2 Bone as the Calcium Nutrient Reserve

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KEY POINTS

- Bone is the body's calcium nutrient reserve.
- This reserve, over the course of evolution, acquired a secondary function—mechanical strength and rigidity—serving to support work against gravity.
- The reserve is added to or drawn upon by net addition or removal of microscopic units of bony tissue, not by simple withdrawal or addition of calcium atoms.
- The size of the reserve is determined by a combination of mechanical loading and net dietary calcium availability.
- Calcium is a threshold nutrient, in that bone mass increases as calcium intake increases up to the point where mechanical needs are met; above that level, no further calcium retention occurs and absorbed calcium is simply excreted.

1. INTRODUCTION

In addition to its obvious structural role, the skeleton is an important reservoir of calcium, serving both to maintain plasma calcium concentrations and to make optimal use of ingested calcium. It serves both functions mainly by adjusting the balance between bone formation (which transfers mineral from blood to bone) and bone resorption (which transfers mineral from bone to blood). It is important to stress at the outset that calcium cannot generally be withdrawn from bone *per se;* instead, it is scavenged from the tearing down of structural bony units. Thus, reduction in skeletal calcium reserves is equivalent to reduction in bone mass, and augmentation of the reserve is equivalent to augmentation of bone mass.

These same processes of formation and resorption are what constitute bone structural remodeling, or turnover. Remodeling of bone continues throughout life, and skeletal tissue is replaced every 10 to 12 yr on average. All bone remodeling occurs at anatomical bone surfaces. Bone-resorbing osteoclasts begin the remodeling process by attaching onto a bone surface, sealing it from the rest of the extracellular fluid (ECF); they then extrude packets of citric, lactic, and carbonic acids to dissolve the bone mineral, and proteolytic enzymes to digest the organic matrix. They thereby remove parcels of bone, leaving behind a cavity, or resorption bay. Later, bone-forming osteoblasts synthesize new bone to fill in the cavity and replace the previously resorbed bone.

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Formation and resorption are coupled both systemically and locally, and when resorption is high, formation is generally high as well. But the coupling is neither continuous nor perfect. Resorption normally exceeds formation during fasting, when no calcium is being absorbed from the intestine, and formation normally exceeds resorption during absorption of calcium from ingested food or supplements. This is how the body adjusts to intermittent intestinal absorptive input. Overall, however, the two processes are about equal when averaged over the day. Continuous net imbalances (i.e., changes in the size of the reserve) do occur in several situations. For example, bone formation exceeds resorption during growth, and resorption exceeds formation during lactation, or in the development of osteoporosis, or in the face of ongoing dietary shortage of calcium.

2. A UNIQUE NUTRIENT

Calcium is a unique nutrient in several respects. It is not the only nutrient with a substantial reserve in healthy individuals, but it is the only one for which the reserve has required an important function in its own right. We use the reserve for structural support (i.e., we literally walk on our calcium nutrient reserve). Calcium is unique also in that our bodies cannot store a continuing surplus, unlike, for example, energy or the fat-soluble vitamins. Calcium is stored not as such but as bone tissue, and the quantity of bone tissue is determined by cellular processes, with the responsible bone cellular apparatus controlled through a feedback loop regulated by mechanical forces, not by calcium intake. In brief, given an adequate calcium intake, we have only as much bone as we need for the mechanical loads we currently experience. Once our skeletons have reached their genetically and mechanically determined mass, unless something intervenes such as pregnancy or pharmacotherapy, we cannot accumulate more bone simply by consuming more calcium.

This feature is the basis for the designation of calcium as a "threshold" nutrient with respect to skeletal status, a term that means that calcium retention rises as intake rises, up to some threshold value that provides optimal bone strength (*see* Fig. 1); then, above that level, increased calcium intake produces no further retention and is simply excreted. This threshold intake is the lowest intake at which retention is maximal,that is, it is the minimum daily requirement (MDR) for skeletal health (*see* Chapter 7). The MDR varies with age, and is currently estimated to be approx 20–25 mmol (800–1000 mg/d) during childhood, 30–40 mmol (1200–1600 mg/d) during adolescence, approx 25 mmol (1000 mg/d) during the mature adult years, and 35–40 mmol (1400–1600 mg/d) in the elderly *(2–4)*. As previously noted, the rise in the published requirement in old age reflects an age-related decline in ability to adapt (i.e., to respond to low intakes with improved absorption and retention).

Calcium is unique in another respect related precisely to the reserve function of the skeleton. The best-attested disease manifestation of calcium deficiency (osteoporosis) is due not to impairment of the metabolic functions of calcium (*see* Chapter 3), which would be the case, for example, with the B vitamins, but instead to a decrease in the size of the reserve. For no other nutrient is this the case. Bone strength is a function of bone mass which, in turn, is equivalent to the size of the calcium nutrient reserve. This reserve is vast relative to the demands of calcium for cell signaling and activation, particularly because these metabolic functions do not actually consume calcium. Hence, nutritional calcium deficiency almost never manifests itself as a shortage of calcium ions in critical cellular or physiological processes. With most other nutrients, the reserve must first be exhausted

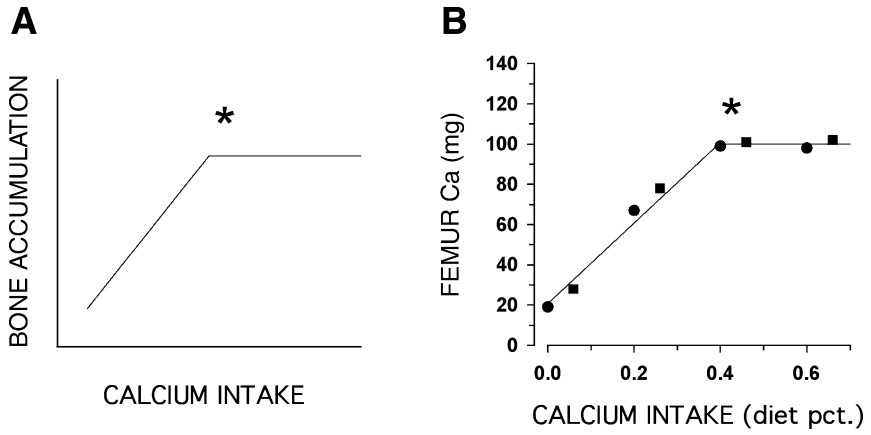

Fig. 1. Threshold behavior of calcium intake. **(A)** Theoretical relationship of bone accumulation to intake. Below a certain value (the threshold, indicated by an asterisk), bone accumulation is a linear function of intake (the ascending line); in other words, the amount of bone that can be accumulated 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. **(B)** Actual data from two experiments in growing rats showing how bone accumulation does, in fact, exhibit a threshold pattern. (Redrawn from data in Forbes et al. *[1]*. Copyright Robert P. Heaney, 1992. Used with permission.)

before clear manifestations of disease or dysfunction develop. But for calcium, it is the simple reduction in skeletal mass that reduces bone strength and accordingly increases fracture risk. In brief, calcium intake insufficient to offset obligatory losses leads to reduction in bone mass, and is thus one of the causes of osteoporosis.

When excretory and dermal losses exceed absorbed dietary intake, the mechanisms designed to protect ECF [Ca^{2+}] tear down bone to scavenge its calcium. The mechanisms by which the reserves are accessed or augmented are set forth in detail in Chapter 10. Here we note only that parathyroid hormone (PTH) is evoked by a fall in calcium intake. At the same time, PTH is responsible for regulating the prevailing level of bone remodeling. PTH activates remodeling loci, which proceed through an orderly sequence of events consisting of (1) activation, which is manifested morphologically as retraction of lining cells from the bone surface about to undergo remodeling; (2) resorption of bone by osteoclasts; (3) replacement of the osteoclasts by osteoblasts, which lay down new bone to fill the hole created by osteoclastic resorption; and (4) return to the resting state, with the bone surface once again covered by a sheet of lining cells. The destructive, resorptive phase typically takes 3 wk in healthy adults, and the formative, reconstructive phase takes 3–6 mo.

Millions of such remodeling loci, each at different stages of this process, are going through this sequence at any time in the skeleton as a whole, some adding calcium to the blood, and some taking it up into new bone. An acute increase in remodeling activity initially creates an excess of resorption (because the new loci are all in the initial resorptive phase of the cycle). In this way, an increase in remodeling allows bone to contribute calcium to the blood. Conversely, an acute decrease in remodeling initially creates a

temporary excess of formation. These imbalances are how the bone accommodates a relative surplus or shortfall of absorbed calcium, hour by hour and day by day.

In providing the calcium needed to maintain critical body fluid concentrations, the reserve is functioning precisely as it should. But sooner or later there has to be payback, or the reserve becomes depleted, with an inescapable weakening of skeletal structures. During growth, on any but the most severely restricted of intakes, some bony accumulation will usually occur, but the result of an insufficient calcium intake is usually failure to achieve the full genetic potential for bone mass. Later in life, the result is failure to maintain the mass achieved. As also noted in Chapter 24, both low bone mass and osteoporotic fractures have many causes other than low calcium intake. Nevertheless, under prevailing conditions in the industrialized nations, at mid-to-high latitudes, the importance of calcium intake is considerable. Calcium-supplementation trials, even those of short duration, have resulted in reductions in fracture in the elderly amounting to 30% or more *(5,6)*.

3. EVIDENCE LINKING CALCIUM INTAKE TO BONE HEALTH

In addition to a large effect size, the evidence for calcium's role is itself very strong. There have been roughly 80 published reports of investigator-controlled increases in calcium intake with skeletal endpoints, most of them randomized, controlled trials and most of them published since 1990 *(7)*. The vast majority demonstrated either greater bone mass gain during growth, reduced bone loss with age, and/or reduced osteoporotic fractures. The exceptions among these studies were, for example, a supplementation trial in men in which the calcium intake of the control group was itself already high (nearly 1200 mg/d) *(8)*, and a study confined to early postmenopausal women *(9)* in whom bone loss is known to be due predominantly to estrogen deficiency.

Complementing this primary evidence are roughly 130 observational studies testing the association of calcium intake with bone mass, bone loss, or fracture *(7)*. It has been shown elsewhere *(10)* that such observational studies are inherently weak, not only for the generally recognized reason that uncontrolled or unrecognized factors may produce or obscure associations between the variables of interest, but because the principal variable in this case, lifetime calcium intake, cannot be directly measured and must be estimated by dietary recall methods. The errors of such estimates are immense and have been abundantly documented (*11,12; see also* Chapter 4). Their effect is to bias all such investigations toward the null. Nevertheless, more than three-fourths of these observational studies reported a significant calcium benefit. Given the insensitivity of the method, the fact that most of these reports are positive emphasizes the strength of the association; at the same time, it provides reassurance that the effects achievable in the artificial context of a clinical trial can be observed in real-world settings as well.

4. CALCIUM INTAKE, BONE REMODELING, AND SKELETAL FRAGILITY

These observations show clearly that variations in calcium intake in the range commonly encountered in the industrialized nations have substantial influences on the osteoporotic fracture burden (when intakes are low) or protect against fracture (when intakes are high). The most obvious explanation is the effect of calcium intake on opti-

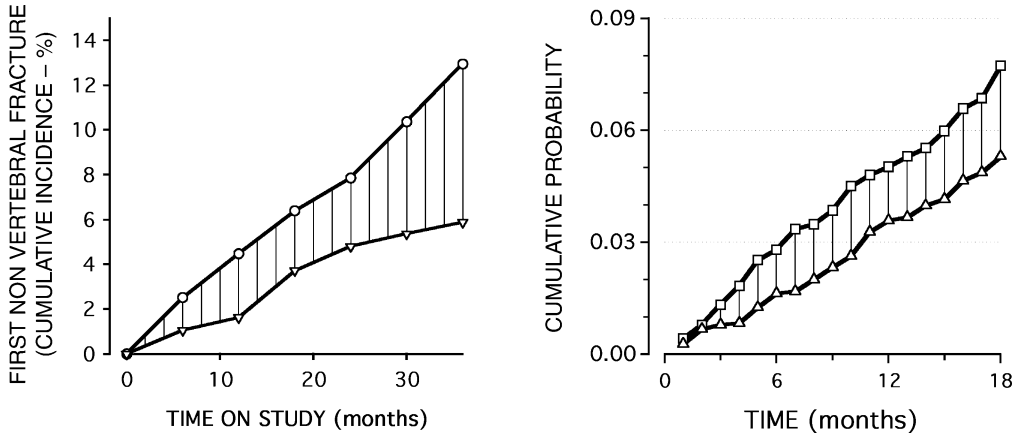

Fig. 2. Plots of the cumulative incidence of fractures, redrawn from the studies of Chapuy et al. *(5)* (right) and Dawson-Hughes et al. *(6)* (left). In both cases, the upper line represents the placebo control subjects, and the lower line represents the calcium and vitamin D-treated subjects. The shaded zones represent the reduction of fracture risk, which, as can be readily seen, starts with the very beginning of treatment. (Copyright Robert P. Heaney, 2004. Used with permission.)

mizing the size of the calcium reserve. But it is likely that there is a second aspect of the reserve involved in bony fragility as well. Examination of the cumulative fracture plots of the calcium intervention trials of Chapuy et al. *(5)* and Dawson-Hughes et al. *(6)* shows that the reduction in fracture risk begins almost immediately after supplementation is started—too soon for there to have been an appreciable effect on bone mass (Fig. 2).

Recent appreciation of the role of bone quality , as distinct from bone quantity , has led to an understanding of the fact that remodeling loci themselves directly contribute to fragility *(13)*, independently of bone mass. Remodeling rate doubles through menopause and continues to rise throughout the remainder of life *(14)*, in part because of inadequate calcium and vitamin D intakes. The immediate effect of calcium and/or vitamin D supplementation in typical postmenopausal women is a reduction of PTH secretion and with it, a corresponding and immediate reduction of bone remodeling. As the data assembled in Fig. 2 show, there is an immediate reduction in bony fragility as well. In brief, not only does low calcium intake contribute to bony fragility by depleting the reserve, but the very process of accessing the reserve itself renders bone fragile. Slowing that process confers an immediate benefit.

Several factors influence the size of the calcium reserve by direct action on bone (rather than by way of the calcium economy). Among these are smoking, alcohol abuse, hormonal status, body weight, exercise, and various medications. Smoking and alcohol abuse exert slow, cumulative effects by uncertain mechanisms that result in reduced bone mass and increased fracture risk. Low estrogen status and hyperthyroidism produce similar net effects, although probably by very different mechanisms. Bone mass rises directly with body weight, again by uncertain mechanisms. Exercise, particularly impact loading, is osteotrophic and is important both for building optimal bone mass during growth and for maintaining it during maturity and senescence.

5. CONCLUSIONS

The body possesses reserve supplies of most nutrients, which it uses to ensure smooth functioning in the face of irregular nutrient intake. Bone is the body's calcium reserve. This reserve is larger than for any other nutrient mainly because it has acquired a secondary, nonnutrient role—internal stiffening and mechanical support of our bodies. The size of the bony reserve is limited at its upper bound by mechanical need, and below that, by net calcium intake. Because the reserve is large, nutritional calcium deficiency virtually never compromises the basic metabolic functions of calcium. Rather, by depleting the reserve, the body weakens bone and jeopardizes its mechanical function. As a consequence and unlike with most other nutrients, reduction in the size of the nutrient reserve has immediate health consequences.

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