Calcium absorption revisited

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Calcium intake, absorption, and excretion make up the 3 components of the calcium paradigm. To remain in calcium balance, net absorbed calcium (the difference between dietary intake and fecal output) has to equal calcium losses in the urine and through the skin. If that is not achieved, the calcium balance becomes negative and the difference between intake and output is drawn from the skeleton to maintain the (ionized) calcium in the extracellular fluid. Sooner or later, probably in a matter of days, this requires bone breakdown and the development of osteoporosis (“too little bone in the bone”), which is why Heaney has called osteoporosis the “index disease for calcium deficiency” (1). The key to this paradigm is the tight regulation of calcium homeostasis whereby the long-term intraindividual CV of ionized calcium is only 1.3% and interindividual CV only 2.5% (2), no doubt due to the vital role of ionized calcium in neuromuscular and cardiac function.

In the early 20th century, calcium absorption was measured by classical balance studies in which an equilibration period on a standard calcium intake after fecal collections that were pooled and analyzed on a 3–6 d basis. Among the earliest studies of this kind were those of Telfer [see review (3)] which were the first to show that childhood rickets was associated with malabsorption of calcium and which naturally, but unfortunately, led to the assumption that malabsorption of calcium was the cause of the disease. This was illogical in light of the determination 20 y earlier (3) (and confirmed many times since) that calcium deficiency causes osteoporosis—not rickets—in experimental animals. Low calcium intake and malabsorption of calcium would surely be expected to have the same effects on bone, but this fallacy continues to this day and creates ambiguity about the relative roles of calcium and vitamin D in osteoporosis and osteomalacia/rickets.

With the advent of calcium isotopes, both radioactive and stable, the measurement of calcium absorption entered a new phase, encouraged by the International Atomic Agency (4), in the second half of the 20th century. One of the earliest double-isotope procedures was published in 1965 (5) and one of the earliest single-isotope procedures in that same year (6). The validity of double-isotope procedures, which can be used with any amount of carrier, is not in question, but single-isotope procedures have followed 2 paths: a low-carrier procedure with the use of 20–50 mg of calcium (6–8) originally on the basis of analysis of the serum radioactivity/time curve in the first 2 h, but later simplified to one 60-min sample (9); and a high-carrier test with 200 mg of calcium (10) in which serum radiocalcium is measured after 5 h. The low-carrier procedure probably measures the active transport component of calcium absorption (11) and has been shown in calcium balance studies to correlate with net absorbed calcium corrected for calcium intake (12). The high-carrier procedure is promoted as a better measure of calcium absorption from a real meal, but this is controversial.

In the current issue of the Journal, Aloia et al (13) have tested the report by Heaney et al (14) that calcium absorption, estimated from the rise in serum calcium after a calcium load, is a function of the serum 25-hydroxyvitamin D (calcidiol). Heaney et al’s report, published in 2003, has created the impression that calcidiol regulates calcium absorption in its own right despite the much greater affinity of the 1,25-dihydroxy metabolite (calcitriol) for the vitamin D receptor (15) and strong evidence that it is the main regulator of calcium absorption (16). Moreover, subsequent studies from Adelaide, Australia, with the use of the low-carrier test, showed that the univariate correlation with serum calcidiol becomes nonsignificant when adjusted for serum calcitriol (17) and that malabsorption of calcium is a very late manifestation of vitamin D deficiency because secondary hyperparathyroidism maintains the serum calcitriol concentration until the deficiency is so severe that the serum calcitriol falls due to exhaustion of substrate (18).

Aloia et al (13) have used the high-carrier radiocalcium absorption test to confirm that calcium absorption is a function of serum calcitriol rather than serum calcidiol and also, incidentally, that calcium absorption is lower for any given calcitriol concentration in post- than premenopausal women. This confirms a previous report with the low-carrier test (19) in which the correlations between serum calcitriol and calcium absorption were perhaps stronger.

It is of course gratifying to know that the low- and high-carrier tests give comparable results, but the implications of Aloia et al’s article (13) go beyond that simple conclusion. If the sole or main effect of vitamin D deficiency was to cause calcium deficiency from malabsorption of calcium, it would be hard to explain why calcium and vitamin D deficiency have such different outcomes—osteoporosis in the former and osteomalacia in the latter. The explanation is that vitamin D regulates calcium homeostasis in other ways than simply by controlling calcium absorption. This

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First published online August 4, 2010; doi: 10.3945/ajcn.2010.30136.
was first demonstrated in 1957 when Carlsson and Lindquist showed that progressively increasing doses of vitamin D in rachitic rats continued to increase serum calcium after calcium absorption had plateaued (3). This implies a “calcemic” action of vitamin D on bone which is independent of calcium absorption and accounts for the secondary hyperparathyroidism which is a well-documented effect of vitamin D deficiency (15) and occurs long before calcium malabsorption has developed (18).

Whatever the mechanism at the cellular or molecular level (15, 20), this central action of vitamin D explains not only why vitamin D and calcium deficiency lead ultimately to different bone disorders but also why there is an overlap between them on the way. On the one hand, calcium deficiency in young animals can cause hypocalcemia and rickets, though this does not happen in adults. On the other hand, vitamin D deficiency can cause osteoporosis by way of secondary hyperparathyroidism and increased bone resorption long before it causes osteomalacia. The “calcemic” action of vitamin D, known for >50 y, but not generally recognized in the current paradigm, allows a missing piece of the puzzle to fall into place; if the article by Aloia et al (13) gives it wider recognition it will have made a significant contribution to osteoporosis research.

The author did not have a conflict of interest to declare.

REFERENCES