Vitamin D and calcium interactions: functional outcomes

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ABSTRACT
I present the results of published studies and original data and describe the functional outcomes of effects related to the interaction between vitamin D status and calcium intake. These effects fall into 3 broad categories: 1) synergistic effects of vitamin D status and calcium intake on calcium absorption; 2) effects of calcium intake on vitamin D status; and 3) largely observational data suggesting an association between calcium and vitamin D status and nonskeletal outcomes, such as cancer. To a considerable extent, both vitamin D status and the benefits associated therein appear to be dependent on, or at least augmented by, calcium intakes at or above currently recommended levels. Am J Clin Nutr 2008;88(suppl):541S–4S.

INTRODUCTION
The charge of this brief review is to consider the functions of vitamin D that involve an interaction with calcium. I focus on 3 broad categories of these functions: calcium absorptive effects, the influence of calcium intake on vitamin D status, and a large array of nonskeletal effects suggesting a constructive interaction between calcium and vitamin D. The pertinent evidence has been developed largely in adult humans.

CALCIUM ABSORPTION
The classic effect of vitamin D is to facilitate the intestinal absorption of calcium by mediating active calcium transport across the intestinal mucosa. Vitamin D acts in this system by both genomic and nongenomic mechanisms (1, 2). These mechanisms involve, among other effects, synthesis of a calcium transport protein (calbindin), which shuttles calcium from the brush border across to the basolateral side of the mucosal cell. Although much is still being learned about the molecular basis of this transport, the qualitative effects of its dependence on vitamin D during most of the human lifespan have been well established for many years.

What has not been adequately studied, however, is the quantitative relation between vitamin D status and the efficiency of absorptive transport. Such research can only be done at a high level of organization, preferably in intact humans. Certain quantitative aspects of the action of vitamin D in adult women aged 35–65 y are set forth in Figure 1. The figure is based on >500 double-tracer studies performed under full metabolic balance controls. These studies measured both fractional intestinal absorption of ingested calcium and secretion into the gut of endogenous calcium (in the form of digestate and sloughed mucosal cells). Figure 1 is predicated on passive absorption at $\approx 2.4 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ of endogenous calcium. Because passive absorption generally ranges between 10% and 15% of intake (3) and the endogenous entry of calcium is a measured value (5–7), the relations depicted in the figure are approximately correct for midlife women; ie, this is not a theoretical or idealized diagram.

A few features of Figure 1 stand out. First, net absorption increases as calcium intake increases, irrespective of whether any active, vitamin D–mediated absorption occurs. For any given degree of active absorption, the higher the ingested intake, the higher the absorbed quantity of calcium. This is because passive absorption is a linear function of intake, with a slope (discussed above) of $\approx 0.125$. Active absorption both raises the net absorption contour and increases its slope. The result is that extraction of calcium from the digestate becomes more and more efficient as the active component of absorption rises. Second, at low calcium intakes, net absorption is low (necessarily), irrespective of vitamin D status, and can even be negative when endogenous secretion is greater than gross absorption. Third, as the contours indicate, it is extremely difficult to absorb sufficient calcium in the absence of active vitamin D–mediated absorption (see the zero active absorption line in Figure 1). Note that in the absence of active transport, a net absorption of zero (which is not nutritionally helpful, but is at least not harmful) requires that calcium intake be $\approx 1100 \text{ mg/d}$. For net absorption to reach 200 mg/d, the amount typically required to offset cutaneous and renal losses (8), calcium intake would have to approach 3000 mg/d.

In brief, a person needs both calcium and vitamin D to ensure sufficient net absorption of calcium for meeting various body needs from commonly available food sources. An inescapable conclusion of these quantitative relations is that, given prevailing intakes of both nutrients, clinical trials or observational studies that fail to take this dual need into consideration will often produce null results, and systematic reviews that fail to weed out such studies will produce misleading conclusions.

The several active absorption lines in Figure 1 imply both that active absorption is a regulated function and that regulation may be limited by vitamin D status. Regulation of active absorption is a well-established fact of endocrine physiology, and the ability of vitamin D to limit active absorption is supported by studies...
Absorptive efficiency increases as serum 25-hydroxyvitamin D [25(OH)D] rises, up to ~80 nmol/L; above this level, additional increases in vitamin D status have no further effect on absorptive regulation. This point is illustrated in Figure 2, which shows a plateau for unidirectional (gross) fractional absorption of ~0.30 for ingested calcium loads of 300 mg (equivalent to one serving of dairy foods). This plateau is reached at a serum 25(OH)D concentration of ~80 nmol/L (32 ng/mL). The broad arrows above and below that plateau represent the body’s ability to up- and down-regulate active absorption [usually through parathyroid hormone-mediated synthesis of 1,25-dihydroxyvitamin D (1,25(OH)₂D)].

In brief, vitamin D is an enabling agent that, when present in optimal concentrations, has no perceptible effect on calcium absorption in its own right; however, it permits or facilitates flexible physiologic response to varying calcium need. This physiologic regulation functions around a unidirectional (ie, gross) absorption fraction of ~0.30. At suboptimal levels, vitamin D’s availability limits this physiologic control.

The independent variable in Figure 2 is serum 25(OH)D, the accepted indicator of vitamin D nutritional status (10). How is it possible that, at serum 25(OH)D concentrations below ~80 nmol/L, calcium absorption is subphysiologic? Could not the parathyroid glands, sensing calcium insufficiency, increase their secretion of parathyroid hormone, thereby upregulating renal 1α-hydroxylation of 25(OH)D and increasing calcium absorption to physiologically appropriate levels? In fact, the parathyroid glands do respond qualitatively in exactly this way, but the elicited absorptive response is quantitatively not sufficient. This is reflected in the suboptimal absorption (and improvement) along the ascending limb of the curve in Figure 2.

The reason for this insufficient absorptive response is twofold. First, parathyroid hormone increases bone resorption, making some of the needed calcium available from that source. (The resulting decrease in bone mass and increase in bone remodeling are the bases for the negative effect of low vitamin D status on bone strength.) Second, 25(OH)D appears to augment absorption directly, possibly by the rapid-response binding to membrane receptors described by Norman et al (2). This is shown by the fact that orally administered 25(OH)D increases calcium absorption in typical adult humans without changing serum 1,25(OH)₂D concentrations (12), and also by the observation that serum 25(OH)D concentrations correlate with absorptive efficiency in adults but serum 1,25(OH)₂D concentrations do not (13, 14). Essentially the same conclusion follows from the recognized fact that calcium absorption is poor in patients with osteomalacia, despite their often normal or high levels of serum 1,25(OH)₂D [but always low concentrations of 25(OH)D].

These observations do not suggest that 1,25(OH)₂D is not the active form of the vitamin, but simply underscore that, for optimal absorptive function, it appears that both metabolites of the vitamin must be present and that the mechanism of the absorptive response to vitamin D is more complex than once thought. This seems to be an area warranting further investigation.

INFLUENCE OF CALCIUM INTAKE ON VITAMIN D STATUS

Extensive clinical experience has shown that serum 25(OH)D concentrations (and hence vitamin D status) vary greatly between individuals, even when cholecalciferol inputs are apparently similar. When the vitamin D input is cutaneous, one might expect some variability in status because efficacies of cutaneous synthesis differ from person to person. But even when the input is oral (and therefore accurately known), the variance of serum 25(OH)D responses is still very large.

One example is presented in Figure 3. This graph plots the increase in 25(OH)D to the Cₘₐₓ after a single oral dose of 100 000 IU (2500 μg) cholecalciferol in 64 healthy adults (15). The measured increments range from only 12 nmol/L to as much

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**Figure 1.** Quantitative relations between net calcium absorption, calcium intake, and percentage active absorption. Calcium intake is shown on the horizontal axis, net absorption (difference between ingested intake and fecal output, which is the nutritionally relevant variable here) on the left vertical axis, and percentage of ingested calcium absorbed by active transport (ranging from 0% to 48%). Reproduced with permission from reference 3.

**Figure 2.** Plateau relation of intestinal calcium absorption fraction (for an ingested calcium load of ~300 mg) to vitamin D status, expressed as serum 25-hydroxyvitamin D [25(OH)D]. Arrows above and below the plateau level represent physiologic regulation unlimited by vitamin D status. Reproduced with permission from reference 11.
as 76 nmol/L—a greater than 6-fold range in response from low to high. The size of the increment was not related to the starting value, as might be expected if there were appreciable regression to the mean. After we adjusted for body weight, the range narrowed only slightly, from 20 to 66 nmol/L.

Mechanistically, only a few reasons for this variation seem possible: variable vitamin D absorption, variable 25-hydroxylation, and variable metabolic degradation or consumption. This review focuses on interaction with calcium, and existing data do not suggest that calcium intake alters either intestinal absorption of vitamin D or hepatic 25-hydroxylation. However, some data do suggest that calcium intake can influence 25(OH)D metabolic consumption (16–20). Clements et al (16, 17) showed both in rats and in humans that the half-life of serum 25(OH)D varies inversely with the serum 1,25(OH)₂D concentration, which in turn reflects absorbed calcium status. The longer half-life of 25(OH)D, which reflects decreased metabolic use or degradation produced by calcium-mediated reduction in 1,25(OH)₂D synthesis, would predictably raise serum 25(OH)D concentration. More directly, Berlin and Björkhem (19) supplemented normal adults with 2000 mg Ca/d for 6 wk, lowering serum 1,25(OH)₂D concentrations by 20% and raising serum 25(OH)D concentrations by 30%.

However, not all investigators have found this effect. Gousous et al (21), using a calcium supplement of 1000 mg/d for 3 mo, found no difference in 25(OH)D concentrations, but these investigators did not succeed in reducing serum 1,25(OH)₂D concentrations appreciably in the experimental group compared with the control group. As Clements et al showed, it is the change in serum 1,25(OH)₂D concentration that mediates the change in metabolic consumption of 25(OH)D. We also know that serum 25(OH)D concentrations and 25(OH)D half-time rise after surgical removal of parathyroid adenomas (18), an effect shown by Clements et al to be due to the postsurgical drop in serum 1,25(OH)₂D concentration.

Thus, some aspect of the variability in 25(OH)D response to standard vitamin D inputs could be due to interindividual differences in calcium status. How much of that variability at prevailing calcium intakes is due to this mechanism is uncertain, and research is needed to shed more light on this relation if we are to optimize vitamin D status in the population.

**NONSKELETAL EFFECTS OF CALCIUM AND VITAMIN D**

Beyond the arena of the skeletal and calcium economies, the connection between calcium and vitamin D becomes more circumstantial and the underlying physiology, to the extent that it might be pertinent, less well elucidated. Nevertheless, several recent observations suggest such a connection.

Bérubé et al (22, 23), in 2 different cohorts, showed a significant inverse association between mammographic densities and intakes of both vitamin D and calcium. Although some of the apparently dual association might be because calcium and vitamin D concentrations co-vary in the diet, this does not fully explain the reported association. Research has shown that vitamin D status is inversely correlated with breast cancer risk (24); hence, an association between vitamin D and mammographic densities is not surprising. But the mechanism of the calcium association, if causal, remains unclear.

Nevertheless, Women’s Health Study investigators recently reported a strong parallel, in which risk of breast cancer (particularly in premenopausal women) was inversely associated with both calcium and vitamin D intakes (25). Similarly, the randomized controlled trial of Lappe et al (26) showed a significant reduction in incident all-cancer risk for a combination intervention involving calcium and vitamin D supplementation. Principal cancers in this study were breast, colon, lung, and marrow/lymphoma. In this study, there was a calcium-only arm as well, and the calcium-treated individuals showed a degree of reduction in cancer intermediate between the double placebo-treated women and those receiving calcium plus vitamin D. This finding is suggestive of a contribution of calcium in its own right. For colon cancer at least, such a connection would be plausible, because an earlier randomized controlled trial showed reduction in colon adenoma recurrence with calcium supplementation (27), and there is a compelling body of animal data showing that high calcium intakes serve as anti-promoters for colon cancer and thereby reduce experimental colon cancer incidence substantially (28, 29).

All of the foregoing studies relate specifically to cancer risk, but research has shown similar associations for disorders as diverse as hypertension (30–34) and polycystic ovary syndrome (35–37). For both of these disorders, calcium and vitamin D appear to exhibit independent associations with disease risk. The associations for hypertension are particularly strong. Both controlled trials and meta-analyses have shown a protective effect of high calcium intake for both pregnancy-related and essential hypertension (32–34), whereas risk of incident hypertension is inversely related to antecedently measured serum 25(OH)D concentrations (31). Most studies on this topic did not examine the interaction (if any) between calcium and vitamin D. Hence, we need further studies examining possible interactions of the 2 nutrients in the same population.

From a mechanistic perspective, it would seem important to separate the effects of calcium and vitamin D, but from a more pragmatic perspective, doing so may be less relevant, because the population intakes of both nutrients are recognized to be inadequate and to be in need of improvement (38, 39). Furthermore, an
excessively reductionistic approach may be intrinsically inappropriate, because most nutrients act in concert with one another, and the attempt to establish efficacy for one apart from the other, as if they were drugs, may be misguided (40).

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REFERENCES