Vitamin D deficiency
Epidemic or hysteria?

PETER J. SIMM MB BS(Hons), MD, FRACP

The role of vitamin D in health and disease needs clarification, particularly with regard to the ongoing contentious nature of links between vitamin D deficiency and extraskeletal effects.

Key points

- **Vitamin D insufficiency and deficiency are extremely common in the Australian population.**
- **Routine screening of otherwise healthy young people and adults is not supported by the current evidence.**
- **Routine supplementation, even in groups at high risk of vitamin D deficiency, can be undertaken without testing serum vitamin D levels.**
- **Postulated extraskeletal effects of vitamin D are intriguing, but are largely based on association studies and require further evidence from randomised controlled trials to show causality.**

ENDOCRINOLOGY TODAY 2017; 6(2): 27-29

Dr Simm is a Consultant Paediatric Endocrinologist at the Royal Children's Hospital Melbourne; and an Honorary Fellow at the Murdoch Childrens Research Institute and the Department of Paediatrics, University of Melbourne, Melbourne, Vic.

© VITALINKA/STOCK.ADOBE.COM MODEL USED FOR ILLUSTRATIVE PURPOSES ONLY

Awareness of vitamin D deficiency and insufficiency, both among people who are at high risk and among the broader community, has increased dramatically. This has led to vitamin D being attributed a role in many other conditions with which it is epidemiologically associated, including cancer and the metabolic syndrome, and in immune function (both infection control and autoimmunity). However, there is a lack of good-quality evidence for the effect of vitamin D beyond the domains of the skeleton, muscle or overall mortality, as discussed below.

For the purposes of this article, the term vitamin D is taken to mean 25-hydroxyvitamin D, the predominant stored and circulating form of this important factor and the most useful level to measure clinically. This article discusses, from a paediatric endocrinologist's perspective, the role of vitamin D in health and disease. Discussion about vitamin D metabolism and the role of other metabolites is beyond the scope of this article.

Defining vitamin D status

The first stumbling block to discussing the role of vitamin D and its impact in different clinical scenarios is defining deficiency. Recent paediatric global consensus guidelines define vitamin D status within the context of preventing nutritional rickets. Sufficiency is defined as a serum vitamin D level of greater than 50 nmol/L, insufficiency as 30 to 50 nmol/L and deficiency as less than 30 nmol/L.[1] However, many laboratories still report levels of less than 75 nmol/L as deficiency. Ongoing problems with standardising vitamin D assays further complicate the problem.[2]

Adult cutoff levels are more debatable, given the evidence for increased falls and muscle weakness being associated with vitamin D levels of up to 75 nmol/L. However, Australasian guidelines in 2012 recommended that 50 nmol/L should be the lower cutoff at the end of winter, with an extra 10 to 20 nmol/L required in late summer to allow for seasonal variation.[3]

Awareness of vitamin D deficiency has increased remarkably between 2000 and 2010, with a 94-fold increase in vitamin D testing according to Australian Medicare billing data. However, the lack of clear evidence of adverse effects in otherwise healthy people with low levels of vitamin D makes widespread nontargeted screening difficult to justify, either on an individual level or a community health level.[4,5] Similar conclusions have been reached in New Zealand, where the health system faced a ballooning in requests for measurement of vitamin D levels and experts called for a more targeted approach to screening.[6] The development of screening programs that target people who

Downloaded for personal use only. No other uses permitted without permission. © **Medicine**Today 2017.

are at high risk of vitamin D deficiency and people in whom vitamin D supplementation is clearly shown to be of benefit, such as elderly patients and patients with bone health issues or mineral disturbances, will enable the most cost-effective and clinically relevant management of this issue.

Does addressing vitamin D deficiency lead to clinical benefits?

Discussion of the role of vitamin D in treating and preventing disease is hampered by patients who have musculoskeletal problems such as nutritional rickets being considered alongside healthy people who are incidentally discovered to be vitamin D deficient.

The benefits of vitamin D supplementation in children with or at high risk of nutritional rickets are well supported by evidence.[1] The risk factors for vitamin D deficiency outlined in the global consensus guidelines include lack of infant vitamin D supplementation, prolonged breastfeeding beyond six months with no appropriate complementary feeding or supplementation, living at higher latitudes in winter and spring, dark skin pigmentation and restricted sun exposure (such as predominantly indoor living).[1] However, there is limited evidence for any therapeutic benefits of vitamin D supplementation for young people beyond treating nutritional rickets and preventing rickets in children who are at risk. The consensus guidelines also conclude that simple vitamin D deficiency (i.e. in the absence of rickets) has not been shown to be associated with an increased risk of fracture in this younger population.[1]

There have also been many excellent reviews of the evidence related to vitamin D supplementation in adults. One review discussed the pitfalls of a broad, unfocused screening program by highlighting the areas in which vitamin D supplementation has been shown to be effective, such as fracture prevention in elderly women who are vitamin D deficient.[5] The authors also highlighted reports of survival benefits for older women with significant comorbidities; however, they pointed out that vitamin D levels may be reduced by chronic illness, rather than being causative, citing evidence that vitamin D supplementation had few beneficial effects across several conditions.

Similarly, causality between vitamin D and cardiovascular disease has not been shown, despite epidemiological associations.[7] Vitamin D has been found to have antiproliferative and prodifferentiation effects in vitro, and animal studies have also demonstrated benefit, but clinical trials of supplementation in patients with malignancies have shown mixed results and no clear evidence for reduction in cancer risk or progression.[8] The vitamin D receptor is involved in immune regulation, which, intriguingly, suggests a link between immune function and vitamin D deficiency, particularly with regard to effective immunoregulation and therefore the subsequent risk of autoimmune disease; however, again the large volume of association studies that exist do not prove causation. Trials of vitamin D supplementation are providing further interesting results, but there remains insufficient evidence to recommend widespread screening and/or supplementation at a population level to prevent or modify autoimmune disorders.

Many large, population-based randomised controlled trials are under way exploring the effects of vitamin D supplementation in different populations and geographical locations, including the USA, Scandinavia and Australia. It is important to note, however, that many of the participants are likely to already be vitamin D sufficient, as vitamin D deficiency is not a criterion for recruitment. Despite this, these studies may at last provide clarity about the roles of vitamin D beyond the skeleton and show whether the association studies, in vitro evidence and data from animal studies that show positive effects of vitamin D are truly representative of a broad range of therapeutic benefits of vitamin D sufficiency.

Preventing and managing vitamin D deficiency

The vast majority of people living in Australia obtain most of their vitamin D requirement through dermal synthesis on exposure to sunlight, and only 5 to 10% of vitamin D is gained from dietary sources. The risk of overexposure to ultraviolet light and malignancy is high, as evidenced by the extremely high rates of skin cancer seen in Australia. However, individual prescriptions (or broader public health campaigns) outlining appropriate amounts of sun exposure to ensure vitamin D sufficiency are highly problematic because of the variations in ultraviolet intensity at different latitudes and across seasons, skin pigmentation, cloud cover and clothing.

Supplementation at the population level with vitamin D fortification of food is limited, despite studies showing its efficacy. On an individual level, oral vitamin D supplementation is the mainstay of limiting any potential negative health outcomes of deficiency. The Australasian guideline (based on US Institute of Medicine publications) recommends supplementation with colecalciferol (vitamin D_3) at a dose of 600 IU/day (15 μg/day) for people from 1 year of age up to 70 years of age and 800 IU/day (20 μg/day) for people 71 years of age or older.[3] Most available supplements for adults are available as tablets or capsules each containing 1000 IU (25 μg) colecalciferol. In the first year of life, a daily supplement of 400 IU colecalciferol liquid is recommended, independent of an infant's mode of feeding.[1]

If a person is known to have vitamin D deficiency, higher doses of vitamin D will be required to boost depleted stores before supplementation doses can be resumed to maintain sufficiency. Where compliance is an issue, megadose therapy can be a useful strategy. Australian paediatric guidelines support megadose therapy beyond the age of 3 months in appropriate situations, although low-dose supplementation will usually be required to maintain normal levels.[9]

Vitamin D toxicity is extremely rare, especially when using daily dosing for supplementation, although toxicity has been reported as a result of megadose therapy. Toxicity leads to hypercalcaemia and hypercalciuria and, although these conditions usually resolve spontaneously in time, in extreme cases patients will require supportive care. Genetic variations can affect vitamin D metabolism. A mutation in the vitamin D-metabolising enzyme CYP24A1, for example, reduces the efficiency of deactivating vitamin D and therefore people with this mutation are more sensitive to increased vitamin D intake

Downloaded for personal use only. No other uses permitted without permission. © MedicineToday 2017.

and in turn at higher risk of toxicity with replacement therapy. In addition, megadose therapy and smaller intermittent doses of 60,000 IU/month have been associated with an increased risk of fractures and falls in older people. Nevertheless, supplementation at recommended daily doses as outlined above is extremely unlikely to result in toxicity or other adverse events and therefore presents no need to routinely check levels.

Conclusion

The answer to whether the vitamin D debate really represents an epidemic or hysteria likely lies somewhere in the middle. Severe sequelae of vitamin D deficiency such as rickets are being seen more frequently, and the numbers of falls and fractures among elderly people are increasing with the ageing of the Australian population. Studies exploring possible extraskeletal benefits of vitamin D are interesting; however, data are insufficient to demonstrate a causal relationship between vitamin D deficiency and any extraskeletal effects. Similarly, there is no conclusive evidence to guide the management of otherwise healthy people in whom low serum vitamin D levels are detected. Therefore, testing of vitamin D levels should be targeted to high-risk populations who either already have, or are at significant risk of, musculoskeletal sequelae. Oral supplementation should be undertaken for all individuals at high risk of deficiency. The outcomes of ongoing randomised controlled trials may reshape these recommendations. **ET**

References

1. Munns CF, Shaw N, Kiely M, Specker BL, Thacher TD, Ozono K, et al. Global consensus recommendations on prevention and management of nutritional rickets. J Clin Endocrinol Metab 2016; 101: 394-415.
2. Binkley N, Dawson-Hughes B, Durazo-Arvizu R, et al. Vitamin D measurement standardization: the way out of the chaos. J Steroid Biochem Mol Biol 2016; 12 Dec. pii: S0960-0760(16)30341-7. (Epub ahead of print.)
3. Nowson CA, McGrath JJ, Ebeling PR, et al. Vitamin D and health in adults in Australia and New Zealand: a position statement. Med J Aust 2012; 196: 686-687.
4. Bilinski K, Boyages S. Evidence of overtesting for vitamin D in Australia: an analysis of 4.5 years of Medicare Benefits Schedule (MBS) data. BMJ Open 2013; 3(6): e002955.
5. Glendenning P, Chew GT. Controversies and consensus regarding vitamin D deficiency in 2015: whom to test and whom to treat? Med J Aust 2015; 202: 470-471.
6. Bolland MJ, Grey A, Davidson JS, Cundy T, Reid IR. Should measurement of vitamin D and treatment of vitamin D insufficiency be routine in New Zealand? N Z Med J 2012; 125: 83-91.
7. Wimalawansa SJ. Vitamin D and cardiovascular diseases: causality. J Steroid Biochem Mol Biol 2016; Dec 24. pii: S0960-0760(16)30363-6. (Epub ahead of print.)
8. Scaranti M, Junior Gde C, Hoff AO. Vitamin D and cancer: does it really matter? Curr Opin Oncol 2016; 28: 205-209.
9. Paxton GA, Teale GR, Nowson CA, et al. Vitamin D and health in pregnancy, infants, children and adolescents in Australia and New Zealand: a position statement. Med J Aust 2013; 198: 142-143.

COMPETING INTERESTS: None.

Downloaded for personal use only. No other uses permitted without permission. © **Medicine**Today 2017.