The roles of calcium and vitamin D in skeletal health: an evolutionary perspective

R.P. Heaney
Robert P. Heaney is John A. Creighton University Professor, Creighton University, Omaha, Nebraska, United States.

Hominid evolution took place in an environment (equatorial East Africa) that provided a superabundance of both calcium and vitamin D, the first in available foods and the second through conversion of 7-dehydrocholesterol to pre-vitamin D in the skin, a reaction catalysed by the intense solar ultraviolet (UV) radiation. Seemingly as a consequence, the evolving human physiology incorporated provisions to prevent the potential of toxic excesses of both nutrients. For vitamin D the protection was of two sorts: skin pigmentation absorbed the critical UV wavelengths and thereby limited dermal synthesis of cholecalciferol; and slow delivery of vitamin D from the skin into the bloodstream left surplus vitamin in the skin, where continuing sun exposure led to its photolytic degradation to inert compounds. For calcium, the adaptation consisted of very inefficient calcium absorption, together with poor to absent systemic conservation. The latter is reflected in unregulated dermal calcium losses, a high sensitivity of renal obligatory calcium loss to other nutrients in the diet and relatively high quantities of calcium in the digestive secretions.

Today, chimpanzees in the original hominid habitat have diets with calcium nutrient densities in the range of 2 to 2.5 mmol per 100 kcal, and hunter-gatherer humans in Africa, South America and New Guinea still have diets very nearly as high in calcium (1.75 to 2 mmol per 100 kcal) (Eaton and Nelson, 1991). With energy expenditure of 3 000 kcal per day (a fairly conservative estimate for a contemporary human doing physical work), such diets would provide substantially in excess of 50 mmol of calcium per day. By contrast, median intake in women in North America and in many European countries today is under 15 mmol per day.

Two factors altered the primitive situation: the migration of humans from Africa to higher latitudes and the adoption of agriculture. The first reduced environmental vitamin D availability, and the second, the calcium content of the diet.

MIGRATION AND THE VITAMIN D SYSTEM
The vitamin D system began its evolutionary adaptation much earlier than the calcium system. Long before the adoption of agriculture and a settled mode of existence, waves of humans left East Africa and populated higher latitudes. Since, with the exception of oily fish, available foods did not provide significant quantities of vitamin D, these populations lost most or all of their skin pigmentation and thereby improved their production of vitamin D to compensate for the lower solar UV radiation at the higher latitudes. Rickets and osteomalacia, still common today in dark-skinned immigrants to northern Europe and North America, would presumably have placed nomadic tribes at a severe reproductive disadvantage (rickets being a disorder of the pre-reproductive years); thus the evolution of reduced skin pigmentation must have occurred relatively rapidly. Still, it should be noted that the evolutionary trend of decreasing skin pigmentation with increasing latitude has manifest limits. At far northern and southern latitudes, the angle of the sun during most of the year is so low, even at noon, that effectively no UV radiation reaches the surface of the earth. Thus, the further north one lives, the greater the dependence on food (or, today, pharmaceutical) sources of vitamin D.

Calcium, by contrast, would still have been abundant in the food of hunter-gatherer nomads in Europe and Asia. Leafy greens, nuts, roots, tubers and the other foods in a typical hunter-gatherer's diet tend to be quite calcium rich. Indeed, the annual rack of antlers produced by deer species in northern latitudes is testimony to the environmental abundance of calcium.

DEVELOPMENT OF AGRICULTURE AND THE CALCIUM SYSTEM
The paleolithic high calcium intake probably prevailed for the human race as long as humans followed a hunter-gatherer economy, that is until about 10000 BC in the Fertile Crescent and until perhaps no more than 2 000 to 3 000 years ago in the Western Hemisphere. Thus the number of elapsed generations from the shift to an agriculture-based economy has not been sufficient to permit substantial evolutionary change in calcium physiology.

The adoption of agriculture, mandated in part by population pressures, would have meant a substantial fall in the calcium content of the diet, since cereals have very

low calcium density. Foraging would still have provided some roots and tubers, but their contribution to the diet would have been limited by the fact that agriculture required the community to be relatively settled, thus limiting the range over which they could roam for food. However, even in early farming communities calcium intake was probably not as low as the composition of the cereal grains might suggest. In the Fertile Crescent, for example, there is abundant evidence that limestone mortars and querns were used for the processing of cereal grains (Molleson, 1994). Grinding of grains would have contributed substantial quantities of calcium carbonate to the resulting flour; thus the product may be thought of as the first known fortified food. With the development of metallurgy and the ability to fabricate harder and harder millstones (mostly silicon-based, rather than calcium-based), this source of calcium was gradually lost.

From the Iron Age to the present there were even fewer generations to permit human physiologies to adapt to the reduction in calcium intake. Furthermore, the principal skeletal consequence of a low calcium diet, osteoporosis, is a disease of the post-reproductive years; therefore calcium deficiency would give affected populations a less severe reproductive disadvantage than environmental vitamin D deficiency.

CALCIUM AND VITAMIN D REQUIREMENTS

It has been understood for over a century (even since before vitamin D was identified) that absence of vitamin D produces manifest disease. It was less clear, at least until recently, that low calcium intakes had any untoward consequences. Clearly, the fact that calcium intake was high under primitive conditions does not mean, in its own right, that people need that much or that the requirement today is higher than the amount contemporary diets provide. In fact, until quite recently, significant components of the scientific community were of the opinion that there was, for all practical purposes, no calcium deficiency disease in humans and, correspondingly, that there was, effectively, no calcium requirement (Kanis and Passmore, 1989). In other words, it was held that even the relatively restricted calcium intakes of contemporary industrialized nations provided sufficient calcium to meet the needs of almost everyone. That position is no longer tenable.

In the early days of nutritional science, requirements were estimated by determining the intakes of populations in which particular deficiency diseases were and were not prevalent; the requirement was defined as the lowest intake prevailing in populations with low occurrence rates of the deficiency state. The criteria for recognition of deficiency in the early

years of the twentieth century were necessarily crude, and the understanding of the biochemistry of the vitamins very rudimentary at best. Much more sensitive and specific criteria have been established in recent years, and it has become clear that mere absence of clinically apparent disease is not the same thing as health. Thus requirements today are increasingly being defined on the basis of the intake required to maintain optimal functioning of the systems in which the nutrients operate.

Factors influencing calcium requirements

Calcium occupies a nearly unique position among the essential nutrients. Like many of the vitamins and trace minerals, it has key roles in signal transduction and catalytic protein activation at the most fundamental levels of cell biology. Furthermore, a constantly maintained concentration of calcium ions in the extracellular fluid (ECF) is critical for optimal functioning of the neuromuscular and blood coagulation systems, among others. These roles are so critical to life, both of the cell and of the organism itself, that systems have evolved for extraordinarily tight regulation of ECF calcium ion concentration.

Aquatic vertebrates had two mechanisms to buffer calcium ion concentration: transfer of ions across the gill membrane and transfer of ions in and out of bone. The first predominated, with the calcium-rich external aquatic environment serving both as the reserve (to be called upon in situations of need) and the sink (to be used for disposal of excess). As vertebrate evolution progressed to life outside a supporting aquatic medium, the bone mechanism assumed increased importance. It was now the only source and sink for buffering ECF calcium ion concentrations, and at the same time it provided the internal structural rigidity needed for locomotion and gravity-resisting activity. With the exception of energy (stores of which serve as thermal insulation), calcium is the only nutrient known for which the reserve has acquired a function in its own right, distinct from its fundamental metabolic role. In brief, humans walk about on their calcium reserve.

In adult humans, total body calcium amounts to about 400 mmol per kilogram, of which less than 0.1 percent is in the critical ECF compartment. Thus, the reserve is vast relative to the metabolic pool of the nutrient, and for all practical purposes metabolic calcium deficiency probably never exists, at least not as a nutritional disorder. However, because of the structural significance of the nutrient reserve, i.e. of the skeleton, it follows that any decrease in the size of the reserve relative to the genetically determined optimum will result in a corresponding decrease in bone strength.

Thus, unlike requirements for all other nutrients, the requirement for calcium relates not to maintenance of the metabolic function of the nutrient, but to the maintenance of an optimal reserve and the support of the reserve's function.

Small fluctuations around the optimum reserve size have no practical structural significance, but protracted, unbalanced withdrawals from the skeletal reserves produce inescapable structural consequences. It is now quite clear that this occurrence explains the rapid bone loss and at least some of the skeletal fragility of the elderly (Chapuy *et al.*, 1992; McKane *et al.*, 1996). Because the effect of unbalanced withdrawals from the calcium reserve accumulates over many years, the frequency of osteoporotic fractures tends to rise with age.

It must be stressed that reduced bone mass is not the only factor in osteoporotic fragility, and low calcium intake is not the only factor causing reduced bone mass. Osteoporotic fractures are complex phenomena involving not just intrinsic bone strength or fragility, but age-related neuromuscular changes that determine both the frequency and types of falls, as well as other critical factors. All these factors increase in intensity with age.
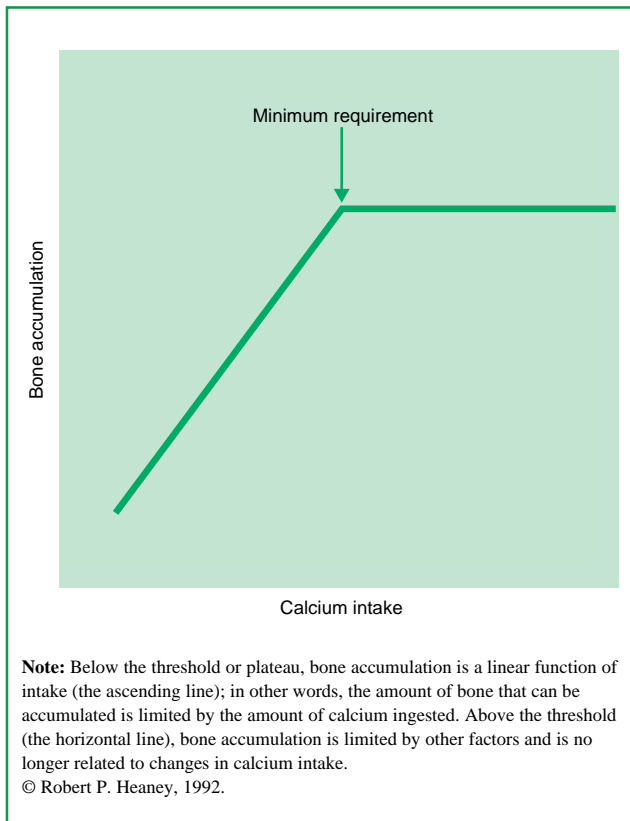
Calcium is virtually unique among nutrients in a second sense: the relationship between the size of the reserve and the environmental availability of the nutrient is asymmetric. (By contrast, energy, the fat-soluble vitamins and many trace minerals exhibit symmetrical reserve behaviour, i.e. their reserves can expand as well as shrink, virtually without limit.) In the face of environmental calcium shortage, the organism cannot build or maintain an optimal reserve; but in the face of surplus, the size of the reserve is completely determined not by the diet but by non-nutritional forces. Because ECF calcium concentration is rigidly regulated at levels equal to only about half the calcium and phosphate solubility product (Ca × P), excess absorbed calcium is spilled into the urine, not accumulated as calcific deposits. Bone mineralization requires active metabolic work. In brief, calcium is stored not as such, but as bone tissue, i.e. a composite of a protein matrix encrusted with mineral crystals. This composite is laid down as a result of cell-based activity, which, in turn, is determined by the combined effects of genetics and mechanical usage.

The importance of mechanical loading for optimal bone health is now well recognized. Bone, in essentially all vertebrates studied to date, has a density that permits bending of about 0.1 to 0.15 percent under the kinds of loads routinely imposed upon it by the organism. More massive bone is stiffer, bends less and is recognized by the organism as excess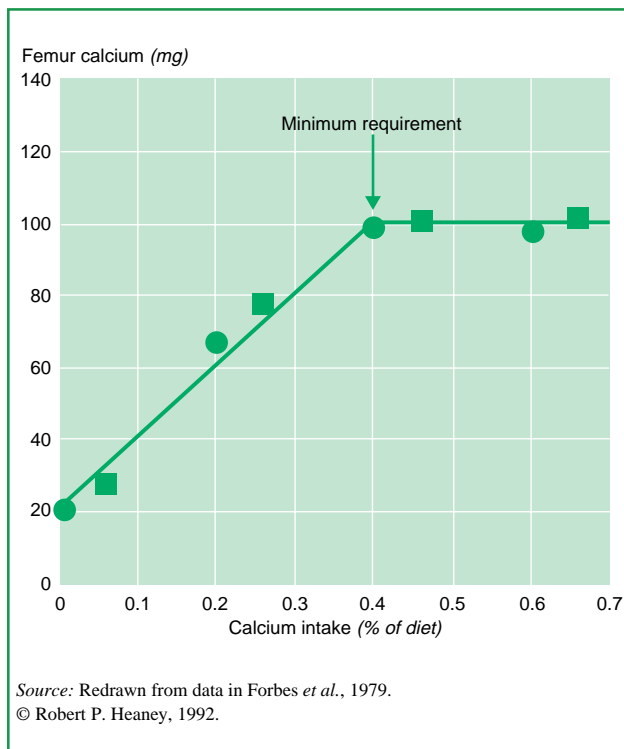ively heavy. As a consequence, some of the excess bone is removed in an ongoing remodelling process until the stiffness reaches the evolutionary optimal figure of 0.1 to 0.15 percent bending. Conversely, bone that bends more than the reference amount is recognized as flimsy, and the organism attempts to strengthen it by adding more bone through the normal remodelling. A surplus of calcium will not prevent the downward remodelling of excessively massive bone, but calcium deficiency will prevent the strengthening of flimsy bone.

Because of the asymmetric relationship between nutrient intake and the size of the reserve, calcium functions as a "threshold" or "plateau" nutrient, illustrated schematically in Figure 1. At suboptimal intakes the size of the reserve, i.e. the ability of the organism to store calcium as bone tissue, is limited by the intake of the nutrient. But above the quantity of bone determined as optimal for genetic and mechanical purposes, further increases in intake are not stored. As already noted, humans can store fat and fat-soluble vitamins virtually without limit, i.e. to the point of producing disease and/or toxicity. Calcium, however, can only be stored as bone, and increasing calcium intake beyond the amount that produces the optimal bone mass will not result in more bone, any more than increasing iron intake beyond the amount that produces the optimal haemoglobin mass will result in more blood. The requirement for such a nutrient can be visualized as the intake at, or just above, the knee of the curve in Figure 1.

Figure 2 shows the operation of this system from experiments in growing rats. Femur calcium content is seen to be a rising linear function of intake at low intake levels, but it does not change further above a threshold intake value. This behaviour is easy to demonstrate and understand in such animal models, particularly during growth. However, if body retention of calcium is substituted for bone mass in the figure, then the figure works for humans as well and, more important, for all ages. The concept leads to an approach to defining the calcium requirement based on maximal calcium retention. The calcium retention that is maximal will, of course, be quite different for different life stages. It should be positive during growth and pregnancy, stable during most of the adult years and probably somewhat negative during the declining years of life (as the skeleton adapts to the reduced mechanical loading associated with ageing). Whatever the retention value may be (positive, zero or negative), it is maximal with respect to intake when further increase in steady-state intake produces no further increase in retention. This approach has now been formally adopted in the United States for estimation of recommended calcium intakes (United States National Academy of Sciences, 1997).

Note: Below the threshold or plateau, bone accumulation is a linear function of intake (the ascending line); in other words, the amount of bone that can be accumulated is limited by the amount of calcium ingested. Above the threshold (the horizontal line), bone accumulation is limited by other factors and is no longer related to changes in calcium intake.
© Robert P. Heaney, 1992.

1

Theoretical relationship of bone accumulation to calcium intake

Source: Redrawn from data in Forbes *et al.*, 1979.
© Robert P. Heaney, 1992.

2

Data from two experiments in growing rats, showing how bone accumulation exhibits a threshold pattern

Recommended calcium intakes in the United States and Canada

Life stage (years of age)	Recommended intake[a] (mmol/day)
4-8	20
9-13	32.5
14-18	32.5
19-30	25
31-50	25
51-70	30
>70	30

[a]Average requirements for the ages concerned.
Source: Data from United States National Academy of Sciences, 1997.

Average requirements for individuals living in the United States and Canada estimated using this criterion are given in the Table. (NB: recommended dietary allowances [RDAs] will be approximately 20 percent higher than the values in the Table.)

It should be stressed that there are important genetic and environmental influences on these average requirements, which will result in substantial differences both in the requirement for various national or ethnic groups and in the relationship of calcium intake to fracture risk.

The genetic influences, briefly, include such factors as bone architecture and geometry (e.g. hip axis length, vertebral cross-section) which have important effects on the structural properties of the bone and corresponding effects on fracture risk. Thus, while the basic relationship between bone mass and fracture risk and between bone mass and calcium intake is the same in Asians and Caucasians (Hu *et al.*, 1993), Asians have about half the hip fracture rate of Caucasians (Lau *et al.*, 1991), probably mainly because of a genetically shorter hip axis length (Cummings *et al.*, 1994). Ignorance of the importance of these structural features has led in the past to the erroneous conclusion that calcium intake was not related to fracture risk.

There are also important differences in responsiveness of bone to the hormones that mediate the function of bone as the body's calcium nutrient reserve. Blacks, with substantially heavier skeletons than Caucasians or Asians, both absorb and retain calcium more efficiently than Caucasians (Abrams *et al.*, 1995), probably as a consequence of somewhat reduced skeletal responsiveness to the action of parathyroid hormone. In other words, in the face of exogenous deficiency, the bone reserves are slightly less readily available, resulting in higher secretion of parathyroid hormone and better intestinal absorption and urinary retention (both also effects of parathyroid hormone). Thus, blacks have stronger skeletons than Caucasians, despite generally lower calcium intakes. Each racial group exhibits the same basic relationship between bone mass and calcium intake, only the equilibrium values are different.

The environmental influences on the calcium requirement include such factors as other constituents of the diet and the degree of mechanical loading imposed upon the skeleton in everyday life. As has already been noted, because calcium was a surfeit nutrient in the primitive environment, there was no need for evolving hominid physiology to develop means of conserving calcium. This lack is expressed in a unique sensitivity of the calcium economy to other constituents of the diet. Urinary calcium losses, for example, rise with both sodium intake (by 0.5 to 1 mmol of calcium per 100 mmol of sodium) and protein intake (by 0.025 mmol of calcium per gram of protein ingested) (Nordin *et al.*, 1993; Heaney, 1996). At protein and sodium intakes typical of the industrialized nations, these effects result in average obligatory urinary calcium loss of 2 to 3 mmol per day, and in some individuals the loss is substantially greater. This effect would create no problem in the face of calcium surfeit, but it can be severely limiting in individuals with low calcium intakes, since the influence of these other nutrients restricts the ability of the organism to reduce calcium losses.

It is likely that the acid-ash residue of a high-meat diet has a similar effect, since substitution of chloride by organic anions in various diets has been shown to reduce urinary calcium loss dramatically (Berkelhammer, Wood and Sitrin, 1988; Sebastian *et al.*, 1994). It is sometimes mistakenly said that there is a difference in this regard between animal and vegetable proteins, but the protein *per se* is probably not responsible for any difference that may exist. Rather, adequate protein from both sources will have approximately the same content of sulphur-containing amino acids (which become oxidized to sulphate). Instead, any difference would result from the different content of organic anions in vegetable and meat sources. (Incidentally, dairy products, though animal products, are alkaline-ash, rather than acid-ash, foods.)

These considerations mean that the calcium requirement, i.e. the intake necessary to reach the plateau of Figure 1, is substantially influenced by other constituents of the diet. Because net absorption of an increment in calcium intake is only about 10 percent, and because even the resulting small absorptive increase in ECF calcium concentration will cause some of that absorbed increment to be spilled into the urine, changes in obligatory losses through the skin and kidney are amplified by a factor of about 20-fold in their effect on the requirement. Thus, at low sodium and low protein intakes, the requirement may be as low as 12.5 mmol per day, whereas for typical Western diets, the requirement may be as high as 50 mmol per day. Therefore, the recommendations produced for North America are specifically intended to describe the requirement for

individuals in the population there, and should not automatically be extrapolated to other population groups.

Factors influencing vitamin D requirements

The vitamin D requirement has been exceedingly difficult to define. The requirement was once defined by the absence of rickets and/or osteomalacia, which are now recognized to be manifestations of extreme deficiency. Lesser degrees of inadequacy (termed "insufficiency" in current jargon) limit the ability of the organism to adapt to low calcium intake with an appropriate increase in calcium absorption efficiency, and thus aggravate the prevailing low calcium intakes of many populations. In addition, it is likely that at high calcium intakes there is very little active transport of calcium mediated by vitamin D, but at low calcium intakes vitamin D is essential for the induction of a calcium-binding transport protein in the intestinal mucosa which enhances calcium extraction from the digestate. Thus the vitamin D requirement may in part be inversely related to prevailing calcium intakes.

Defining the requirement is complicated further by the fact that some fraction of the daily need is typically met from solar exposure, even in northern latitudes, and total body production from this source has never been adequately quantified.

One approach to estimating the requirement, useful with many other nutrients, is to determine the input required to offset daily consumption, utilization and loss of the nutrient. In an experiment involving persons living on atomic submarines who were deprived of all solar exposure for many months at a time, levels of serum 25-hydroxyvitamin D [25(OH)D] were maintained constant at oral intakes of 600 IU (15 µg) per day (Holick, 1994). This is three times the 1989 RDA for vitamin D in the United States (United States National Academy of Sciences, 1989). In the 1997 United States recommendations, the 1989 recommendation of 200 IU (5 µg) is maintained for young adults, who are likely to have substantial amounts of solar exposure, but for people in the middle and older age groups the recommendation has been raised to 400 and 600 IU per day, respectively, reflecting the fact that skin vitamin D synthesis declines with age and that solar exposure of the skin frequently declines as well (United States National Academy of Sciences, 1997).

A second approach to determining the vitamin D requirement is based on the determination of the level of serum 25(OH)D that is required to maintain optimal functioning of the calcium economy. It is well recognized that in northern Europe and North America serum 25(OH)D levels decline in late winter and early spring and reach an

annual peak in late summer and early fall (Webb, Kline and Holick, 1988; Salamone *et al.*, 1993). It was once thought that these changes reflected only changes in the size of the vitamin D reserve. However, it now seems clear that 25(OH)D levels below 80 to 110 nmol per litre in late winter or early spring (or, for that matter, at any time of year) result in increased release of parathyroid hormone, increased serum alkaline phosphatase, increased bone remodelling and decreased bone mass (Dawson-Hughes *et al.*, 1991; 1997; Rosen *et al.*, 1994). These changes are a clear indication that extraction efficiency of calcium from the diet declines at low serum 25(OH)D levels, and that the body is therefore forced to draw upon the skeletal reserves. Because these seasonal responses can be abolished by maintaining the serum 25(OH)D level in the range of 80 to 110 nmol per litre or higher (Dawson-Hughes *et al.*, 1991; 1997; Rosen *et al.*, 1994), the vitamin D requirement can be defined as the daily intake and/or production that results in such a serum 25(OH)D level.

Unfortunately, the precise relationship between daily input of vitamin D and serum 25(OH)D levels has not yet been adequately worked out. Nevertheless, clinical experience in the United States and Canada with therapeutic use of oral 25(OH)D indicates that doses in the range of 10 to 20 µg per day result in serum 25(OH)D levels in the desired range. If it is assumed that quantitative, steady-state conversion of vitamin D to 25(OH)D takes place on a mole-to-mole basis under physiological conditions, it follows that the requirement for vitamin D would be in the same range (effectively the requirement put forth by the United States National Academy of Sciences).

Incidentally, it is worth noting that young adults in North America typically have 25(OH)D levels well above 100 nmol per litre, and that seasonal outdoor workers frequently have levels above 150 nmol per litre at the end of the summer. Such levels are not known to be associated with toxicity or even perceptible physiological effects. Hence, maintaining a serum 25(OH)D level above 80 nmol per litre would seem to be safe as well as optimal.

CONCLUSION

Nutrition is only one component of skeletal health and fracture risk. The nutrients that are most important in this regard are protein, calcium, vitamin D, copper, zinc and ascorbic acid. Of these, calcium and vitamin D are the nutrients most likely to be limiting in the industrialized nations. The optimal calcium intake in the industrialized, northern nations, given existing dietary patterns, is probably in the range of 30 to 40 mmol per day. Because of the major influence of both environmental and genetic factors on the calcium requirement, there can be no single requirement for the world population. At least as far as skeletal health is concerned, the calcium requirement will usually be lower for blacks than for Asians and Caucasians. Since both salt and protein increase obligatory calcium losses, estimation of the calcium requirement must take into consideration other constituents of the diet. Finally, vitamin D should be provided in sufficient quantity to optimize the physiological control of the calcium economy. In brief, sun, food and/or supplements should combine to produce a year-round serum 25(OH)D level above 80 nmol per litre. ◆

REFERENCES

Abrams, S.A., O'Brien, K.O., Liang, L.K. & Stuff, J.E. 1995. Differences in calcium absorption and kinetics between black and white girls aged 5-16 years. *J. Bone Miner. Res.*, 10: 829-833.

Berkelhammer, C.H., Wood, R.J. & Sitrin, M.D. 1988. Acetate and hypercalciuria during total parenteral nutrition. *Am. J. Clin. Nutr.*, 48: 1482-1489.

Chapuy, M.C., Arlot, M.E., Duboeuf, F., Brun, J., Crouzet, B., Arnaud, S., Delmas, P.D. & Meunier, P.J. 1992. Vitamin D$_3$ and calcium to prevent hip fractures in elderly women. *N. Engl. J. Med.*, 327: 1637-1642.

Cummings, S.R., Cauley, J.A., Palermo, L., Ross, P.D., Wasnich, R.D., Black, D. & Faulkner, K.G. 1994. Racial differences in hip axis lengths might explain racial differences in rates of hip fracture. *Osteoporosis Int.*, 4: 226-229.

Dawson-Hughes, B., Dallal, G.E., Krall, E.A., Harris, S., Sokoll, L.J. & Falconer, G. 1991. Effect of vitamin D supplementation on wintertime and overall bone loss in healthy postmenopausal women. *Ann. Intern. Med.*, 115: 505-512.

Dawson-Hughes, B., Harris, S.S., Krall, E.A. & Dallal, G.E. 1997. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. *N. Engl. J. Med.*, 337: 670-676.

Eaton, S.B. & Nelson, D.A. 1991. Calcium in evolutionary perspective. *Am. J. Clin. Nutr.*, 54: 281S-287S.

Forbes, R.M., Weingartner, K.E., Parker, H.M., Bell, R.R. & Erdman, J.W. Jr. 1979. Bioavailability to rats of zinc, magnesium and calcium in casein-, egg- and soy protein containing diets. *J. Nutr.*, 109: 1652-1660.

Heaney, R.P. 1996. Nutrition and risk for osteoporosis. *In* R. Marcus, D. Feldman & J. Kelsey, eds. *Osteoporosis*, p. 483-505. San Diego, California, USA, Academic Press.

Holick, M.F. 1994. Vitamin D – new horizons for the 21st century (McCollum Award Lecture 1994). *Am. J. Clin. Nutr.*, 60: 619-630.

Hu, J.-F., Zhao, X.-H., Jia, J.-B., Parpia, B. & Campbell, T.C. 1993. Dietary calcium and bone density among middle-aged and elderly women in China. *Am. J. Clin. Nutr.*, 58: 219-227.

Kanis, J.A. & Passmore, R. 1989. Calcium supplementation of the diet – I and II. *Br. Med. J.,* 298: 137-140, 205-208.

Lau, E.M.C., Cooper, C., Donnan, S. & Barker, D.J.P. 1991. Incidence and risk factors for hip fractures in Hong Kong Chinese. *In* C. Christiansen & K. Overgaard, eds. *Osteoporosis 1990*, p. 66-70. Copenhagen, Denmark, Osteopress ApS.

McKane, W.R., Khosla, S., Egan, K.S., Robins, S.P., Burritt, M.F. & Riggs, B.L. 1996. Role of calcium intake in modulating age-related increases in parathyroid function and bone resorption. *J. Clin. Endocrinol. Metab.*, 81: 1699-1703.

Molleson, T. 1994. The eloquent bones of Abu Hureyra. *Sci. Am.*, 271: 70-75.

Nordin, B.E.C., Need, A.G., Morris, H.A. & Horowitz, M. 1993. The nature and significance of the relationship between urinary sodium and urinary calcium in women. *J. Nutr.*, 123: 1615-1622.

Rosen, C.J., Morrison, A., Zhou, H., Storm, D., Hunter, S.J., Musgrave, K., Chen, T. & Holick, M.F. 1994. Elderly women in northern New England exhibit seasonal changes in bone mineral density and calciotropic hormones. *Bone Miner.*, 25: 83-92.

Salamone, L.M., Dallal, G.E., Zantos, D., Makrauer, F. & Dawson-Hughes, B. 1993. Contributions of vitamin D intake and seasonal sunlight exposure to plasma 25-hydroxyvitamin D concentration in elderly women. *Am. J. Clin. Nutr.*, 58: 80-86.

Sebastian, A., Harris, S.T., Ottaway, J.H., Todd, K.M. & Morris, R.C. Jr. 1994. Improved mineral balance and skeletal metabolism in postmenopausal women treated with potassium bicarbonate. *N. Engl. J. Med.*, 330: 1776-1781.

United States National Academy of Sciences, Food and Nutrition Board. 1989. *Recommended dietary allowances.* Washington, DC, USA, National Academy Press. 10th ed.

United States National Academy of Sciences, Food and Nutrition Board. 1997. *Dietary reference intakes for calcium, magnesium, phosphorus, vitamin D, and fluoride.* Washington, DC, USA, National Academy Press.

Webb, A.R., Kline, L. & Holick, M.F. 1988. Influence of season and latitude on the cutaneous synthesis of vitamin D_3: exposure to winter sunlight in Boston and Edmonton will not promote vitamin D_3 synthesis in human skin. *J. Clin. Endocrinol. Metab.*, 67: 373-378. ◆

The roles of calcium and vitamin D in skeletal health: an evolutionary perspective

Because hominid evolution took place in an environment with an abundance of calcium and vitamin D, human physiology prevents toxic excesses of both nutrients. In the case of calcium, the protection consists of inefficient calcium absorption and poor systemic conservation. For vitamin D, the protection was provided by skin pigmentation and slow delivery of the vitamin from the skin into the bloodstream. With the migration of humans out of Africa to higher latitudes, the availability of vitamin D was reduced, and this resulted in evolutionary adaptation of the vitamin D system. The adoption of agriculture and a cereal-based diet lowered calcium intakes, but this occurred too recently to permit substantial change in calcium physiology.

Calcium plays key roles in signal transduction and catalytic protein activation at the most fundamental levels of cell biology, and a constantly maintained concentration of calcium ions in the extracellular fluid (ECF) is critical for optimal functioning of the neuromuscular and blood coagulation systems, among others. These roles are so critical to life that systems have evolved for extraordinarily tight regulation of ECF calcium ion concentration. However, less than 0.1 percent of total body calcium is in the ECF. The vast reserve is stored in the skeleton, where it has acquired a structural role. Thus the requirement for calcium relates not to maintenance of its metabolic function, but to the maintenance of an optimal reserve – the skeleton – and to supporting the skeleton's function. Protracted, unbalanced withdrawals from the skeletal reserves produce inescapable structural consequences.

Vitamin D inadequacy limits the body's ability to adapt to low calcium intake with an appropriate increase in calcium absorption efficiency, and thus aggravate the prevailing low calcium intakes of many populations. The vitamin D requirement may in part be inversely related to prevailing calcium intakes. Defining the requirement is complicated because some of the daily need is met from solar exposure, and total body production from this source has never been adequately quantified. The vitamin D requirement is also based on the determination of the level of serum 25(OH)D which is required to maintain optimal functioning of the calcium economy.

The nutrients that are most important for skeletal health are protein, calcium, vitamin D, copper, zinc and ascorbic acid. Of these, calcium and vitamin D are most likely to be limiting in the industrialized nations. The optimal calcium intake in these countries, given existing dietary patterns, is probably in the range of 30 to 40 mmol per day. Because of the major influence of both environmental and genetic factors on the calcium requirement, there can be no single calcium requirement for the world population.

Rôle du calcium et de la vitamine D dans la santé du squelette: une perspective évolutive

L'évolution humaine s'est déroulée dans un environnement riche en calcium et en vitamine D, et c'est pourquoi la physiologie humaine empêche l'assimilation d'excès toxiques de ces deux éléments. En ce qui concerne le calcium, la protection consiste en une absorption peu efficace et une faible assimilation du calcium. Pour la vitamine D, la protection est assurée par la pigmentation cutanée et par la lenteur du passage de la vitamine de la peau dans le sang. La migration des hommes depuis l'Afrique vers des latitudes plus élevées a réduit la disponibilité de vitamine D, ce qui a entraîné, lors de l'évolution humaine, une adaptation du système d'absorption de cette substance. L'avènement de l'agriculture et un régime à base de céréales pauvre en calcium se sont traduits par une baisse des apports en calcium.

Le calcium joue des rôles essentiels dans la transduction des signaux et l'activation catalytique des protéines aux niveaux les plus fondamentaux de la biologie cellulaire, et une concentration constante d'ions de calcium dans le liquide extracellulaire (LEC) est fondamentale pour un fonctionnement optimal de certains systèmes tels que le système neuromusculaire et celui de la coagulation du sang. Ces fonctions sont si vitales que les systèmes ont évolué pour permettre une régulation extrêmement fine de la concentration d'ions de calcium. Toutefois, moins de 0,1 pour cent du calcium corporel se trouve dans le LEC. La très grande réserve est stockée dans le squelette, où il joue un rôle structurel. Ainsi, le calcium ne sert pas à assurer la fonction métabolique du nutriment, mais à entretenir une réserve optimale dans le squelette et à permettre son fonctionnement. Une mise à contribution prolongée et excessive des réserves du squelette aura des conséquences structurelles inévitables.

L'insuffisance de vitamine D limite la capacité du corps à compenser un faible apport en calcium par une meilleure efficacité d'absorption, ce qui aggrave les carences observées dans de nombreuses

populations. Les besoins en vitamine D peuvent être, en partie, inversement proportionnels aux apports en calcium. Ces besoins sont difficiles à estimer car une partie des besoins journaliers sont satisfaits par l'irradiation solaire et il n'a jamais été possible de préciser la quantité totale de vitamine D que l'organisme tire de cette source. Les besoins en vitamine D sont par ailleurs fondés sur la détermination du taux sérique 25(OH)D nécessaire pour maintenir le fonctionnement optimal de l'équilibre calcique.

Les protéines, le calcium, la vitamine D, le cuivre, le zinc et l'acide ascorbique sont les nutriments les plus importants pour assurer la santé du squelette. Parmi ces substances, le calcium et la vitamine D sont celles qui font probablement le plus défaut dans les pays industrialisés. L'apport optimal en calcium dans ces pays, compte tenu de leurs habitudes alimentaires, se situe probablement aux alentours de 30-40 mmoles/jour. On ne peut définir les besoins en calcium de manière uniforme pour l'ensemble de la population mondiale car ils dépendent considérablement de facteurs d'ordre génétique et environnementaux.

Las funciones del calcio y de la vitamina D en la salud del esqueleto: una perspectiva evolutiva

Dado que la evolución de los homínidos tuvo lugar en un entorno en el que abundaban el calcio y la vitamina D, la fisiología humana evita que la ingesta excesiva de ambos nutrientes tenga efectos tóxicos. En el caso del calcio, la protección consiste en una absorción ineficiente y una escasa conservación sistémica de este elemento. En lo que respecta a la vitamina D, la protección consistió en la pigmentación cutánea y la lenta liberación de esta vitamina de la piel y su paso al torrente sanguíneo. La migración de seres humanos procedentes de Africa a latitudes superiores redujo la disponibilidad de vitamina D, mientras que la adopción de una agricultura basada en los cereales rebajó el contenido de calcio en la alimentación.

El calcio tiene una importancia decisiva en la transducción de señales y la activación catalítica de las proteínas en los niveles más fundamentales de la biología celular, mientras que el mantenimiento de una concentración constante de iones de calcio en el líquido extracelular es fundamental para el funcionamiento óptimo de los sistemas neuromuscular y de coagulación de la sangre, entre otros. Estas funciones son tan esenciales para la vida que los sistemas han evolucionado de manera que la concentración de iones de calcio en el líquido extracelular está regulada con extraordinaria precisión. Sin embargo, menos del 0,1 por ciento del calcio total del organismo se encuentra en el líquido extracelular. La mayor parte de la reserva se encuentra en el esqueleto, donde ha adquirido una función estructural. Las necesidades de calcio no guardan, por consiguiente, relación con el mantenimiento de la función metabólica del nutriente, sino con la conservación de una reserva óptima, es decir el esqueleto, y con el apoyo a su función. Un recurso prolongado y excesivo a las reservas óseas tiene inevitablemente consecuencias estructurales.

La insuficiencia de vitamina D limita la capacidad del organismo para adaptarse a una ingesta baja de calcio aumentando oportunamente la eficiencia de la absorción de éste, lo cual agrava la baja ingesta de calcio predominante en muchas poblaciones. Las necesidades de vitamina D pueden estar en parte inversamente relacionadas con la ingesta de calcio. Es complicado determinar la cantidad de vitamina D que se requiere, porque las necesidades diarias se cubren en parte con la exposición a los rayos del sol y nunca se ha cuantificado debidamente la producción total del organismo a partir de esta fuente. La definición de las necesidades de vitamina D se basa asimismo en la determinación del nivel de suero 25(OH)D que se requiere para mantener un funcionamiento óptimo de la economía del calcio.

Los nutrientes más importantes para el buen estado de los huesos son las proteínas, el calcio, la vitamina D, el cobre, el zinc y el ácido ascórbico. De ellos, el calcio y la vitamina D son los que más probabilidades tienen de producir efectos limitativos en los países industrializados. Teniendo en cuenta los hábitos alimentarios existentes en esos países, la ingesta óptima de calcio oscila probablemente entre 30 y 40 mmol/día. Dado que los factores ambientales y genéticos influyen considerablemente sobre las necesidades de calcio, no es posible establecer una cantidad única para las necesidades de calcio de la población mundial. ◆