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EDITORIAL

Vitamin D: Present and future

Vitamina D: presente y futuro



Varsavsky et al.¹ provide a useful overview of the important, but controversial, subject of vitamin D and health, currently the focus of much attention.² The critical issues which they raise include the following:

Optimal levels

The authors align with the American Endocrine Society in stating that 25(OH)D levels should be greater than 30 ng/mL (75 nmol/L) for optimal health. This is highly controversial, and is directly in conflict with the more authoritative recommendations of the Institute of Medicine which regards 40 nmol/L as being the median requirement, but recommends 50 nmol/L across the whole population.³ The only clearly established adverse effect of vitamin D deficiency in humans is osteomalacia, and this only occurs at 25(OH)D levels substantially less than 25 nmol/L. Therefore, aiming for >75 nmol/L has no evidence base from randomized trials and is unjustified. Accepting a definition of deficiency as <40 nmol/L greatly decreases the prevalence of vitamin D deficiency and the number of individuals requiring supplementation. Indeed, it is the view of the Institute of Medicine and the United States Preventative Services Task Force that the majority of healthy adults do not require vitamin D supplementation.^{4,5}

When to measure 25(OH)D

If 40 nmol/L is regarded as the threshold for intervention, then the need for measurements of serum 25(OH)D almost completely disappears. The great majority of individuals at risk of such low levels of 25(OH)D can be identified by clinical risk factors (such as frailty resulting in being permanently indoors, being veiled, or being dark-skinned and living in a temperate climate). Those who show these risk factors should be provided with supplements of vitamin D3 or vitamin D2 in doses of 400–800 IU/day, which will maintain 25(OH)D >40 nmol/L.⁶ Calcitriol should not be used for treating vitamin D deficiency since it replaces only one of

the active metabolites, and is much less efficient for treatment of osteomalacia than vitamin D itself. Its use is mainly in those with severe renal impairment.

Vitamin D effects on fracture and bone density

Recent meta-analyses indicate that vitamin D monotherapy has no influence on fracture rates,^{7,8} and our recent meta-analysis of its effects on bone density showed no benefit in the lumbar spine, total hip, total body, or forearm, and an average 0.8% increase over two years in the femoral neck.⁹ The fact that the femoral neck changes are not reflected at the total hip, suggests that this difference might have occurred by chance. In any case, the effect at the femoral neck is not large enough to be clinically significant. In contrast, there appear to be small effects of calcium plus vitamin D on total fracture number, but these are not different from those seen with calcium alone,¹⁰ suggesting that it is the calcium which is the active constituent. The Bischoff-Ferrari meta-analysis,¹¹ which the authors cite, is likely to be misleading since it effectively compares a group of subjects complying with calcium plus D supplementation with a group of subjects who were not, and we already have other evidence that placebo compliers have lower fracture rates than placebo non-compliers.¹² Thus, the only established benefit of vitamin D supplementation is the prevention of osteomalacia. This is a very uncommon problem in the non-frail, adult European population and can be prevented with small doses of vitamin D.

Effects of vitamin D on muscle strength and falls

Muscle has long been regarded as a target for vitamin D, though some recent work has suggested that the vitamin D receptor is not found in muscle, and that the myopathy of osteomalacia results from phosphate deficiency.^{13,14} These results might account for the inconsistent results of studies of vitamin D supplements for falls prevention. We have

recently reviewed this question and found no convincing evidence of efficacy, except possibly in the very frail and infirm.¹⁵ It is likely that maintaining 25(OH)D levels above the threshold of 40 nmol/L, will prevent adverse effects on muscle function.

Non-skeletal effects

There is a large literature documenting the association of vitamin D deficiency with almost all known diseases.² It is most unlikely that vitamin D plays a pathogenic role in all, or even most, of these conditions. There has been a notable failure of intervention studies to demonstrate prevention of cardiovascular disease and cancer with vitamin D, as our recent trial sequential analysis demonstrated.¹⁶ Further, this study suggested that it was likely to be futile to continue to carry out such studies, since the amount of data already available is sufficient to rule out a biologically significant effect in the populations studied to-date. A possible exception to this is mortality, where current meta-analyses suggest there may be a reduction of the order of 4–5%, though this is of borderline statistical significance. Clearly this is an important question that requires further careful investigation.

Safety

The authors suggest that the only toxicity from vitamin D supplementation is hypercalcaemia, a problem that only occurs with very high doses of vitamin D taken over a long period of time. However, as the authors point out, several recent studies have shown increases in falls and fractures from the use of high doses of vitamin D.^{17–19} These findings are of great concern and suggest that advocacy for high doses of vitamin D could result in these adverse effects. Therefore, it is not appropriate to use high-dose vitamin D supplements until both efficacy and safety are established.

Conclusion

Vitamin D is clearly a biologically active substance and it has the possibility for both beneficial and adverse effects. It should be used with care. Providing doses of 400–800 IU/day in those with clinical risk factors for deficiency (defined as 25(OH)D <40 nmol/L) is the safe and appropriate way to proceed at the present time.

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