

Vitamin D, many associations but few that seem to matter

P.L.A. van Daele

Department of Internal Medicine, Erasmus MC, Rotterdam, the Netherlands, tel.: +31 (0)10-7040704,
email: p.l.a.vandaele@erasmusmc.nl

In the current issue of the journal, Keshavarz et al. describe the association between vitamin D levels and metabolic disturbances in patients with polycystic ovary syndrome (PCOS).¹ Only about 3% of patients in this study had normal vitamin D levels, which they define as a vitamin D level above 30 ng/ml. On top of this, they find an association with various clinical and metabolic parameters.

Vitamin D, a nutrient in name, but much more a hormone in function, has been extensively studied in many diseases, not only in endocrine disorders, but also for instance in cardiovascular disease, cancer, psychiatric disease and autoimmunity.²⁻⁵ It appears that almost invariably, an association is found making vitamin D a very rewarding topic for researchers and an important issue for decision makers. Searching the Cochrane Library for vitamin D already yielded almost 10,000 hits.

But studies looking for associations do not provide evidence of causality. For causality to be plausible either experiments examining or demonstrating a pathogenetic mechanism involving vitamin D or clinical trials showing benefit of supplementation are necessary.

Metabolic bone disease fulfills both. Vitamin D, or rather its metabolites, are important in bone metabolism and deficiency is associated with bone disease. Furthermore, already in the 1930s, vitamin D supplementation was shown to be beneficial in rickets.⁶

Yet, for most other conditions for which an association with vitamin D levels has been demonstrated neither is true; no well-established pathogenetic mechanism and, not surprisingly, many clinical trials on vitamin D supplementation come out negative or at best show conflicting results. This suggests that in several diseases in which an association is found, this indicates consequence rather than causality.

Keshavarz concludes that there is a need to perform intervention trials to examine the causal relationship, hoping that intervention may also lead to improvement. In fact, this has already been done. A recent meta-analysis once more showed a lack of effect of vitamin D supplementation, this time in PCOS.⁷

Should we stop doing association studies on vitamin D? In my opinion yes, given the abundance of negative trials after supplementation, unless there is a sound pathogenetic concept.

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