

Megadose therapy for vitamin D deficiency

Treating the paradox of an important emerging public health problem

The international perception of bronzed Australians inhabiting a “sunburnt country” is under threat. Most Australians, including children, now sensibly avoid excessive sun exposure to reduce the risk of skin cancer. However, other Australians, particularly those who are older, disabled or institutionalised often do not receive even modest levels of sunlight exposure. This has led to the paradox of vitamin D deficiency emerging as a public health issue in sunny Australia.

Besides older and institutionalised Australians, others particularly at risk of vitamin D deficiency are people with pigmented skin from Africa, India and Pakistan; women who practise veiling; those on certain medications (eg, anti-epileptic drugs); and those with malabsorption or a low vitamin D intake. Even young Australians, pregnant women and their infants are at risk of this emerging health problem.¹ The prevalence of vitamin D deficiency among Indigenous Australians has not been determined, but is likely to be high.

The problem was highlighted recently in the Journal in a position statement on vitamin D and bone health in adults.²

Vitamin D deficiency is usually classified as mild (25-hydroxyvitamin D [25OHD] level, 25–49 nmol/L), moderate (12.5–24 nmol/L) or severe (<12.5 nmol/L). The Geelong Osteoporosis Study detected mild or moderate deficiency in more than one in three women surveyed in summer, which rose to one in two in winter.³ Even in south-east Queensland, Western Australia, New South Wales and Victoria, nearly a third of men and women have mild to moderate vitamin D deficiency.⁴ Almost half of nursing home patients, and almost all patients in aged care facilities surveyed have at least mild vitamin D deficiency.

Thus, despite Australia being a “sunburnt country”, vitamin D deficiency is common. But why is it important?

Severe vitamin D deficiency results in osteomalacia in adults and rickets in children. Milder vitamin D deficiency results in secondary hyperparathyroidism and increased bone turnover, predisposing to osteoporosis. Proximal myopathy and muscle pains may occur in moderate or severe vitamin D deficiency, and the incidence of falls is increased.⁵ Less well known is the impact of vitamin D deficiency on depression, immunity and autoimmunity, obesity, and the progression of type 2 diabetes mellitus.

It is also important to correct vitamin D deficiency to optimise the effects of other anti-osteoporotic drugs. In a recent United States study of 1536 women receiving anti-osteoporotic therapy, 52% had vitamin D deficiency.⁶ Treatment with intravenous or (more rarely) oral bisphosphonates may also cause severe hypocalcaemia in people with severe vitamin D deficiency,^{7,8} so it is prudent to screen for vitamin D deficiencies before initiating bisphosphonate therapy.

In the broad context of vitamin D deficiency as an emerging public health issue, the article by Diamond et al in this issue of the Journal (*page 10*)⁹ is timely. Their prospective open label study of 50 elderly women and men with vitamin D deficiency showed that a single intramuscular injection of 600 000 IU (or 15 mg) of cholecalciferol (vitamin D₃) increased serum 25OHD concentra-

tions to above 50 nmol/L in all patients. Over 12 months, serum 25OHD concentration rose, on average, by 128% to 73 nmol/L — a level most would consider to be optimal. Secondary hyperparathyroidism, present in about 50% of participants, was abolished in most. The complications of the therapy were mild hypercalcaemia in two participants (4%) and fasting hypercalciuria in 10 participants (20%) tested at 12 months.

The study by Diamond and colleagues represents a step forward in currently available treatment options for vitamin D deficiency. Currently, this is limited to doses of 200–1000 IU of either vitamin D₂ (ergocalciferol) or vitamin D₃ (cholecalciferol). The commonest form is 1000 IU of ergocalciferol (Ostelin; Boots Healthcare Australia). Loading doses of 3000–5000 IU per day are required to treat severe vitamin D deficiency and, as commercially available

radioimmunoassays do not always measure vitamin D₂ as well as vitamin D₃, measuring treatment response is difficult. Daily dosing is also difficult or unrealistic for many community-dwelling older people in whom compliance would be expected to be poor. A single

intramuscular “megadose” of cholecalciferol would overcome this compliance issue in a simple and cost-effective manner. The mild hypercalcaemia and fasting hypercalciuria are of concern, but further controlled trials are planned, which will include 24-hour urine calcium excretion measurements, to evaluate the safety of “megadose” cholecalciferol therapy. The effect of this treatment on fracture risk is not established. A recent British study of 9440 community-dwelling participants aged 75–100 years, randomly allocated to receive either an annual injection of 300 000 IU cholecalciferol or placebo, showed no reduction in fracture rate.¹⁰ Nevertheless, the greatest clinical utility of an annual megadose injection is likely to be in older institutionalised people, most of whom are vitamin D deficient.

The most important outcome in osteoporosis prevention or treatment is a reduction in fracture risk. Some data suggest treating vitamin D deficiency may prevent low-trauma fractures. A large French study in institutionalised, ambulatory older women found that daily doses of 800 IU of cholecalciferol and 1.2 g of calcium significantly decreased the incidence of hip and non-vertebral fractures compared with placebo after 18 months.¹¹ Daily vitamin D and calcium treatment also reduced non-vertebral fractures in community-dwelling older American men and women.¹² A recent large trial in community-dwelling British men and women aged over 65 years showed that a large oral dose of cholecalciferol (100 000 IU) every 4 months reduced osteoporotic fractures by 33%.¹³ The RECORD trial attempted to determine the relative contribution of calcium versus vitamin D on fractures. Ambulatory patients (5292) who had sustained a low-trauma fracture were randomly allocated to receive calcium (1000 mg/day), vitamin D₃ (800 IU/day), a combination of the two, or placebo. After at least 24 months, fracture rates did not differ between the four groups. However, compliance at 2 years was poor.¹⁴ Further large studies of vitamin D and its effects on fractures and falls are still needed, particularly in populations at risk of vitamin D deficiency; these

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studies need to use varying oral doses of vitamin D and to include men.

The treatment described by Diamond et al is a good start to introducing new alternatives for treatment of vitamin D deficiency in targeted people. However, much more work is needed to identify successful public health approaches that can be more broadly applied to this emerging public health problem.

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