See corresponding Perspective on page 1384.

Calcium requirement is a sliding scale[1,2]

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INTRODUCTION

It must be a source of some surprise to rational scientists that the human requirement for calcium, an apparently inoffensive nutrient that contributes so much to our physical stability, arouses strong emotions in many breasts. Calcium requirements and allowances seem to attract more controversy and generate more heat than do the requirements and allowances for any other nutrient, the latest example of this being a recent controversy in the columns of the *New York Times* (1). The problem may be that calcium turnover is too slow and the effects of deprivation and replenishment too gradual to be easily demonstrated in humans; perhaps it is the very efficacy of the calcium homeostatic system that makes this system difficult to study. Whereas plasma concentrations of other nutrients (eg, sodium, potassium, phosphorus, and magnesium) can be lowered relatively easily and quickly by experimental deprivation (2), plasma (ionized) calcium is so well protected through access to the reserve stores in the skeleton that it cannot be used as a marker of calcium nutrition. Although there is overwhelming evidence that calcium deprivation causes osteoporosis in experimental animals (3), it would be both immoral and impractical to try to reproduce such experiments in humans. The calcium requirement therefore must be estimated by indirect means that, even if they satisfy many of the experts in the field, are open to criticism by others. Nonetheless, there is no smoke without fire and it may be that this controversy does reflect a deeper reality, although not perhaps the one that the critics of the calcium story envisage.

EXPERIMENTAL BACKGROUND

The first step toward unraveling the effect of a nutritional deficiency is generally to study an experimental animal model. This has been done with calcium since 1885 when Pommer (4) first described and defined the histologic difference between osteomalacia (osteoid-covered bone) and osteoporosis (bone deficit with normal osteoid). Once that was established, it was shown in observational and experimental studies in dogs, cats, rats, rabbits, and other animals that calcium deficiency causes osteoporosis, at least in adult animals (3), and this is now the standard osteoporosis model alongside the oophorectomy model (5–8). The current consensus is that the same chain of events must occur in human adults if calcium intake falls short of requirement. At issue is what this requirement actually is and how much human osteoporosis can be attributed to calcium deficiency, ie, to a state of primary negative calcium balance, and how much to primary changes in bone with secondary negative calcium balance. Both types of osteoporosis must exist. In hyperthyroidism, for example, there is agreement that the bone effects are primary and the negative calcium balance is the result rather than the cause of the bone disease. In the postmenopausal state, by contrast, there is reason to believe that the rise in urinary calcium (9) and the fall in calcium absorption (10, 11) are primary events and that the rise in bone resorption is essentially a response to this increased calcium requirement, exacerbated by the loss of some action of estrogen on bone (12). This interpretation of menopause is borne out by the effectiveness of calcium supplements in preventing postmenopausal bone loss (11) and in enhancing the bone effects of estrogen (13). The formulation of calcium requirements and allowances must be seen in this light.

CALCIUM INTAKE AND CALCIUM BALANCE

For obvious reasons, we cannot reproduce in humans the calcium deficiency experiments performed in animals. To establish an incontrovertible experimental link between calcium deficiency and osteoporosis, we would have to ask volunteers to restrict their calcium intake for ≥1 y before we could hope to show a significant decrease in bone density. Deliberately withholding a nutrient for long periods would be unacceptable today, and when this was in fact done with Norwegian prisoners some 50 y ago (14), bone densitometry was not available to document the outcome. However, prolonged calcium balance studies can be regarded as a surrogate for bone densitometry; it is reasonable to assume that the mean calcium requirement is the mean calcium intake at which output and input are equal and that prolonged negative calcium balance must lead to osteoporosis. Thus, it is a critical fact that many of the Norwegian prisoners studied by Malm went into negative balance at calcium intakes less than ≈500 mg/d and remained in negative balance for ≥1 y. When the final calculations were made on the subjects at the end of the study, the mean calcium requirement of the fully adapted men was 420 mg/d (14). This relatively low value was achieved at the expense of an unspecified amount of bone loss.

Before Malm carried out this remarkable work, some hundreds of calcium balance studies had been published in the United

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States, yielding estimates of calcium requirements ranging from 400 to 800 mg/d, with a median value of ≈600 mg/d (15). It seems that when the FAO/WHO Expert Group met in Rome in 1960 and recommended an adult calcium allowance of 400–500 mg/d (16), few of these studies were available, apart from some short balance studies in Peruvian prisoners [which yielded an estimated requirement of 200 mg/d (17)] and Malm's Norwegian data referred to above. The Expert Group interpreted Malm's data to mean that humans could "adapt" to low calcium intakes by increasing their absorption, reducing their excretion of calcium, or both. The Expert Group was clearly also influenced by the prevalence of low calcium intakes without obvious injurious effect in many developing countries. The rather low recommendations of this group were followed by several countries (18), including the United Kingdom in 1969 (19). The United States adhered to the figure of 800 mg/d (20), whereas Australia recommended a less specific calcium intake of 400–800 mg/d (21). In the meantime, an analysis published in 1976 of 212 balance studies suggested a calcium requirement of 540 mg/d and an allowance of 800 mg/d (2). A balance study published in 1978 by Heaney et al (22) pointed to a requirement of 975 mg/d in premenopausal women. Since then, most national recommendations have crept up and are now 800 mg/d in Australia (23), 700 mg/d in the United Kingdom (24), 700 mg/d in the European Union (25), and 1000 mg/d in the United States and Canada (26).

In the meantime, 2 developments occurred that must influence scientific thinking on this subject. First, technically acceptable methods have emerged for the measurement of insensible calcium losses (eg, through the skin), which probably amount to ≥40 mg/d (27). Because of the kinetics of calcium absorption, this addition of 40 mg Ca to the body's obligatory losses through the bowel and kidneys needs to be offset by an increase in dietary calcium of some 200 mg, which increases the mean requirement from ≈550 to 750 mg/d (28) and must increase the recommended allowance from 800 to 1000 mg/d. The only authority to have taken this into account so far is the joint US and Canadian committee (26), which is one reason their recommendations are relatively high. Second, and even more importantly, it has become increasingly clear that obligatory urinary calcium, and therefore the calcium requirement, is strongly influenced by intakes of protein and sodium and possibly of other nutrients. These intakes need to be taken into account when calcium allowances are determined.

Published sources show that each gram of animal protein consumed increases urinary calcium by 1 mg (9, 11, 29–31) and that every gram of sodium ingested increases urinary calcium by ≈15 mg (9, 11, 32, 33). These may look like small effects at first glance but they signify that a 40-g reduction in animal protein intake reduces urinary calcium by ≈40 mg, which reduces the calcium requirement by ≈200 mg. Similarly, a reduction in dietary sodium of 2.3 g reduces urinary calcium by 40 mg, which reduces the calcium requirement accordingly. Differences of this order can occur in individuals from day to day, can be found between individuals within one culture, and without question are found between cultures. This has profound implications for the calculation of calcium requirements in different countries.

IMPLICATIONS

The implications of these data are particularly important at the transnational level. Although there is a shortage of data on the prevalence of osteoporosis in the developing world, there is evidence that hip fracture rates in many of these countries are much lower than in the West despite lower calcium intakes in developing countries (34, 35). Prentice et al (36) reported that despite the low daily calcium intake in The Gambia (360 mg), osteoporotic fractures are rare. Thus, there is a strong suggestion that the relatively low calcium intakes in many parts of the world are not accompanied by the increased prevalences of osteoporosis that might be expected.

This finding may be explained, at least in part, by the fact that animal protein intake varies across the world in parallel with calcium intake. The mean calcium intake in the developing world in 1990 was given as 344 mg/d, compared with 850 mg/d in the developed world (37); the corresponding total protein intakes were 59.9 and 103.0 g/d and animal protein intakes were 13.3 and 60.1 g/d. Thus, the paradox that calcium intakes are low where fracture rates are low and high where fracture rates are high probably signifies that high (animal) protein intakes increase the risk of osteoporosis because they increase urinary calcium (38, 39), as suggested by Hegsted (40) many years ago. This concept is supported by the results of a prospective study that showed that wrist fractures in American women were weakly but significantly related to animal protein intake (41). Dietary sodium is probably equally important but the shortage of international data on this nutrient makes it harder to define the worldwide implications of sodium intake. Note, however, that the effects of animal protein and sodium restriction on urinary calcium are likely to be additive because they exert their effects in different ways: sodium by competing with calcium for renal tubular reabsorption (32) and protein by virtue of its phosphate (and possibly sulfate) end products, which complex calcium in the renal tubules and take it out in the urine (9, 11). Thus, populations with low animal protein and sodium intakes are likely to have a very low calcium requirement.

From the available data, we can calculate what the calcium requirement might be at different animal protein or sodium intakes. These calculations show that a reduction in animal protein intake from a reference value of 60 to 20 g/d or a reduction in sodium intake from 150 to 50 mmol/d reduces the theoretical calcium requirement from ≈750 to 550 mg/d (29). The combination of both restrictions would reduce the calcium requirement to 400 mg/d (29). This suggests that the calcium requirements and allowances promulgated by developed nations in the past few years, although probably valid for their own countries and dietary cultures, cannot be extended to nations with different dietary cultures whose populations consume different amounts of animal protein or sodium. In addition, factors that influence calcium absorption may also need to be taken into account because this modality is such a central component of the calcium system. An example of such a factor is vitamin D, largely derived from sunlight, the supply of which depends mainly on latitude. Vitamin D may be another factor contributing to low fracture rates in developing countries at low latitudes (34). In fact, high calcium absorption (resulting from a high serum 1,25-dihydroxyvitamin D concentration) and low urinary calcium were reported in Gambian women (42–44) and these 2 factors in combination would greatly reduce the calcium requirement.

Although negative calcium balance must lead to osteoporosis, the amount of calcium required to prevent such negative balance varies not only from individual to individual but also from culture to culture. The conclusion is inescapable that there is no single, universal calcium requirement, only a requirement linked to

the intake of other nutrients. Future recommendations—particularly those from international bodies—will need to take this into account despite the opinion of the US and Canadian committee that it is too early to do so (26).

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