Validating the effects of correcting vitamin D deficiency; time for reappraisal of clinical trial design

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Gorey et al.[1] report many reasons for vitamin D [VitD] supplementation trials producing disparate results. Additionally, investigating causality for the inverse associations consistently seen between VitD status and health risks[2], and suggested by many specific mechanistic effects, requires RCT designs suitable for nutrients, not pharmaceuticals. Rises in serum 25(OH)D concentrations and in the biological effectiveness of VitD when supplementing deficiency are both 'S-shaped'. This means that failure to increase deficient 25(OH)D values up onto the steep part of these dose-response curves will have no noticeable health benefits and neither does the supplementation of replete subjects as increases in their serum 25(OH)D will usually be small as they will be on the flat upper part of the S shaped curves.[,3] The common practice of giving single doses of vitamin D3 without adjustment so as to achieve repletion perpetuates these effects, whilst very high dosages, often given at long intervals, frequently lead to detrimental health effects, as the authors point out.[1] However, RCT data analyses for initially deficient subjects [using 'Individual Participant Data'] overcomes these major problems and are revealing significant health benefits with reductions, for example, in upper respiratory tract infections [by -70%],[4] and significant reductions also in acute asthma exacerbations, in overall mortality [by 25% when supplementing subjects with baseline vitamin D deficiency][5] and often from meta analyses including many RCTs of vitamin D supplementation that had initially been reported as having produced no benefits.[4]

Target tissue Vitamin D_3 activation is up regulated by serum 25(OH)D concentration, independent of parathyroid hormone, likely explaining the consistent associations of serum 25(OH)D with health-benefits.[2,6] The 25(OH)D concentration thresholds at, and above which, benefits are found observationally and in RCTs also vary[7] [e.g. at 50nmol/l for bone health and 80nmol/L for reducing abnormal insulin resistance]. Additionally, 25(OH)D measurements vary, despite widespread use of international quality control schemes while High Pressure Liquid Chromatography/Tandem Mass Spectroscopic [HPLC/TMS] technology produces higher 25(OH)D values than do immunoassays [by amounts averaging +5nmol/l, but up to 33nmol/l]. Thus, increasing use of the harmonization of immunoassay data to HPLC/TMS data on standards[8] will raise both the thresholds for achieving various health effects and the cut-offs used to define various degrees of vitamin D deficiency and repletion. Clearly, these difficulties will require rationalisation of the criteria used in future studies at an International level.

Several other nutrients are known to affect Vitamin D efficacy, including excessive vitamin A intakes, [common in affluent countries], which inhibit the gene modulating mechanistic effects of calcitriol at the vitamin D receptor [VDR] level. Inadequate provision of magnesium impairs overall enzyme activity, including those in the vitamin D activating cascade. Adequate calcium intakes facilitate vitamin D activity, and insufficiency prejudices the non-genetic actions of calcitriol which are induced through rapid increases in

intracellular calcium ion concentrations. Furthermore, polymorphisms of the VDR, of vitamin D binding proteins and of the various vitamin D activating enzyme genes affect serum 25(OH)D concentrations. Ideally, therefore, RCTs designed allowing for all these factors are required to improve vitamin D RCT outcome reliability.

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