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25-Hydroxyvitamin D – Should labs be measuring it?

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Perception of vitamin D supplementation as a panacea for good health continues. Media coverage proclaims widespread vitamin D deficiency, with supplementation needed to prevent disease,[1] despite most research covered being epidemiological association studies beset by confounding and reverse causality. Commercial interests promoting supplementation influence advocacy organizations and academia.[2] However, high-quality evidence indicates that vitamin D supplementation does not improve musculoskeletal outcomes, other than preventing rickets and osteomalacia in high-risk groups.[3,4] Effects on non-musculoskeletal outcomes, such as cancer, cardiovascular disease and mortality, are unconvincing.[3,4] Nevertheless, vitamin D has become medicalized,[5] driving demands for predominantly inappropriate measurement of 25-hydroxyvitamin D (25OHD), the metabolite best reflecting tissue stores.[6–8] Most Scottish laboratories limit testing to one/year/patient, but >1% of the population have 25OHD measured annually (Karen Smith, personal communication). Between 2008 and 2014, 25OHD testing in English children in primary care rose from 43/100,000 to 768/100,000 with an estimated cost in 2014 of £1.69 million.[7]

The unequivocal phenotype of vitamin D deficiency is impaired bone mineralisation (childhood rickets and adult osteomalacia), caused by impaired intestinal absorption of calcium and phosphorus, with characteristic biochemical, radiological and clinical features. What concentration of 25OHD indicates a genuinely increased 'risk of deficiency' and thus an increased risk of osteomalacia or rickets? The US Institute of Medicine[9] thought <30 nmol/L (12 ng/mL); the UK Scientific Advisory Committee on Nutrition[10] decided 25 nmol/L. These bodies reviewed old studies with unreliable 25OHD assays, and a study of postmortem bone biopsies from victims of unnatural causes of death,[11] which has been criticized for uncertain histomorphometric criteria and questionable validity of postmortem 25OHD.[12] 25OHD thresholds for rickets or osteomalacia could not be clearly identified by these reports, but it is likely that very low 25OHD must occur for several months before bone mineralization is impaired. Whether dietary calcium can prevent rickets or osteomalacia in vitamin D deficiency is uncertain.[10]

How commonly does rickets or osteomalacia from vitamin D deficiency occur? Figures for proven osteomalacia in industrialized societies are lacking. In the UK and Ireland, vitamin D deficiency increased from 3/100,000 to 261/100,000 person-years between 2000 and 2014 for children aged 0–17 years, but the basis for diagnosis was either unspecified, rickets, prescription of higher dose vitamin D, or 25OHD <25 nmol/L, so much of the apparent increase probably related to more testing.[13] In contrast, the annual incidence of childhood hypocalcaemic seizures due to vitamin D deficiency is 3.49/million.[14] Annual incidence of symptomatic childhood vitamin D deficiency is also very low in Denmark (2.9/100,000), Canada (2.9/100,000) and

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Norway (3/100,000), but higher among children from immigrant families.[14,15]

If we use serum 25OHD to diagnose an increased risk of deficiency, are analytical methods adequate? The two main forms of vitamin D – cholecalciferol/vitamin D_3 from endogenous formation or supplementation, and ergocalciferol/vitamin D_2 from supplementation – may be determined differently in immunoassays.[16,17] The majority of 25OHD is bound to vitamin D binding protein (DBP),[18] an acute phase protein, such that 25OHD may be unreliable in illness.

24,25-Dihydroxyvitamin D is formed in the degradation of 25OHD and interferes in some 25OHD immunoassays.[17,19] Without an extraction step, matrix problems may limit further improvement in immunoassay quality control.[19]

Liquid chromatography-tandem mass spectrometry (LC-MS/MS) is the gold standard for measuring 25OHD and its metabolites, but is used by only about 20% of labs participating in DEQAS (vitamin D External Quality Assessment Scheme).[17,19] Harmonization between LC-MS/MS and immunoassay is challenging, especially at lower 25OHD concentrations: in a recent study, 69% of samples were <30 nmol/L using an immunoassay, compared with 46% using LC-MS/MS.[20] Standardization of 25OHD measurement has improved with external quality assurance schemes, but many difficulties remain.

If the acknowledged clinical phenotype of vitamin D deficiency is rare, and clinical trial evidence demonstrates no benefits from supplementation, is there a place for 25OHD measurement? The US Preventive Services Task Force found insufficient evidence to support screening.[21] There seems little justification for measurement in osteoporosis, where patients are often routinely prescribed vitamin D. Recommendations, such as those from Public Health England,[22] to routinely supplement high-risk groups (housebound, dark skin and little sun exposure, breastfed babies <1 year and all children 1–4 years) with 400 IU (10 μg) of vitamin D/day are likely to prevent the rare cases of osteomalacia and rickets, are unlikely to cause harm and make testing for the majority of the population redundant.

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