Searching for the determinants of intestinal calcium absorption\textsuperscript{1–3}

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The amount of calcium consumed regulates the efficiency of intestinal calcium absorption; calcium absorption efficiency (fractional calcium absorption) increases when calcium intakes are low and decreases when calcium intakes are high \textsuperscript{(1)}. Low-calcium diets increase fractional calcium absorption via a complex mechanism involving changes in circulating ionic calcium concentrations that are detected by a calcium-sensing receptor in the parathyroid gland, which modulates the production and secretion of parathyroid hormone. During low calcium intakes, plasma parathyroid hormone increases and stimulates the renal conversion of 25-hydroxyvitamin D to the active form of vitamin D, 1,25-dihydroxyvitamin D. This vitamin D metabolite is a steroid hormone that acts on several tissues, including the intestine, via a nuclear vitamin D receptor and regulates the expression of vitamin D–dependent genes. Among these vitamin D–dependent genes in the mammalian intestine is calbindin D\textsubscript{9k}, a cytosolic protein believed to be the rate-limiting molecule in vitamin D–induced intestinal calcium transport \textsuperscript{(2)}. Increased cellular calbindin D leads to increased active calcium transport across the enterocyte and helps to maintain long-term calcium homeostasis in the face of low calcium intakes.

Low net calcium absorption (calcium intake minus fecal calcium loss) may occur subsequent to low calcium intakes, consumption of diets with low calcium bioavailability, increased calcium secretion into the gut, or a low efficiency of true intestinal calcium absorption. In young people, low net calcium absorption could limit the achievement of optimal peak bone mass; in adults and the elderly, low net calcium absorption can lead to negative calcium balance and bone loss. High dietary calcium loads are absorbed primarily by a vitamin D–independent paracellular transport pathway in the intestine and have salutary effects on calcium balance via increases in net calcium absorption and subsequent reductions in bone resorption. Adequate intakes of calcium and vitamin D throughout the life cycle are needed to optimize calcium absorption and promote bone health. In addition to dietary calcium intake and vitamin D status, other factors have been reported to influence calcium absorption performance, including body weight, estrogen status \textsuperscript{(3)}, smoking \textsuperscript{(4)}, and intestinal transit time \textsuperscript{(5)}.

Aging is associated with increases in bone loss and osteoporotic fracture, especially in women. The pathogenesis of osteoporosis and osteoporotic fracture is multifactorial. From a physiologic perspective, age-associated bone loss represents an uncoupling of bone formation and resorption during bone remodeling. Because 99\% of total body calcium is found in bone, higher rates of bone resorption then bone formation during the bone-remodeling cycle is reflected as a state of negative calcium balance and bone loss. In men and nonpregnant or lactating women, negative calcium balance results when net calcium absorption is unable to replace urinary calcium losses, neglecting the usually small amounts of miscellaneous dermal calcium loss.

Reviews or textbook chapters focusing on the causes of osteoporosis often give little emphasis to the important role of intestinal calcium absorption in the pathogenesis of this disease. To a large extent, this omission may reflect primary attention on bone mineral density as the proximate correlate of bone fracture and the recent explosion in knowledge about bone cell biology. An additional drawback is the absence of a convenient specific endogenous biomarker of calcium absorption efficiency, as were identified, for example, for estimating the equally complex processes of bone formation and resorption rates. Although there are several techniques available to estimate intestinal calcium absorption, they are too cumbersome both in the amount of time and effort required for use in most large-scale investigations. As a consequence, until quite recently, there has been no large-scale epidemiologic study documenting directly the importance of low calcium absorption efficiency as a significant risk factor for osteoporotic fracture. However, this important information is now available from the Study of Osteoporotic Fractures Research Group \textsuperscript{(6)}. This study showed that low fractional calcium absorption efficiency (less than the median) significantly increases the risk (relative risk: 2.5) of subsequent hip fracture in women, especially those with low calcium intakes. Thus, given the role of calcium absorption in osteoporotic fracture risk, it is all the more important to reinvigorate the search to identify the important determinants of performance.

In the current issue of the Journal, Heaney \textsuperscript{(7)} reports on his investigations of the association between dietary protein and phosphorus intake and fractional calcium absorption in women. In this longitudinal study, fractional calcium absorption was

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measured in 191 middle-aged Roman Catholic nuns at \( \approx 5 \)-y intervals by using a calcium double-isotope absorption test. These measurements provided 567 observations of fractional calcium absorption over > 30 y. The protein and phosphorus intakes of the subjects were determined by analysis of duplicate weighed diets. Protein and phosphorus intakes varied among subjects by \( \approx 5 \)-fold. Fractional calcium absorption, corrected for calcium intake, varied among subjects \( \approx 7 \)-fold. However, although the number of observations and the variation in dietary intake and calcium absorption were large, no significant relation was evident between the intake of protein or phosphorus and fractional calcium absorption. This negative finding is important because it expands our understanding of which dietary factors influence calcium absorption in humans and which do not, and in the words of the investigator “these observations allay concern about any deleterious effects of the amount of phosphorus or protein intake in the American diet on absorption of calcium.”

However, these observations are particularly important in regard to protein intake because the absence of an increase in intestinal calcium absorption efficiency when consuming a high-protein diet is maladaptive because high-protein diets can increase urinary calcium excretion and result in negative calcium balance (8). Another notable point about this study is that after correction for the predicted influence of calcium intake on the calcium absorption efficiency, other predictive factors such as age, body weight, and estrogen status explained only 6% of the variance in relative calcium absorption efficiency among these middle-aged women. Thus, additional factors affecting calcium absorption performance must be important and need to be identified. Additional areas that warrant further investigation are age-associated intestinal resistance to vitamin D (9) and individual genetic influences on calcium absorption, as were illustrated, for example, in some studies by the association of calcium absorption and vitamin D receptor polymorphisms (10).

REFERENCES