New *et al.* 1997; Fig. 7). In a second study (*n* 62) women with low intakes of these same nutrients were found to have lower forearm bone mass and higher bone resorption (New *et al.* 2000; Fig. 8), findings which were again independent of important confounding factors. With financial assistance, initially from the Department of Health and MRC and more recently from the Food Standards Agency (formerly Ministry of Agriculture, Fisheries and Food), APOSS longitudinal data now make up the largest nutrition, genetic and bone health dataset currently available worldwide, involving approximately 4000 women. Preliminary analysis indicates a positive influence of alkaline-forming foods on post-menopausal bone loss and bone turnover markers (Macdonald *et al.* 2001*a*, 2002*a,b*). Further exploration of the data will enable determination of potential relationships between nutrient–gene interactions and bone health, with a specific focus on the role of the skeleton in acid–base maintenance.

Potassium bicarbonate administration and bone: clinical applications

The clinical application of the effect of normal endogenous acid production on bone is of considerable interest, with extensive work in this area by Lemann (at the subject level; (Lemann *et al.* 1967, 1979, 1986, 1989, 1991) and Bushinsky (at the cellular level; (Bushinsky *et al.* 1983, 1993, 1994, 1997; Bushinsky & Sessler, 1992; Bushinsky, 1997). Sebastian *et al.* (1994) demonstrated that $KHCO_3$ administration resulted in a decrease in urinary Ca and P, with overall Ca balance becoming less negative (or more positive). Changes were also seen in markers of bone metabolism, with a reduction in urinary excretion of hydroxyproline (bone resorption) and an increased excretion of

Table 3. Potential renal acid load (PRAL) values of a variety of foods and food groups (Remer & Manz, 1995)

Food or food group	PRAL mEq/100 g edible portion	Food or food group	PRAL mEq/100 g edible portion
Fruits and fruit juices:		Milk, dairy products and eggs:	
Apples	−2·2	Milk (whole, pasteurised)	0·7
Bananas	−5·5	Yoghurt (whole milk, plain)	1·5
Raisins	−21·0	Cheddar cheese (reduced fat)	26·4
Grape juice	−1·0	Cottage cheese	8·7
Lemon juice	−2·5	Eggs (yolk)	23·4
Vegetables:		Meat, meat products and fish:	
Spinach	−14·0	Beef (lean only)	7·8
Broccoli	−1·2	Chicken (meat only)	8·7
Carrots	−4·9	Pork (lean only)	7·9
Potatoes	−4·0	Liver sausage	10·6
Onions	−1·5	Cod (fillets)	7·1
Grain products:		Beverages:	
Bread (white wheat)	3·7	Coca Cola	0·4
Oat flakes	10·7	Coffee (infusion)	−1·4
Rice (brown)	12·5	Tea (Indian infusion)	−0·3
Spaghetti (white)	6·5	White wine	−1·2
Cornflakes	6·0	Red wine	−2·4

Table 4. Impact of fruit and vegetables on bone: a review of population-based studies showing a positive link

Reference	Details	Findings
Eaton-Evans *et al.* (1993)	Seventy-seven females, 46–56 years	✓ Vegetables
Michaelsson *et al.* (1995)	175 females, 28–74 years	✓ K intake
New *et al.* (1997)	994 females, 45–49 years	✓ K, Mg, fibre, vitamin C ✓ Past intake: fruit and vegetables
Tucker *et al.* (1999)	229 males, 349 females, 75 years	✓ K, Mg, fruit and vegetables
New *et al.* (2000)	Sixty-two females, 45–54 years	✓ K, Mg, fibre, vitamin C ✓ Past intake: fruit and vegetables
Jones *et al.* (2001)	215 boys, 115 girls, 8–14 years	✓ K, urinary K
Chen *et al.* (2001)	668 females, 48–62 years	✓ Fruit
Miller *et al.* (2001)	300 males, 50–91 years	✓ K, Mg
Stone *et al.* (2001)	1075 men, ≥65 years	✓ K, lutein
New *et al.* (2002*b*)	164 females, 55–87 years	✓ K, fruit and vegetables

✓, positive association.

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serum osteocalcin (bone formation). Concern has been raised that the level of protein consumed by the women in the study was higher than is typical of American women in this age-group, and there has been a call for further studies to be undertaken with dietary protein being consumed at a more reasonable level (Wood, 1994). However, the study by Sebastian's group (Sebastian *et al.* 1994) is of major clinical importance and may have valued implications for the prevention and treatment of post-menopausal osteoporosis (Morris, 2001). Whilst long-term studies are of course required, administration of alkali may provide women with an alternative therapy for ageing bone loss (Sebastian *et al.* 1990; Kraut & Coburn, 1994).

Net endogenous acid production and the skeleton

Determination of the acid–base content of diets consumed by individuals and population groups is a useful way forward in relation to the role of the skeleton in acid–base homoeostasis. Since 24 h urine collections (considered as the gold standard for acid–base research) are entirely inappropriate for population-based studies, an alternative is to examine the net acid content of the diet. Sebastian's group (Frassetto *et al.* 1998) has found that the protein:K value predicts net acid excretion and, in turn, net renal acid excretion predicts Ca excretion. They propose a simple algorithm to determine the net rate of endogenous non-carbonic acid production from considerations of the acidifying effect of protein and the alkalising effect of K.

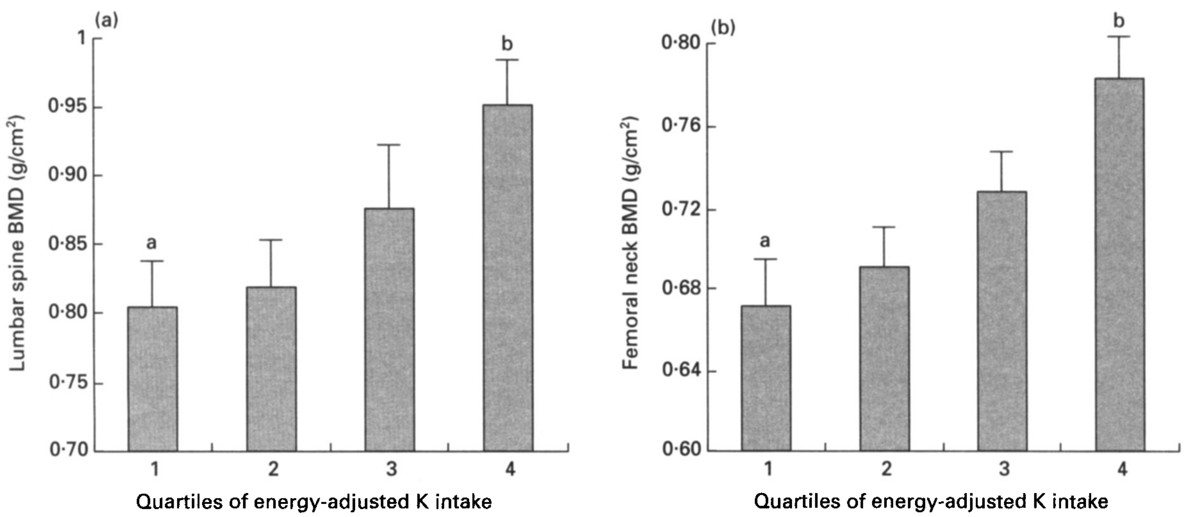

Fig. 7. Fruit and vegetable intake and bone mineral density (BMD) in women (*n* 994); evidence of a positive link? Baseline values are shown for (a) lumbar spine BMD and (b) femoral neck BMD from study 1 of the Aberdeen Prospective Osteoporosis Screening Study. Values are means with their standard errors represented by vertical bars.[a,b] Mean values with unlike superscript letters were significantly different ($P<0{\cdot}01$). (From New *et al.* 1997.)

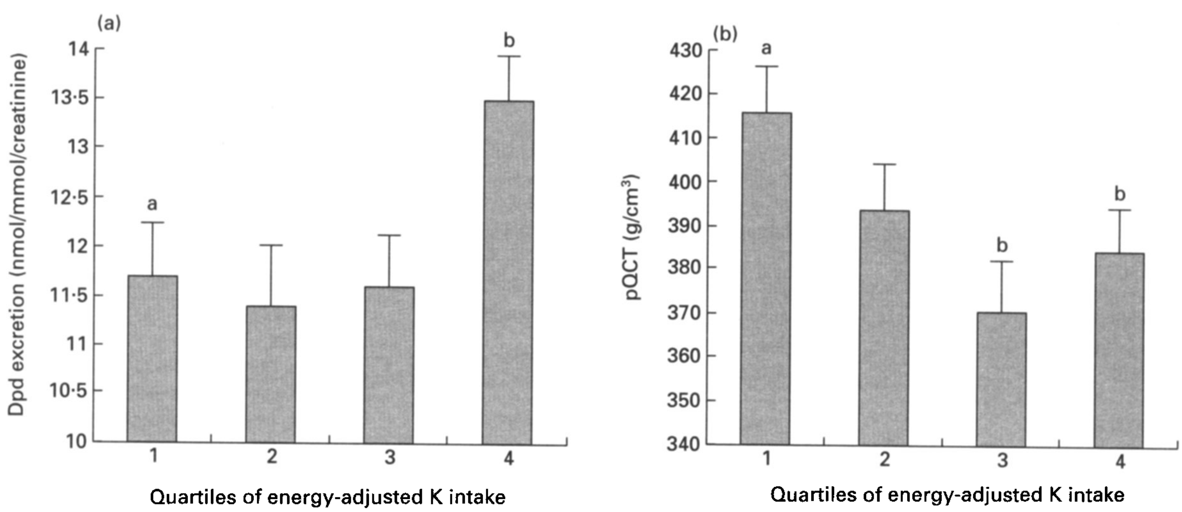

Fig. 8. Fruit and vegetable intake and bone metabolism in women (*n* 62); evidence of a positive link? Baseline values are shown for (a) deoxy pyridinoline (Dpd) excretion and (b) peripheral qualitative computed tomography (pQCT) data from study 2 of the Aberdeen Prospective Osteoporosis Screening Study. Values are means with their standard errors represented by vertical bars.[a,b] Mean values with unlike superscript letters were significantly different ($P<0{\cdot}01$). (From New *et al.* 2000.)

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To examine this theory further, net endogenous acid production from the baseline data of APOSS was calculated. Women with the lowest net endogenous acid production were found to have a higher lumbar spine bone mineral density (Fig. 9) and significantly lower urinary pyridinium cross-link excretion (pyridinoline ($P<0{\cdot}004$) and deoxy-pyridinoline ($P<0{\cdot}02$); Fig. 10; New *et al.* 2001*c*). Furthermore, preliminary analyses of the APOSS longitudinal dataset indicate significantly higher net endogenous acid production in women who had suffered any fracture compared with those in the non-fracture group ($P<0{\cdot}03$; HM Macdonald, SA New, DA Grubb, MHN Golden and DM Reid, unpublished results; Fig. 11).

Findings of the Dietary Approaches to Stopping Hypertension I and II fruit and vegetable intervention trials: implications for bone health

Further support for a positive link between fruit and vegetable intake and bone health can be found in the results of the Dietary Approaches to Stopping Hypertension (DASH) I and II intervention trials. In DASH I diets rich in fruit and vegetables were associated with a significant fall in blood pressure compared with baseline measurements (Appel *et al.* 1997). However, of particular interest to the bone field were findings that increasing fruit and vegetable intake from 3·6 to 9·5 daily servings decreased the urinary Ca excretion from 157 mg/d to 110 mg/d (Appel *et al.* 1997). The authors suggested this difference was due to the high fibre content of the diet possibly impeding Ca absorption. However, a more likely explanation, put forward by Barzel (1997), was a reduction in the 'acid load' with the fruit and vegetable diet compared with the control diet. This study is the first population-based fruit and vegetable intervention trial showing a positive effect on Ca economy (albeit a secondary finding).

More recently, Lin *et al.* (2001) have reported the findings of the DASH II (DASH-Sodium) trial. The impact of two dietary patterns on indices of bone metabolism were examined. The DASH diet emphasises fruits, vegetables and low-fat dairy products, and is reduced in red meats, and in this second DASH II trial three levels of Na intake were investigated (50, 100 and 150 nmol/1). Subjects consumed the control diet at the 150 mmol Na intake/d level for 2 weeks and were then randomly assigned to eat either the DASH diet or the control diet at all three Na levels for a further 4 weeks in random order. The DASH diet, compared with the control diet, was found to significantly reduce both bone formation (by measurement of the marker osteocalcin) and bone resorption (by measurement of the marker C-terminal propeptide). Interestingly, Na intake did not significantly affect the markers of bone metabolism. DASH II is an important intervention study that shows a clear benefit of the high intake of fruit and vegetables on markers of bone metabolism. Research is now required to determine the long-term clinical impact of the DASH diet on bone health and fracture risk, as well as clarification of the exact mechanisms involved with respect to this diet on skeletal protection.

Nutrient–gene interactions and buffering the capacity of bone

The identification of a link between specific gene polymorphisms and bone health lends support to the suggestion that public health strategies should target dietary advice at those women with a genetic predisposition to osteoporosis. Evidence indicates that Ca absorption is dependent on vitamin D receptor genoptype in older women (Dawson-Hughes *et al.* 1995). Recent data from APOSS longitudinal suggests that Ca intake is a determinant of bone mineral density in women with the 'bb' vitamin D receptor genotype

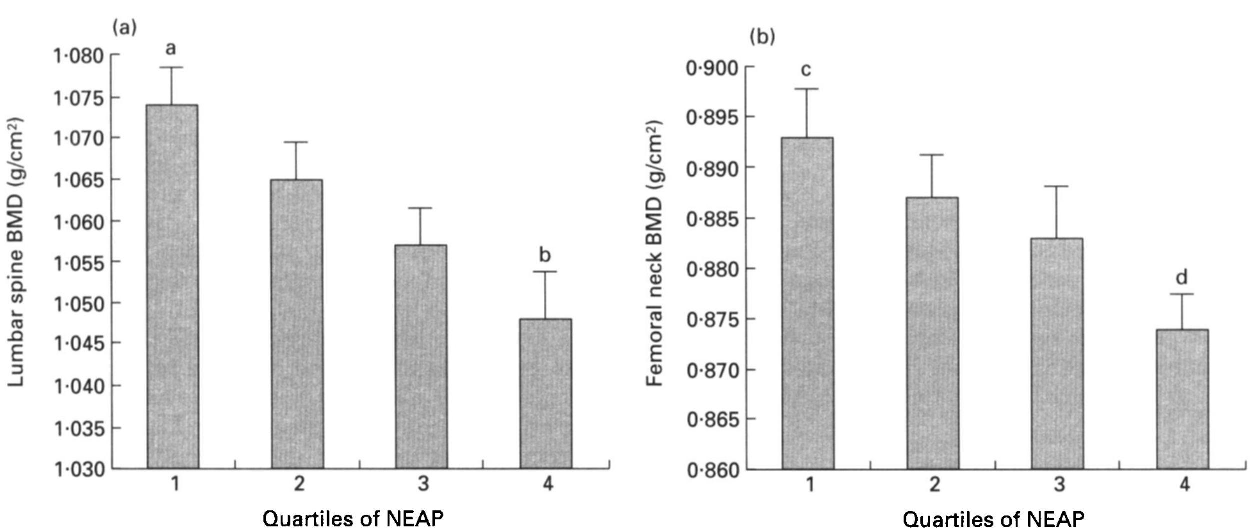

Fig. 9. Association between non-endogenous acid production (NEAP; protein: potassium intake) and bone mass (bone mineral density; BMD) in 994 women participating in study 1 of the Aberdeen Prospective Osteoporosis Screening Study. Values are means with their standard errors represented by vertical bars.[a,b,c,d] Mean values with unlike superscript letters were significantly different: [a,b] $P<0{\cdot}04$; [c,d] $P<0{\cdot}08$. (From New *et al.* 2001.)

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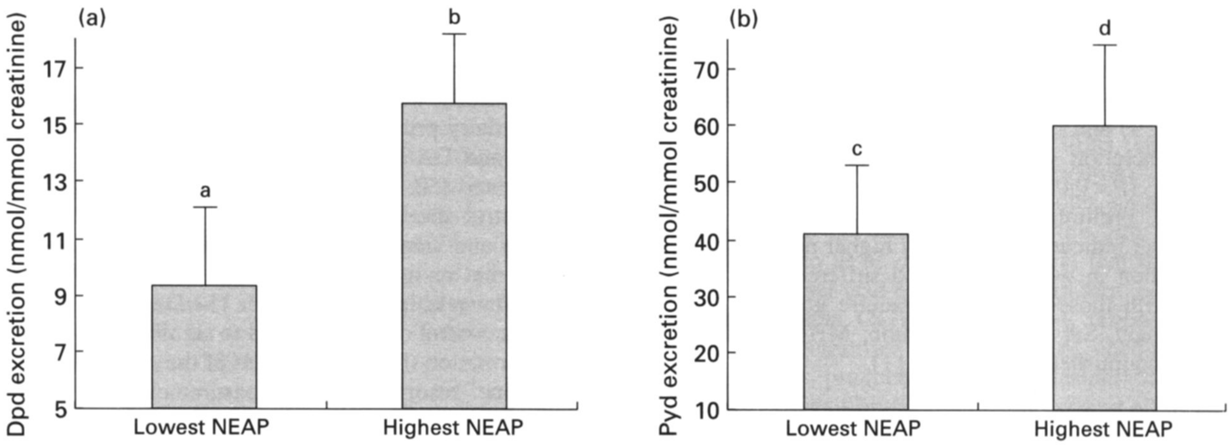

Fig. 10. Association between non-endogenous acid production (NEAP; protein: potassium intake) and bone resorption (deoxypyridinoline (Dpd; a) and pyridinoline (Pyd; b) excretion) in 62 women participating in study 2 of the Aberdeen Prospective Osteoporosis Screening Study. Values are means with their standard errors represented by vertical bars.[a,b,c,d] Mean values with unlike superscript letters were significantly different: [a,b] $P<0.02$; [c,d] $P<0.004$. (From New *et al.* 2001.)

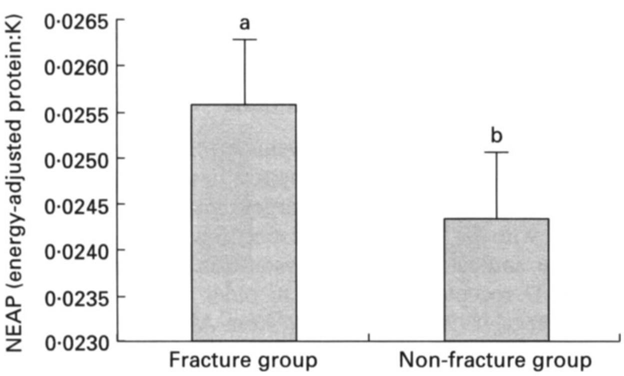

Fig. 11. Non-endogenous acid production (NEAP; protein: potassium intake) in fracture and non-fracture groups of women. Preliminary findings from the Aberdeen Prospective Osteoporosis Screening study. Values are means with their standard errors represented by vertical bars.[a,b] Mean values with unlike superscript letters were significantly different ($P<0.03$). (From HM Macdonald, SA New, DA Grubb, MHN Golden and DM Reid, unpublished results.) (Reproduced with kind permission of Dr HM Macdonald.)

and who are not taking exogenous oestrogen (Macdonald *et al.* 2000), and modest alcohol intake (1–2 units per d) is associated with reduced bone loss in women with the p' allele of the oestrogen receptor genoptype (Macdonald *et al.* 2001*b*). Whether the buffering capacity of bone is susceptible to nutrient–gene interactions remains unknown and is certainly an area which warrants further research.

Future directions

It is widely believed that the diet of 'modern man' is vastly different from that which early man once consumed (Eaton & Konner, 1985). Considerations of the dietary content of pre-agricultural man estimate intakes of Na to be 600 mg/d and those of K to be at levels reaching 7000 mg/d. These data are in stark contrast to published dietary data that estimate population intakes of Na and K at levels of approximately 4000 and 2500 mg/d respectively in the UK, USA and Australia (Gregory *et al.* 1990; Patterson *et al.* 1990). As noted by Eaton *et al.* (1996), our kidneys are designed to excrete more K than Na, because K was plentiful in the diet. This evolutionary mechanism still exists, despite the almost total dietary reversal of consuming more Na than K; hence the term 'today's diet, yesterday's genes' is most fitting.

The evidence currently available from experimental, clinical and observational studies suggests a role for the skeleton in acid–base homeostasis, with confirmation of these findings being seen in the animal model (Muhlbaur & Li, 1999). Future research should focus attention on a number of areas: (1) there is an urgent requirement for intervention trials centred specifically on fruit and vegetables as the supplementation vehicle and assessing a wide range of bone health indices, including fracture risk; (2) experimental studies would be useful to determine whether there are other aspects of fruit and vegetables which are beneficial to bone metabolism, including key micronutrient intake and phytoestrogens; (3) the relationship between net endogenous acid production and skeletal integrity needs to be further defined and, in particular, whether high protein intakes are detrimental to the skeleton in the absence of alkali-forming foods. Conversely, the role of protein in bone health needs to be quantified more fully and, in particular, the interaction between dietary protein intake and insulin-like growth factor I, which is known to have osteotrophic properties; (4) there is a need for re-analysis of existing dietary–bone mass and metabolism datasets to look in particular at the impact of 'dietary acidity' on the skeleton.

Should the findings of these research areas prove conclusive, a 'fruit and vegetable' approach to bone health development and maintenance may provide a very sensible (and natural) alternative therapy for osteoporosis treatment, which is likely to have numerous additional health-related benefits. The road ahead is an exciting one!

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