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Postgraduate Symposium
Positive influence of nutritional alkalinity on bone health

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There is growing evidence that consumption of a Western diet is a risk factor for osteoporosis through excess acid supply, while fruits and vegetables balance the excess acidity, mostly by providing K-rich bicarbonate-rich foods. Western diets consumed by adults generate approximately 50–100 mEq acid/d; therefore, healthy adults consuming such a diet are at risk of chronic low-grade metabolic acidosis, which worsens with age as a result of declining kidney function. Bone buffers the excess acid by delivering cations and it is considered that with time an overstimulation of this process will lead to the dissolution of the bone mineral content and hence to reduced bone mass. Intakes of K, Mg and fruit and vegetables have been associated with a higher alkaline status and a subsequent beneficial effect on bone health. In healthy male volunteers an acid-forming diet increases urinary Ca excretion by 74 % and urinary C-terminal telopeptide of type I collagen (C-telopeptide) excretion by 19 % when compared with an alkali (base-forming) diet. Cross-sectional studies have shown that there is a correlation between the nutritional acid load and bone health measured by bone ultrasound or dual-energy X-ray absorptiometry. Few studies have been undertaken in very elderly women (>75 years), whose osteoporosis risk is very pertinent. The EVAluation of Nutrients Intakes and Bone Ultra Sound Study has developed and validated (*n* 51) an FFQ for use in a very elderly Swiss population (mean age 80·4 (sd 2·99) years), which has shown intakes of key nutrients (energy, fat, carbohydrate, Ca, Mg, vitamin C, D and E) to be low in 401 subjects. A subsequent study to assess net endogenous acid production (NEAP) and bone ultrasound results in 256 women aged ≥75 years has shown that lower NEAP ($P = 0.023$) and higher K intake ($P = 0.033$) are correlated with higher bone ultrasound results. High acid load may be an important additional risk factor that may be particularly relevant in very elderly patients with an already-high fracture risk. The latter study adds to knowledge by confirming a positive link between dietary alkalinity and bone health indices in the very elderly. In a further study to complement these findings it has also been shown in a group of thirty young women that in Ca sufficiency an acid Ca-rich water has no effect on bone resorption, while an alkaline bicarbonate-rich water leads to a decrease in both serum parathyroid hormone and serum C-telopeptide. Further investigations need to be undertaken to study whether these positive effects on bone loss are maintained over long-term treatment. Mineral-water consumption could be an easy and inexpensive way of helping to prevent osteoporosis and could be of major interest for long-term prevention of bone loss.

Dietary alkalinity: Bone health: Acid–base balance: Elderly

Osteoporosis is a skeletal disorder characterised by low bone mass and microarchitectural deterioration of bone tissue, leading to bone fragility and an increased risk of fracture. Optimum bone health is achieved through the contribution of numerous factors such as genetics, health and nutrition. It is common to consider bone health in

terms of Ca intake only. Ca is indeed a critical component of the skeleton; however, bone health is much more complex. Whilst the optimum diet for osteoporosis prevention remains unknown, a variety of nutrients are important to the ageing skeleton including protein and micronutrients such as Ca, K and vitamin K[1,2]. There is a growing belief that the Western diet may be a risk factor for osteoporosis through excess acid supply. Fruit and vegetable intake may balance the excess acidity by providing K[1,2]. As the major determining factor for osteoporosis is an individual's genetic makeup, which cannot be modified, it is important to identify modifiable risk factors that contribute to bone health and use them in prevention messages to the population. Nutrition is a modifiable factor that has the potential to be altered relatively easily and cheaply.

Osteoporosis

Definition

In 1994 the WHO Working Group defined osteoporosis according to measurements of bone mineral density (BMD) using dual-energy X-ray absorptiometry. Thus, osteoporosis is defined as a bone density T-score of ≤ 2.5 SD below normal peak values for young adults[3]. These criteria were initially established for the assessment of osteoporosis in Caucasian women.

Epidemiology

Recent epidemiological data estimate that one in two women and one in five men aged >50 years will suffer from an osteoporotic fracture[4]. Thus, it is urgent for public health strategies to reduce the predicted increase in osteoporosis within the aging population by undertaking prevention campaigns. A public health strategy for optimising bone health throughout the life cycle is critically important.

Osteoporosis affects an estimated seventy-five million individuals in Europe, USA and Japan. In 2000 there were approximately 9×10^6 new osteoporotic fractures[5]. Recent epidemiological data from the Third National Health and Nutrition Examination Survey indicate that 13–18% of white American women aged ≥ 50 years have osteoporosis of the hip[6]. The lifetime risk in the UK for a hip, spine or forearm fracture at the age of 50 years has been estimated to be 53% in women and 21% in men[7]. The projected rise in osteoporotic fracture worldwide clearly demonstrates that the future impact of osteoporosis will be enormous; the worldwide incidence of hip fracture in men is projected to increase by 310% and 240% in women by 2050[8].

In Switzerland between 2000 and 2020 osteoporotic hip, vertebral and forearm fracture are predicted to increase by 33%, 27% and 19% respectively if present prevention and treatment patterns stay unchanged[9]. In terms of duration of hospital stay, the annual cost of hospitalisations for osteoporotic fractures is higher than those for myocardial infarction, stroke and breast cancer[10]. In 2000 62 535 hospitalisations for fractures were registered. The direct medical cost of hospitalisations of patients with osteoporosis and/or related fractures was 357×10^6 Swiss Francs (£15×10^6), with hip fractures accounting for approximately half these costs[11].

Acid–base balance

Disturbances of acid–base balance in the body are classified as either acidosis, indicating an excess of H^+ ions (leading to an acid environment; e.g. metabolic, latent or respiratory acidosis), or alkalosis (leading to a reduction in H^+ ions and therefore a more alkaline environment). Such disturbances of acid–base balance are relevant to bone health. *In vitro* studies have shown that there is an induced Ca efflux from bone as a result of metabolic acidosis[12], which is the only form of acidosis relevant to bone. A moderate increase in alkaline equivalents (90 mmol potassium citrate/d) has been shown to reduce bone resorption, increase bone formation and improve Ca balance in postmenopausal women[13].

Measuring acid–base status

During the past few decades a number of researchers have used *in vitro* methods that are inappropriate to specifically determine the acid- or alkaline-producing potential of the diet[14]. An *in vitro* measurement of acid:base has been made by using a calculation model[15,16]. The net acid load is estimated from average intestinal absorption rates of ingested S-containing protein (cysteine and methionine) and additional minerals as well as an anthropometry-based estimate for organic acid excretion:

$$\text{estimated net endogenous acid production (NEAP;}$$
$$\text{mEq/d}) = \text{PRAL (mEq/d)} + \text{OA}_{est}(\text{mEq/d})^{[17,]}$$

where PRAL is potential renal acid load and OA_{est} is estimated organic acids, i.e. estimated urinary organic anions, with these two components calculated as follows (we did not include Na and Cl in the PRAL equation because they are usually balanced in the diet):

$$\text{PRAL (mEq/d)} = 0.49 \times \text{protein (g/d)} + 0.037$$
$$\times \text{P (mg/d)} - 0.021 \times \text{K (mg/d)} - 0.026$$
$$\times \text{Mg (mg/d)} - 0.013 \times \text{Ca (mg/d)};$$
$$\text{OA}_{est}(\text{mEq/d}) = \text{individual body surface area}$$
$$\times [0.007184 - \text{height}^{0.725}(\text{cm}) - \text{weight}^{0.425}(\text{kg})] \times 41/1.73.$$

Determination of acid:base of foods contributing to the overall diet consumed by individuals and population groups is a practical and useful method that can be used in assessing the role of the skeleton in acid–base homeostasis[18]. PRAL has been estimated for a variety of foods items using nutrient data expressed on a per 100 g food basis for protein (methionine, cysteine), P, Cl, K, Mg, Ca and Na (Table 1)[16].

Nutritional factors that influence acid–base balance

Nutrition has long been known to strongly influence acid–base balance in human subjects[19]. Intakes of K, Mg and fruit and vegetables have been associated with a more

Table 1. Estimated potential renal acid load (PRAL) in a variety of foods items (from Remer & Manz[16])

Food group	PRAL (mEq/100 g)
Hard cheese	23·6
Meat and meat products	9·5
Bread	3·5
Milk and non-cheese products	1
Vegetables	−2·8
Fruits	−3·1

alkaline environment in the human body and therefore have a beneficial effect in relation to bone health[20].

Indeed, Western diets consumed by adults generate 50–100 mEq acid/d[21]. Thus, healthy adults consuming such a diet are at risk of chronic low-grade metabolic acidosis, which worsens with age as a result of a decline in kidney function[22].

Role of the skeleton

Maintenance of acid–base homeostasis is tightly regulated in the extracellular fluid at pH 7·4 ±0·05[18]. Almost every biological process in the human body is dependent on the acid–base balance, including bone metabolism. Bone contributes to acid–base homeostasis as it delivers cations such as Mg, K, Ca and Na, which can be associated with alkali salts such as citrate or carbonate. Over time, an over-stimulation of this process will lead to the dissolution of the bone mineral content and hence to a reduction in bone mass[18,22]. Thus, long-term nutritional acid load may be harmful to bone health.

Protein

Protein is an important macronutrient contributing to BMD. Indeed, sufficient dietary intake appears to have a beneficial effect on bone healing. Supplementation with 20 g protein improves fracture healing and reduces bone loss in elderly subjects; the mechanism appearing to be at least partially through an increase in insulin-like growth factor 1, which stimulates proliferation and differentiation of osteoblasts[23]. However, protein has an acidic effect on bone, which is thought to be undesirable. More precisely, two mechanisms come into play: excess protein induces an increase in renal Ca excretion; the metabolism of the S amino acids (methionine and cysteine) generates an acid load, which results in a reduction in blood and urinary pH[22,24,25]. However, it has been suggested that high-protein diets are associated with an increased risk of fracture when Ca is low, but there is no overall association between total protein and fracture risk with high Ca intake[26]. Furthermore, a study of 161 post-menopausal women has suggested that protein intake is positively associated with areal BMD, but benefit at the lumbar spine is offset by a negative impact of the protein S acid load[27]. However, it has also been suggested that the negative association between meat intake and BMD may be a reflection of an inadequate consumption of fruit and vegetables rather than an excessive consumption of meat[28].

In vitro *studies*

In vitro studies have shown that metabolic acidosis induces a Ca efflux from bone[12]. It has been demonstrated that the acidification of bone may not be linked only to osteoclastic activity; cultured osteoblasts show reduced collagen synthesis and mineralisation in an acidic environment[29,30]. In both the animal and human model an acid environment is associated with a negative Ca balance and increased bone loss[31–33]. Any reduction in extracellular pH enhances osteoclastic activity[34]. Even a small change in pH, approximately (pH 7·1) but not exactly at the physiological level (pH 7·4), stimulates osteoclasts[35]. On a long-term nutritional acidic load, pH is kept constant at the expense of bone, which delivers the buffering substances through bone resorption[36].

In vivo *studies*

In vivo studies in healthy subjects have shown that supplements of $KHCO_3$, potassium citrate and even bicarbonate-rich mineral water decrease calciuria and bone resorption markers[13,37–39]. In healthy male volunteers an acid-forming diet increases urinary Ca excretion by 74 % and urinary C-terminal telopeptide of type I collagen (C-telopeptide) excretion by 19 % when compared with an alkali (base-forming) diet[40] (Fig. 1). In cross-sectional studies assessment of the acid:base value has shown that there is a correlation between the nutritional acid load and bone health measured by bone ultrasound[41] or dual-energy X-ray absorptiometry[42]. The Dietary Approaches to Stop Hypertension Trial, which examined the effects of two dietary patterns in 186 adults aged 23–76 years, has compared an experimental Ca-rich diet emphasising fruits, vegetables, whole grains, poultry, fish, nuts and low-fat dairy products with the typical American diet as the control diet. The experimental diet was found to reduce serum osteocalcin by 8–11 % and C-telopeptide by 16–18 % ($P<0·001$)[43]. However, a recent randomised placebo-controlled study has shown no effect of K supplementation[44]. It was found that potassium citrate supplementation for 2 years does not decrease bone turnover or increase BMD at the spine or hip in post-menopausal healthy women. Moreover, in the group of women who received a supplement of 300 g fruit and vegetables no impact on bone turnover or BMD was observed[44]. Furthermore, the findings of the EVAluation of Nutrients Intakes and Bone Ultra Sound Study (discussed later) have led to the hypothesis that very elderly subjects may be more sensitive to nutritional interventions. In a healthy population other factors such as weight and muscle mass have a substantial effect on bone[45,46].

Results from the EVAluation of Nutrients Intakes and Bone Ultra Sound Study

Development of a Swiss FFQ

Few studies have been undertaken in very elderly women (>75 years), who are at major risk of osteoporosis risk. As part of the EVAluation of Nutrients Intakes and Bone
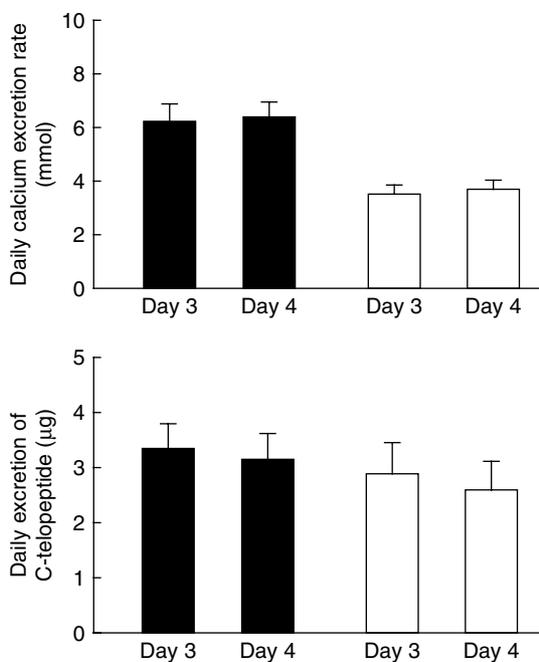
Fig. 1. Mean daily excretion rates of calcium and C-terminal telopeptide of type I collagen (C-telopeptide) for healthy male volunteers (n 8; age 22–31 years) receiving an acid-forming diet (■) or a base-forming diet (□) with no calcium supplement on day 3 and 1 g calcium supplement on day 4 in a double-cross-over design study. To obtain optimal compliance both diets consisted of alternation of two daily menus, one for days 1 and 3, the other for days 2 and 4. Values are means with their standard errors represented by vertical bars. The effect of diet was significant for calcium ($P = 0.0002$) and C-telopeptide ($P = 0.01$). Calcium supplement had no significant effect. (From Buclin *et al.*[40]; with kind permission of Springer Science and Business Media.)

Ultra Sound Study on osteoporosis in a Swiss very elderly population the influence of dietary intake and acid load on bone health indices was examined in a cohort of 401 ambulatory women (mean age 80·6 years) from the Lausanne area, an urban area of approximately 200 000 inhabitants. A detailed FFQ was developed, cross-validated against a further forty-four 4 d weighed records and the short- (1 month; n 15) and long-term (12 months; n 14) reproducibility examined[47]. No significant difference was found between mean energy intakes by 4 d weighed records and the FFQ (6548 (SD 1469) kJ (1565 (SD 351) kcal) and 6867 (SD 2189) kJ (1641 (SD 523) kcal) respectively). Mean crude nutrient intakes were also found to be similar (paired t test), ranging from $P = 0.13$ for K to $P = 0.48$ for Mg. Similar results were found in the reproducibility studies.

Nutrient intake of the EVAluation of Nutrients Intakes and Bone Ultra Sound Study population

The validated FFQ was administered to the cohort of 401 subjects to assess dietary intake[48]. The mean daily energy intake was found to be 6460 (SD 1874) kJ (1544 (SD 447·7) kcal), with a protein intake of 65·2 (SD 19·9) g, i.e. 1·03 g/kg body weight per d. The mean daily intakes for energy, fat, carbohydrate, Ca, Mg, vitamin C, D and E were found

Table 2. A comparison of daily dietary intake, as recorded by FFQ, and recommended nutrient intakes (RNI) for 401 very elderly Swiss women (mean age 80·6 years)

Nutrient	RNI[49]	Recorded intake		
		Mean	SD	% RNI
Energy (kJ)	8657	6460	1874	74·6
Protein (g)	62·7	65·2	19·9	104
Fat (g)	69	63·9	21·3	92·6
Carbohydrate (g)	>259	164	54·4	63·3
Minerals				
Ca (mg)	1000	983	389	98·3
P (mg)	700	1164	392	166
Mg (mg)	300	288	93·1	95·9
K (mg)	2000	2761	875	138
Fe (mg)	10	11·6	3·7	116
Vitamins				
Vitamin B$_6$ (mg)	1·2	1·25	0·44	104
Vitamin C (mg)	100	93·1	45·2	93·1
Vitamin D (µg)	10	2·49	1·45	24·9
Vitamin E (mg)	11	9·39	3·88	85·4
NEAP (mEq)		− 3·22	− 42·4 to + 29·2*	

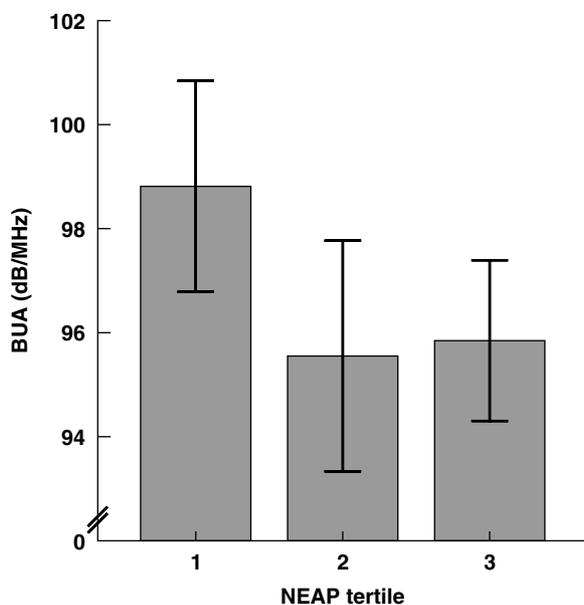NEAP, net endogenous acid production.
*Range.

to be below their respective recommended nutrient intakes[49], while protein, P, K, Fe and vitamin B$_6$ intakes were above their respective recommended nutrient intakes[49] (Table 2). The NEAP for each subject was also calculated using the PRAL equation (Table 2).

Thus, the recommendation to optimise dietary intake is energy-dense foods rich in carbohydrate, Mg, Ca, vitamin D and E as well as regular sunshine exposure.

Association between net endogenous acid production estimates and bone ultrasound

The association between NEAP estimates and bone ultrasound results was assessed in the cohort of 401 subjects[50]. No significant effects of the acid load were observed in the whole group, which led to a separate assessment of those women who had a history of fracture (n 256). Fig. 2 shows broadband ultrasound attenuation (BUA) for these 256 women stratified by tertiles of NEAP. Associations were found between higher BUA and both lower estimates of NEAP (r − 0·142, $P < 0.05$) and higher estimates of Ca and K (r 0·151 and 0·134 respectively, $P < 0.05$), with the differences remaining significant after adjustment for age, BMI and osteoporosis treatment. The stepwise regression analysis included BUA, NEAP, BMI, osteoporosis treatment, mini nutritional assessment and age. It explains 7·6% of the variation in BUA. BMI and osteoporosis treatment explained 6·3% and NEAP 1·3% of the variation ($P < 0.05$); it is known that ≤80% of the variance is explained by genetic factors.

Thus, the findings suggest that lower estimates of NEAP (i.e. more-alkaline diets) are significantly associated with higher BUA measured by bone ultrasound in the subgroup of elderly women who had a history of fractures. High acid load may be an important additional risk factor that might

Fig. 2. Broadband ultrasound attenuation (BUA) in the 256 elderly women from the EVAluation of Nutrients Intakes and Bone Ultra Sound Study with fractures stratified by tertiles of net endogenous acid production (NEAP). Values are means and standard deviations represented by vertical bars for eighty-six, seventy-eight and ninety-two subjects for tertiles 1, 2 and 3 respectively. The mean NEAP values for tertiles 1, 2 and 3 were −15·4, −2·6 and 8·3 mEq/d respectively. The mean scores of BUA for the three groups were significantly different: $P = 0.03$ (one-way ANOVA with a *post hoc* test (Tukey test)); $P = 0.03$ (F test for linearity). Comparison of the means for BUA by tertiles of NEAP (*post hoc* test (Tukey test)) showed trends: tertile 1 *v.* tertile 2, $P = 0.052$; tertile 1 *v.* tertile 3, $P = 0.07$. (From Wynn *et al.*[50].)

be particularly relevant in very elderly patients with an already-high fracture risk. The study adds to knowledge by confirming a positive link between dietary alkalinity and bone health indices in the very elderly.

The influence of drinking mineral water on bone health indices

The positive association between low estimates of dietary acid load and bone ultrasound in women >75 years of age with a history of fracture has led to the investigation of the effect of acid load in a younger population by assessing the effect of drinking mineral water on premenopausal women[51]. The consumption of mineral water may be an easy and cheap way of influencing the acid–base balance.

A comparison was undertaken of the effect of an alkaline (base-forming) mineral water rich in bicarbonate (mg/l; Ca 547, bicarbonate 2172, sulphate 9; PRAL − 11·2 mEq/l) with that of an acid (acid-forming) mineral water rich in Ca only (mg/l; Ca 520, bicarbonate 291, sulphate 1160; PRAL + 9·2 mEq/l) on bone markers in young women with a normal Ca intake. Thirty female dietitians aged 26·3 (SD 7·3) years were randomised into two groups, with each group following an identical weighed balanced diet (965 mg Ca/d) and drinking 1·5
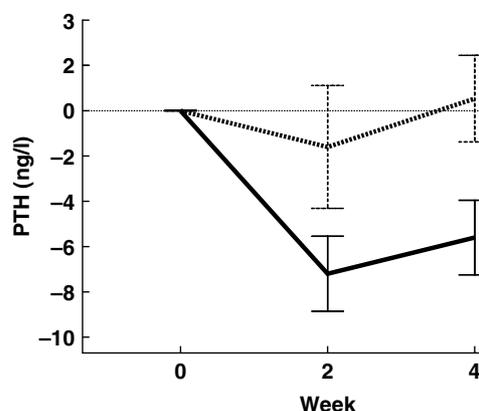
Fig. 3. Mean changes in serum parathyroid hormone (PTH) in premenopausal women (age 26·3 (SD 7·3) years) after 2 and 4 weeks of consuming either an acid-forming mineral water (*n* 15; ■ ■ ■) or a base-forming mineral water (*n* 15; ——) and an identical weighed balanced diet (965 mg Ca/d). Values are with their standard errors represented by vertical bars. For the base-forming mineral water the decrease after 4 weeks was significant ($P = 0.0043$). The difference between the two mineral waters at 4 weeks was significant ($P = 0.022$). (Reprinted from Wynn *et al.*[51], with permission from Elsevier.)
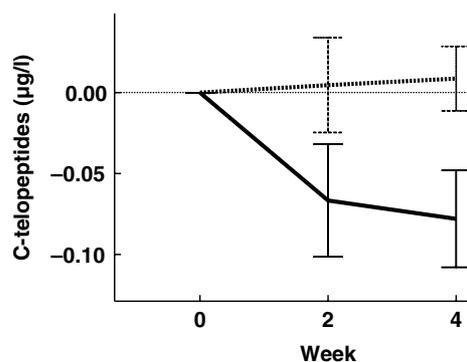
Fig. 4. Mean changes in serum C-terminal telopeptide of type I collagen (C-telopeptides) in premenopausal women (age 26·3 (SD 7·3) years) after 2 and 4 weeks of consuming either an acid-forming mineral water (*n* 15; ■ ■ ■) or a base-forming mineral water (*n* 15; ——) and an identical weighed balanced diet (965 mg Ca/d). Values are with their standard errors represented by vertical bars. For the base-forming mineral water the decrease after 4 weeks was significant ($P = 0.021$). The difference between the two mineral waters at 4 weeks was significant ($P = 0.023$). (Reprinted from Wynn *et al.*[51], with permission from Elsevier.)

litres of the assigned mineral water daily. Changes in blood and urine electrolytes, C-telopeptide, urinary pH and bicarbonate and serum parathyroid hormone were measured after 2 and 4 weeks. No difference was found between the groups at baseline and a similar increase in urinary Ca excretion was observed. Urinary pH and bicarbonate excretion were found to increase with the alkaline mineral water, but not with the acid mineral water. Parathyroid hormone ($P = 0.022$; Fig. 3) and serum C-telopeptide ($P = 0.023$; Fig. 4) were shown to decrease with the alkaline

mineral water but not with the acid mineral water. Thus, in Ca sufficiency an acid Ca-rich water has no effect on bone resorption, while an alkaline water rich in bicarbonate leads to a decrease in serum parathyroid hormone and serum-C-telopeptide[51]. By careful choice of mineral water the population could possibly positively influence their bone health.

Concluding remarks

In the present paper the role of acid–base balance and bone health has been discussed. A dietary acid load appears to have a detrimental effect on bone health indices. Long-term studies in post-menopausal women, the group most affected by osteoporosis, would be of major interest to investigate the effect of an acidic diet and whether there is an influence on fracture risk.

Directions for future research work

Future work needs to be undertaken to assess whether certain fruits and vegetables have a more beneficial effect than others. Furthermore, some currently unidentified compounds found in a number of herbs, salad and vegetables have been shown to play a beneficial role in rats[52] that is not mediated by their alkalinity but by their pharmacological activity; for example, certain phytonutrients, especially polyphenols, increase osteoblastic activity and decrease osteoclastic activity[53]. A recent study has shown that onion consumption might have a beneficial effect on BMD in peri- and post-menopausal white women aged ≥50 years[54]. Thus, increasing the amount of fruit and vegetables in the Western population may be an additional prevention treatment for osteoporosis. However, increasing the daily fruit and vegetable consumption remains a difficult challenge.

It should also be remembered that in man there is a mismatch between the genes and the modern diet that could explain the negative effects of a diet low in K salts on osteoporosis. Man's pre-agricultural hunter–gatherer ancestors consumed wild animal-source foods and uncultivated plant-source foods that would have provided an NaCl-poor K-rich bicarbonate-precursor-rich diet. This K:NaCl has inverted with the dietary shift, as in the modern human diet plant food has fallen and consumption of NaCl has increased[55]. Human genes are not adapted to this modern diet as the shift to this contemporary diet has occurred too recently for the genome to adjust[56,57]. It has been suggested that the dietary patterns responsible for low-grade metabolic acidosis, as well as low K intakes and high NaCl intakes, contribute to the pathogenesis of osteoporosis and other age-related disorders[58,59].

Acknowledgements

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