Issues and Opinions

Passive Diffusion Does Not Play a Major Role in the Absorption of Dietary Calcium in Normal Adults

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ABSTRACT Several authors have indicated recently that passive diffusion is the dominant process by which dietary calcium is absorbed by normal adults. These conclusions have important implications in the maintenance of normal calcium status in humans. They imply that increasing luminal calcium concentration by increasing intake is the most important strategy in promoting calcium absorption. In this issue, I present several studies that dispute this contention and two studies that suggest that passive diffusion is of little practical significance, even in young children. The contribution of passive diffusion is estimated to be between 8 and 23% of the total calcium absorbed by normal adults. Thus, it clearly does not represent the major path by which they absorb calcium. Children lacking the vitamin D receptor system do not absorb enough calcium by passive diffusion to prevent signs of rickets even when diets contain very large amounts of dietary calcium (>2 g/d). The conclusion drawn from this analysis is that passive diffusion (dictated by calcium intake) is not the major mechanism by which dietary calcium is absorbed by normal adults. The vitamin D-dependent processes are more important quantitatively and thus constitute a major determinant of calcium status. Individuals who are not exposed to sunlight may be especially at risk. J. Nutr. 132: 3428–3430, 2002.

The absorption of dietary calcium occurs by two pathways: active transport, which is dependent on vitamin D; and passive diffusion, which is independent of vitamin D. Establishing the relative contribution of these processes is an important nutritional issue because it could provide a rationale for supplementation. If passive diffusion was most important, then simply increasing the luminal concentration of calcium by increasing intake would, by definition, suffice to increase calcium absorption. If the vitamin D-dependent path were more critical, then the amount of calcium consumed would be important but insufficient to promote calcium absorption because it would be determined (regulated) by vitamin D-dependent mechanisms. In promoting calcium nutrition, the emphasis would presumably be different depending on which of these processes was most critical.

Several authors have indicated recently that passive diffusion accounts for “most” of the calcium absorbed by humans under normal conditions. Although “most” is not defined, the inference is that more than half of dietary calcium absorption under normal conditions occurs by this process. If that is true, then much of the calcium absorbed is directly related to intake and thus is independent of vitamin D nutrition/status. In a recent review on calcium absorption, Bronner and Pansu (1) concluded that “passive absorption . . . is the major absorptive process when calcium intake is adequate or high.” They indicate that high calcium intake leads to a “down-regulation” of active transport and that this then leads to a situation in which passive transport becomes dominant. Some of the evidence cited for this conclusion was derived from rat studies but some came from studies of premature infants. For apparently different reasons, this opinion has been reiterated in a newly published textbook of human nutrition. Wood (2) states that “In humans, calcium intakes above as little as 3 mmol (120 mg) in a meal are mostly absorbed by the diffusion-dependent transport route Sheikh (1988).” He then states that “Calcium absorption continues to increase with intake . . . as a result of this diffusion-dependent paracellular route.” The evidence cited by this author appears not to support this conclusion. I will review this study and other evidence that leads to a conclusion different from those stated above, i.e., that vitamin D-independent absorption (passive diffusion) is the major process affecting calcium absorption in normal adults.

Ireland and Fordtran (3) were the first to directly measure calcium absorption in humans. They perfused sections of small intestine of both young and elderly subjects under different dietary conditions. The procedure permitted the authors to directly vary the luminal concentration of calcium in the perfusate and thus to assess the disappearance of calcium at some point distal to the point of infusion. Using this approach the authors also attempted to estimate “passive diffusion.” Figure 1 illustrates the data obtained by these authors and their estimated values for passive diffusion. The first measured experimental point was determined under conditions when the perfusate contained no calcium, i.e., the calcium concentration at distal collection points when the perfusate concentration was zero initially. The change in calcium concentration under these conditions then represented the rate of secretion of calcium into the segment during the perfusion. The second point was predicted by assuming zero diffusion when calcium in the perfusate is equal to the concentration of diffusible calcium in plasma (i.e., 1.5 mmol/L). Using these

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2 Abbreviation used: 1,25 (OH)2 vitamin D3, dihydroxycholecalciferol.
two points and the linear relationship between diffusion and concentration, the contribution of passive diffusion can be estimated. At the highest concentration of calcium in the perfusate (a value simulating a dietary intake of 939 mg/d Ca), 0.13 mmol of calcium was determined to be absorbed by passive diffusion. Because the total absorption was 0.6 mmol/L, 21% (0.13/0.6 \times 100) of the absorption of calcium at the highest intake was due to passive diffusion. This value is remarkably similar to a value reported more recently for normal adults [as cited above by Wood (2)].

Sheikh et al. (4) studied normal and dialysis patients before and after vitamin D therapy. They evaluated net calcium absorption by measuring endogenous calcium secretion into the duodenum and fecal calcium after a meal. They presented a striking correlation between calcium absorption and plasma dihydroxycholecalciferol [1,25 (OH)₂ vitamin D₃] concentration. Using this relationship, they were able to estimate (by extrapolation) passive diffusion by evaluating net absorption of calcium at zero circulating 1,25 (OH)₂ vitamin D₃ levels. Estimates for normal subjects did not differ from other subjects and were 25 and 32 mg at calcium intakes of 120 and 300 mg Ca, respectively (see Fig. 2). These intakes represent low and normal values for healthy adults. For normal patients consuming a normal calcium meal (300 mg), ~32 mg/132 mg or 23% of the total calcium absorption was determined to be passive diffusion (see Fig. 2). The authors note correctly that the majority of the “change” in calcium absorption (as intake is increased from 120 to 300 mg per meal) is due to passive diffusion. The value of 23% is remarkably close to the 21% estimated by Ireland and Fordtran (3) over a decade earlier. A final study reported by Wilz et al. (5) observed a considerably lower value for passive diffusion in studies of healthy adults. Calcium absorption was evaluated as the difference between intake and fecal excretion. Vitamin D-independent calcium absorption was estimated in subjects whose serum 1,25 (OH)₂ vitamin D₃ levels were essentially zero. In these subjects, they observed that ~8% of calcium absorbed at intakes ranging from 6 to 162 mmol/d was due to passive diffusion. They concluded that their data were consistent with the concept that vitamin D is essential for net intestinal calcium absorption in adult humans. In toto, the results of these three studies suggest that passive diffusion accounts for 8–23% of calcium absorbed by normal adults consuming normal dietary calcium. This is by no means “most” or a “majority” of calcium absorption as indicated above. Passive diffusion may, however, represent a contribution that could be important under normal circumstances. Studies of children lacking the vitamin D receptor system, however, suggest that even the practical importance of passive diffusion may be limited.

The role of passive diffusion in the absorption of dietary calcium in children has been evaluated indirectly in two different studies of children who lacked a vitamin D receptor system (6,7). Both studies demonstrated that oral supplementation with calcium was completely ineffective in restoring calcium status. This was particularly evident in the study by Balsan et al. (6), who found that after 6 mo of oral calcium therapy (2.25 g/d Ca plus 72 g/d lactose) there was no

![FIGURE 1](https://academic.oup.com/jn/article-abstract/132/11/3428/4687324)

**FIGURE 1** Absorption of calcium by human subjects as determined by perfusion of segments of the small intestine. The left panel represents total “observed” calcium absorption as a function of calcium concentration in the perfusate. The line crossing the x-axis is an estimate of passive diffusion. The right panel represents the “calculated active transport” or vitamin D-dependent absorption. The original figure was taken with permission from Ireland and Fordtran (3).

![FIGURE 2](https://academic.oup.com/jn/article-abstract/132/11/3428/4687324)

**FIGURE 2** Calcium absorption from two meals of calcium for subjects with three different concentrations of serum 1,25 (OH)₂ vitamin D₃. Arrows were drawn for clarification. Hatched bars represent vitamin D-dependent calcium absorption and open bars represent passive diffusion (vitamin D independent). The original graph was taken with permission from Sheikh et al. (4).
significant effect on serum calcium, alkaline phosphatase or urinary calcium. The patient continued to deteriorate physically due to a lack of appetite and bone pain. Intravenous infusion of calcium, however, completely restored bone lesions and eliminated symptoms of rickets. The beneficial effects of calcium infusion were evident as early as 2 wk later, when bone pain was relieved and the patient’s appetite was restored. After 4 mo of therapy, radiological symptoms of rickets had disappeared completely. Quantitatively similar findings have been obtained in rats deprived of dietary vitamin D but given calcium supplements by infusion (8). Continuous infusion of calcium and phosphorus resulted in a rapid disappearance of the signs of rickets or osteomalacia. Oral calcium, however, was not effective. Collectively, these studies highlight the importance of vitamin D in the absorption of dietary calcium. More importantly, they emphasize that passive diffusion may be of little practical importance, especially in young children. It is possible that higher intakes of calcium (>2.25 g/d) may be required for passive diffusion to contribute physiologically important amounts of calcium.

Most recently a dietary treatment has been developed which appears to provide sufficient calcium through a vitamin D-independent mechanism (passive diffusion). Li et al. (9) reported that 2% dietary calcium plus 20% lactose was capable of normalizing growth and restoring circulating calcium in vitamin D receptor knockout mice. The combination of high dietary calcium and lactose most likely results in an alteration in the site of calcium absorption as demonstrated many years ago by Lengemann et al. (10), as well as in other effects. Nonetheless, this report illustrates that there may be conditions under which passive diffusion does play a role in calcium absorption. Interestingly, Balsan et al. (6) also included lactose (62–82 g/d) when supplementing cannally to the vitamin D receptor-deficient children. Several explanations could account for why Balsan et al. (6) observed no improvement under their conditions. The amount of lactose and/or calcium may have been insufficient relative to that given the knockout mice. It is also possible that young children and mice differ with regard to the mechanism of calcium absorption.

The evidence cited by Bronner and Pansu (1) for the importance of passive diffusion as a route of calcium absorption for normal humans appears to have come largely from rat studies and a study of preterm infants (mean age, 35 wk). The latter study seems to provide evidence that a saturable process (vitamin D dependent) is either nonexistent or completely saturated at the intakes used (11). Because calcium retention increased linearly with calcium intake by these infants, as would be predicted for passive diffusion, the authors concluded that in preterm infants most if not all of the calcium absorption occurs by a “nonsaturable, non-vitamin D dependent, presumably paracellular process.” These results are consistent with those observed in newborn rats, where the vitamin D-dependent process has not yet developed (12). In fact, it is not until ~18 d after birth that the vitamin D-dependent process appears. This suggests that, early in development and for several weeks after birth, calcium absorption depends primarily on passive diffusion, not on vitamin D-dependent processes. Afterward, however, passive diffusion appears to be physiologically (practically) unimportant at worst or quantitatively irrelevant at best. Species difference may also complicate interpretation and/or relative importance.

In conclusion, I have presented evidence that calcium absorption under normal conditions occurs primarily by a saturable process requiring vitamin D. This is in contrast to the interpretation of others who have suggested that passive diffusion is the dominant process. The evidence presented clearly shows that passive diffusion accounts for 8–23% of the total calcium absorbed by adults under normal conditions. Although the practical importance of this for adults is unknown, it appears questionable in children who have no vitamin D receptor system; they are not capable, even in the presence of lactose, of obtaining sufficient calcium from a diet containing >2 g/d Ca. Bizarre diets would be necessary for these children to obtain enough calcium via a vitamin D-independent path to supply their calcium needs. It is likely that such diets would introduce additional problems or side effects. Thus, it would appear that vitamin D-dependent processes are paramount in the normal absorption of dietary calcium. Perhaps vitamin D is a limiting factor in establishing normal calcium nutrition, especially in those individuals who are not regularly exposed to sunlight.

LITERATURE CITED