Vitamin D status and muscle strength

Dear Sir:

In a recent issue of the Journal, in attempting to rationalize the effect of vitamin D status on muscle function and on the risk of falls in the elderly, Janssen et al (1) focused on calcitriol’s direct effects on skeletal muscle, mediated by either nuclear or membrane vitamin D receptors. Such a focus seems likely to be misplaced, in light of the fact that common variations in vitamin D status—as quantified by serum 25-hydroxyvitamin D [25(OH)D] concentrations—have little if any sustained effect on serum calcitriol concentrations. When 25(OH)D is low, up-regulation of parathyroid hormone (PTH) production ensures that calcitriol concentrations remain stable. Thus, even at the higher latitudes, there is little seasonal variation in calcitriol concentrations in either elderly or younger subjects, despite the fact that 25(OH)D varies markedly (2, 3). Calcium intake, however, does have a modulatory effect on calcitriol concentrations: ample dietary intake of calcium is associated with a homeostatically appropriate down-regulation of calcitriol that prevents excessive calcium absorption. To the best of my knowledge, there is no evidence that an increase in dietary calcium intake in the elderly induces muscle weakness or increases the risk of falls. The authors suggested that increased autocrine production of calcitriol from 25(OH)D, in skeletal muscle might account for the effect of supplemental vitamin D on muscle function. Although autocrine production of calcitriol may be of physiologic significance in some tissues—notably, activated macrophages—it is most unlikely that such a pathway is prominent in skeletal muscle. Owing to the fact that skeletal muscle constitutes a large fraction of the body mass, significant autocrine production of calcitriol in skeletal muscle would be expected to have a major effect on systemic calcitriol concentrations, rivaling that of renal 1-alpha hydroxylase, but no such effect is known.

A more likely resolution of this conundrum is that the mild secondary hyperparathyroidism associated with poor vitamin D status mediates the effect of vitamin D deficiency on muscle function. Proximal muscle weakness is a recognized complication of primary hyperparathyroidism (4–6), and it has also been reported in patients with secondary hyperparathyroidism induced by chronic renal failure (7, 8). How hyperparathyroidism induces muscle weakness is not clear; hypercalcemia is unlikely to mediate these effects, inasmuch as serum calcium can be normal or low in persons with renal failure. PTH can act directly on muscle and various other tissues to increase free intracellular calcium concentrations (9); perhaps this chronic increase diminishes the net effect in which the spike in free intracellular calcium triggers muscle contraction or in some other way disrupts muscle structure or function.

Stein et al (10) used multiple regression analysis to determine which hormonal and lifestyle factors best predict the propensity of elderly nursing home residents to fall. Their analysis incorporated serum (or plasma) concentrations of 25(OH)D, calcitriol, PTH, calcium, phosphate, albumin, and creatinine as well as sex, age, weight, and various lifestyle factors. They concluded, “In a multiple logistic regression for falling, higher serum PTH remained independently associated with falling, with an odds ratio for falling of 5.6 per unit of the natural logarithm of PTH. … The association between falling and serum PTH persists after adjustment for other variables.” However, neither calcitriol nor log-transformed 25(OH)D concentrations had any predictive power after adjustment for PTH; indeed, in a univariate analysis, calcitriol did not correlate with the risk of falling. These findings are evidently consistent with the view that secondary hyperparathyroidism mediates the muscle weakness associated with vitamin D deficiency.

Resolving this issue may be of more than just theoretical interest. If secondary hyperparathyroidism mediates the effect of vitamin D deficiency on muscle strength, it would seem to follow that, other factors being equal, a greater intake of calcium and a reduction in dietary salt, both of which would be expected to down-regulate PTH secretion, could likewise aid muscle strength in elderly subjects with poor vitamin D status. I am unaware of any studies examining such a possibility. The tendency of these ancillary measures also to down-regulate calcitriol conceivably could influence their net effect on muscle. In any case, it would be advisable to devote further research attention to the effect of mild secondary hyperparathyroidism—and of various measures that modulate PTH secretion—on muscle strength in the elderly.

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REFERENCES


Reply to MF McCarty

Dear Sir:

We appreciate McCarty’s letter in response to our review on vitamin D deficiency, muscle function, and falls in elderly people. As we stated in our article, the serum 1α,25-dihydroxyvitamin D₃ [1,25(OH)₂D₃] concentration is under tight metabolic control by feedback mechanisms, which will keep it within reference limits (40–140 pmol/L in our laboratory) in case of a moderate shortage in 25-hydroxyvitamin D₃ [25(OH)D₃]; this statement is in agreement with McCarty. However, substrate dependency and seasonal variations in 1,25(OH)₂D₃ have been described in elderly people (1, 2).

Although experimental studies, both in vitro and in vivo, have provided abundant evidence of the mechanisms by which 1,25(OH)₂D₃ directly affects muscle function through a vitamin D receptor (3), the available clinical studies indicate a relation between 25(OH)D₃ and muscle function. In our report, we provided 2 possible explanations for this discrepancy; in McCarty’s letter, another is given. Although we value his suggestion that mild secondary hyperparathyroidism associated with poor vitamin D status mediates the effect of vitamin D deficiency on muscle function, a few remarks on this subject are in order.

Indeed, muscle weakness has been found in some but not all patients with primary hyperparathyroidism (4, 5). After surgery, muscle strength in patients with primary hyperparathyroidism has been found to improve (6, 7), although this improvement did not correlate with serum calcium or parathyroid hormone (PTH) concentrations.

Furthermore, maximum voluntary knee-extension strength was measured in 55 vitamin D–deficient Arab women who underwent high-dose vitamin D and calcium treatment (8). In correlation analysis, it was found that maximum voluntary knee-extension strength was positively correlated with 25(OH)D₃ concentrations and inversely correlated with PTH concentrations, but it was not significantly related to 1,25(OH)₂D₃ concentrations (respectively: r = 0.34, P < 0.001; r = −0.33, P < 0.001; r = −0.14, NS). When multivariate regression analysis between maximum voluntary knee-extension strength and 25(OH)D₃, 1,25(OH)₂D₃, and PTH concentrations was done, only 25(OH)D₃ remained significantly (P = 0.02) related to maximum voluntary knee-extension strength.

This finding contrasts with that in the study of Stein et al (9), in which PTH remained independently associated with falling in multiple logistic regression analysis and 25(OH)D₃ did not. McCarty states that this finding is consistent with the view that secondary hyperparathyroidism mediates the muscle weakness associated with vitamin D deficiency. However, an alternative explanation was provided by Birge (10), who stated in an editorial, “It [PTH] may be a better biological marker than 25(OH)D₃ for vitamin D deficiency at the tissue level. Serum levels of 25(OH)D₃ do not reflect the tissue response to the sterol. This becomes particularly relevant when we consider the variable and increasing resistance to vitamin D with hormonal status and advancing age. In addition, multiple alleles in the vitamin D receptor protein gene also determine tissue responsivity.”

In conclusion, the books are clearly not closed on the mechanisms responsible for vitamin D deficiency and muscle weakness. Substantial evidence points to a direct relation between vitamin D metabolites and muscle function, but we cannot exclude a possible negative synergistic influence of increased PTH and low serum vitamin D metabolites on muscle strength. We agree with McCarty that more research is needed on this matter.

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