Towards a trial-based definition of vitamin D deficiency

Markus Altmann/Corbis

Published Online
March 1, 2016
http://dx.doi.org/10.1016/S2213-8587(16)00079-6

This online publication has been corrected. The corrected version first appeared at thelancet.com/diabetes-endocrinology on March 3, 2016

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Vitamin D is not a vitamin (ie, an essential micronutrient), but rather the parent compound of an endocrine system primarily involved in the regulation of intestinal calcium absorption. It is synthesised in the skin as a result of the action of ultraviolet (UV) light on 7-dehydrocholesterol, and oral intake (other than supplement use) makes a negligible contribution to vitamin D concentration in most people. It is not biologically active, but two metabolites, 25-hydroxyvitamin D (25[OH]D) and 1,25-dihydroxyvitamin D, bind to the vitamin D receptor (the latter with a 1000 times the affinity of the former) and stimulate the active absorption of calcium in the upper small bowel. Both metabolites circulate bound to vitamin D binding protein.

Severe vitamin D deficiency results in hypocalcaemia and hypophosphataemia, resulting in under-mineralisation of bone (osteomalacia). Before skeletal maturity, this deficiency presents as rickets. Circulating concentrations of 25(OH)D are affected by sunlight exposure, and are reduced in people who are seldom outdoors (eg, those who are frail), women who are permanently veiled, and in people with dark skin (in whom melanin absorbs the UV light). Obesity also reduces 25(OH)D, since fat-soluble vitamin D is sequestered into adipose tissue, as do inflammatory states (a poorly understood phenomenon that is partly due to changes in vitamin D binding protein).[1]

Circulating concentrations of 25(OH)D are reduced in almost every medical or psychiatric disorder in which they have been studied,[2] and have a U-shaped association with mortality.[3] In pregnancy, low maternal 25(OH)D concentrations have been associated with gestational diabetes, pre-eclampsia, infants who are small for their gestational age, and lower offspring bone mass.[4] From these associations has arisen the widespread belief that vitamin D deficiency is involved in the causation of a wide range of pathological abnormalities, resulting in advocacy for widespread supplementation.

After a decade of publications demonstrating vitamin D's many disease associations, we are now entering a new era in which trials of vitamin D supplementation are being completed. These offer the possibility of determining which associations represent causation, and of guiding clinical practice. The MAVIDOS study, presented in *The Lancet Diabetes & Endocrinology* by Cyrus Cooper and colleagues,[5] shows that cholecalciferol 1000 IU/day does not affect neonatal bone mineral content (BMC) when given to pregnant women with baseline 25(OH)D concentrations between 25 nmol/L and 100 nmol/L. In a prespecified subgroup analysis, an interaction was noted between the effects of treatment allocation and season of birth on offspring BMC ($p_{interaction}$=0·04): for births occurring in winter, vitamin D supplementation increased neonatal BMC by almost 10% (p=0·004), and fat mass was increased by 17% (p=0·008). Increases in neonatal bodyweight after maternal vitamin D supplementation have been suggested in previous similar trials,[6] and the higher fat mass observed in the supplemented group in Cooper and colleagues' study might be mechanistically related to the bone changes, since fat mass is a dynamic determinant of bone mass in adult life.[7] The subgroup of women who gave birth in winter had a mean 25(OH)D concentration of 30 nmol/L (SD 16) at 34 weeks' gestation, compared with concentrations of 50–60 nmol/L in the summer and autumn birth subgroups, suggesting a threshold at which supplements might be of value.

To the purist, MAVIDOS shows no benefit from vitamin D supplementation in pregnancy. However, the subgroup analysis provides data that might help to address the vexed issue of what constitutes vitamin D deficiency. The findings suggest that when 25(OH)D concentration is lower than 30 nmol/L, neonatal fat and bone mass could be affected by maternal supplementation. This threshold is very similar to that for which beneficial effects on adult bone density and for prevention of osteomalacia have been reported.[8] Similar post-hoc trial evidence has suggested that when 25(OH)D concentration is lower than 25–30 nmol/L, supplementation might reduce exacerbations of chronic obstructive pulmonary disease,[9] and reduce mortality in people who are critically ill.[10] By contrast, Bolland and colleagues[11,12] have produced persuasive evidence that supplements given to cohorts with higher 25(OH)D concentrations (generally >30 nmol/L), do not affect falls, fractures, myocardial infarction, stroke, or cancer.

Together, these findings suggest that vitamin D might be causally associated with some disorders when 25(OH)D concentration is lower than 25–30 nmol/L. The manifold disease associations with higher concentrations

of serum 25(OH)D probably reflect the effects of obesity and inflammatory states, and the fact that individuals who are unwell from any cause spend less time outdoors. Thus, the progressive upward drift in reference ranges for 25(OH)D over the past two decades, which has been based on its disease associations, is inappropriate, and the lower bound of this range should reflect the results from clinical trials of vitamin D supplementation. Future trials of vitamin D supplements should recruit participants with 25(OH)D concentrations of lower than 25–30 nmol/L, since there is little evidence of benefit when baseline 25(OH)D is above this concentration, in pregnancy or other contexts. If we are to embark on such trials, however, their ethics and cost–benefit require careful consideration, since we know that these concentrations of 25(OH)D are associated with osteomalacia and that calciferol 400 U/day (or an equivalent dose at longer intervals) can correct this deficiency safely and at minimal cost. When the 25–30 nmol/L threshold is used, vitamin D deficiency becomes a much less prevalent condition that, in most clinical contexts, can be reliably predicted from clinical risk factors alone.[13] Therefore, in pregnancy and other contexts, we should be moving to targeted supplementation with vitamin D in individuals likely to have concentrations of lower than 25–30 nmol/L, and away from mass medication, which is without proved benefit.

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I have received grants and personal fees from Merck and Amgen, and personal fees and non-financial support from Novartis, outside the submitted work. My work is supported by the Health Research Council of New Zealand.

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PCSK9 inhibition in type 2 diabetes: so far so good, but not there yet

Alirocumab and evolocumab, both fully human monoclonal antibodies that bind to plasma proprotein convertase subtilisin/kexin type 9 (PCSK9), were recently approved for the treatment of hypercholesterolaemia in Europe and the USA. PCSK9 is mainly synthesised by the liver and binds to LDL receptors, thereby precluding their recycling to the hepatocyte surface, reducing LDL clearance from plasma, and thus increasing the concentration of LDL cholesterol.[1]

Type 2 diabetes is associated with an increased lifetime risk of cardiovascular disease, and practice guidelines recommend intensive LDL cholesterol-lowering treatment to prevent major atherosclerotic events.[4] Patients with type 2 diabetes have therefore become a natural population in which to test PCSK9 inhibitors.

In *The Lancet Diabetes & Endocrinology*, Naveed Sattar and colleagues[5] present the results of a meta-analysis of three 12-week phase 3 trials that compared

Published Online February 8, 2016 http://dx.doi.org/10.1016/S2213-8587(16)00014-0

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