
**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)D₃] 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)D₃ 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)D₃ 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)D₃ concentrations (respectively: \( r = 0.34, P < 0.001; r = -0.33, P < 0.001; r = -0.14, \text{NS} \)). When multivariate regression analysis between maximum voluntary knee-extension strength and 25(OH)D₃, 1,25(OH)D₃, 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.

Hennie CJP Janssen
Monique M Samson
Harald JJ Verhaar

**REFERENCES**

9. Stein MS, Wark JD, Scherer SC, et al. Falls relate to vitamin D and
Primary prevention of cardiovascular diseases by α-linolenic acid

Dear Sir:

In a recent primary prevention trial in 266 subjects with multiple risk factors for ischemic heart disease (IHD), Bemelmans et al (1) evaluated the protective effects of α-linolenic acid (ALA) on risk factors and on morbidity and mortality. ALA was compared with linoleic acid (LA); both fatty acids were included in the diet through special margarines. The intakes of ALA and LA were 6.3 and 26.3 g/d, respectively, in the ALA group and 1.0 and 28.8 g/d, respectively, in the LA group.

After 2 y of follow-up, plasma fibrinogen concentrations were lower in the ALA group than in the LA group, but plasma total and LDL cholesterol were not significantly different between the groups. HDL cholesterol was significantly lower, by 0.045 mmol/L, in the ALA group. The conclusion was that the estimated IHD risk of the increased ALA intake was similar to that of LA. Nevertheless, after 2 y of follow-up, the number of cardiovascular events (cardiovascular death, nonfatal myocardial infarction, stroke, and percutaneous transluminal coronary angioplasty or revascularization) was 9 in the LA group but only 2 in the ALA group. This difference was not significant (P < 0.20) but is certainly intriguing because it represents 78% fewer cardiovascular events in the ALA group than in the LA group.

In the Lyon Diet Heart Study, which involved 600 patients with coronary heart disease (2), we observed similar results. After a 27-mo follow-up, we observed no significant changes in total cholesterol or LDL cholesterol between the groups who consumed a diet enriched with ALA and those who consumed a diet enriched with LA. With the ALA diet, HDL cholesterol was lower at 2 y by 0.04 mmol/L (similar to the results of Bemelmans et al’s study), but the number of cardiovascular events were fewer, by 71% (P < 0.001). This suggests that if the trend had continued in the study by Bemelmans et al, the results might have become significant. Another possibility would have been to recruit 600 subjects, as was done in the Lyon Diet Heart Study (2). Under those conditions, if the trend were similar to that in the present study, a significant result (P < 0.02) would be observed in 2 y.

Even if ALA, at the level used in Bemelmans et al’s study (1), does not affect serum cholesterol and lipoproteins, it should not be concluded that the number of cardiovascular events could not be significantly reduced. In the 4 secondary intervention trials published so far, the protective effects of n–3 fatty acids on cardiovascular risk factors, as reviewed recently (9), have also shown protective effects of ALA on nonfatal (6, 7) and fatal (8) cardiovascular events, independent of other dietary or nondietary factors, as reviewed recently (9).


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REFERENCES


Reply to D Lanzmann-Petithory et al

Dear Sir:

We appreciate the comments of Lanzmann-Petithory et al on our MARGARIN (Mediterranean Alpha-linolenic EnRiched Groningen dietARy InTervention) study regarding the effects of