

Should we be giving enhanced vitamin D intakes to all?

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It is widely established that vitamin D is critical for bone health. There is also an increasing body of evidence from observational studies that low levels of vitamin D are associated with a range of other disorders, including cancer and cardiovascular disease. People in temperate climates are often deficient in vitamin D, particularly in wintertime. The key question is whether there is sufficient evidence to justify supplementing vitamin D intakes for all. In this 'Controversy in Medicine', two international experts argue the case 'for' and 'against' universal vitamin D supplementation.

KEYWORDS Vitamin D, 25-hydroxyvitamin D, food supplementation, osteoporosis

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Enhanced vitamin D intakes for all? Why we should say 'yes'

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Those who do not learn from history are doomed to repeat it.¹

Rickets, one of several 'English diseases', appeared during the Industrial Revolution when people moved into towns, summer sunshine was blocked by air pollution and many people worked indoors rather than outdoors, often from early childhood.² Rickets was virtually abolished in the UK in World War II when cod liver oil supplements were offered to all pregnant and nursing mothers and children under five years of age³, and when parents 'aired' their babies outdoors. It took almost a century for the old wives tale (that cod liver oil cured rickets) to be confirmed, and the two forms of vitamin D (cholecalciferol and ergocalciferol), to be discovered.⁴ So how is it that increasing numbers of people have developed vitamin D deficiency-related rickets and osteomalacia, osteoporosis has worsened and falls and fragility fractures have become more common over recent decades? This is mainly because most of us spend less time outdoors as we work, play, socialise, travel and exercise indoors, behind glass windows that block transmission of ultraviolet light (UVB). At the same time, we are advised to avoid midday sunshine in order to reduce skin cancer risks (and skin ageing) by seeking shade, covering up and using powerful sunscreens, especially for children. For the growing proportion of the UK population who are black or Asian, increased skin pigmentation reduces skin synthesis of

vitamin D by UVB, and, the further north we live, the less available UVB there is. Thus, instead of making enough vitamin D ourselves, under tightly regulated feedback systems avoiding toxicity in normal people⁵, we are dependent on dietary or supplemental vitamin D, as a 'vitamin', to avoid overt manifestations of vitamin D deficiency both in the UK and globally as the problem of deficiency becomes increasingly common in both sunny and temperate climates.⁶

Those reading this debate in Scotland are even more likely to be vitamin D insufficient than readers in southern parts of the UK.⁷ The problem gets worse with age as skin synthesis and gut absorption of vitamin D become less efficient.^{8,9} This situation is also exacerbated in those with reduced mobility, loss of independence, and especially in those in residential care.¹⁰ There is a large body of evidence associating hypovitaminosis D with increased risks for many diseases, in virtually all systems of the body and not just in the musculoskeletal system. Serum 25-hydroxyvitamin D (25[OH]D) is generally accepted as a measure of vitamin D repletion (status). The significance of this measurement in the investigation of disease relates to the fact that 25(OH)D is activated locally in target tissues, free of feed-back regulation. This local activation is directly dependent on serum 25(OH)D concentration, explaining the physiological significance of serum 25(OH)D concentration for human health.¹¹⁻¹³

These data cover associations and mechanisms for cardiovascular disease, innate and acquired immunity, infections, autoimmune disease (especially multiple sclerosis), inflammatory disorders and psoriasis. Higher vitamin D status is associated with reduced risks, cross-sectionally and often prospectively, for these disorders, including melanoma, the most aggressive skin cancer and itself triggered by sunburn.¹⁴⁻²¹ However, randomised controlled trial (RCT) data indicating adequate supplementation with vitamin D for non-bony conditions is still insufficient to prove causality. For bone mineral density, muscle strength, falls and fragility fractures, intakes of at least 800 IU/day of vitamin D reduces risk, though massive doses may increase these risks temporarily.²²⁻²⁶ Thus, our evidence base supports the need to return to the situation achieved during World War II, when the reduction in vitamin D deficiency lowered the risks of rickets and osteomalacia; it does not however support the use of supplemental intakes (above 800 to 1000 IU/day) in the long-term in healthy people for reducing non-bony health risks. Indeed, history teaches us that other potential 'magic bullets' thought to reduce several major health risks can prove ineffective and may even increase those risks (e.g. RCTs using beta-carotene with vitamin A for prevention of lung cancer and heart disease).²⁷ The problems with the use of beta-carotene probably resulted from confounding by other dietary factors; similar confounding by unidentified factors affecting vitamin D status cannot as yet be excluded.

These considerations contributed to the recent Institute of Medicine (IOM) recommendations from the US that dietary intakes in the population as a whole should reach 400 IU/day in infants and children, 600 IU/day in adults and pregnant and nursing mothers, and 800 IU/day in older people (and by implication, others at increased risk of D deficiency, e.g. dark skinned, vegetarians and vegans²⁸). Vitamin D deficiency is increasingly common worldwide and is known to increase infant mortality (from acute heart failure or hypocalcaemic fits),³ and is also associated with increased adult mortality.²⁹ Disagreement on defining 'deficiency' based on serum 25(OH)D assays is common. Genetic variation in the vitamin D axis has a small independent effect on serum 25(OH)D concentration, but the literature demonstrates a reasonable consensus that values of <50 nmol/l by any assay reflect a deficiency severe enough to lead to clinically obvious bone problems.^{30,12} Thus, in countries where this value is not reached by the majority of residents across all seasons of the year, the population should benefit, in bone health at least, from increasing vitamin D intakes to achieve 25(OH)D values of at least 50 nmol/l. In the young, 25(OH)D concentrations above 50 nmol/l increase bone density 'dose-wise', reducing bone risks in later life.³² Thus, 50 nmol/l is a serum 25(OH)D target level likely to be raised as new evidence

accrues. In Scotland, a recent report on post-menopausal women showed that they never reach a mean 25(OH)D concentration of 50 nmol/l at any season of the year.³³ In winter, 40% of post-menopausal women in Surrey were deficient (10% of Caucasian and 65% of Asian women). In summer, 16% were deficient (0% of White and >50% of Asian women). Higher values, e.g. 75–110 nmol/l, are associated with health benefits in observational studies. At higher, but non-toxic, concentrations, however, there are suggestions of possible adverse effects that need further investigation.^{34,35} Better maternal vitamin D status improves bone health in children aged 9 years old,³⁶ and other possible transgenerational effects require study.

Vitamin D deficiency (25(OH)D <25 nmol/l) is found at all ages in the UK in 5–15% of Caucasian people. It rises to >20% in those aged between 19–24 years, increasing again after the age 60 and reaching >40% in people in their 80s. A lesser degree of deficiency (25(OH)D <50nmol/l) is never found in less than 20% of the Caucasian population at any age and is found in >40% of people over the age of 11 years old; in >60% of those aged between 19–24 years, and increases in over 65-year-olds, peaking at >80% among those living in an institutional setting.³⁷ This nationwide problem requires urgent attention. Preventative public health measures would be more cost-effective than medical management: provision of 400–800 IU/day using Healthy Start supplements costs less than £4/year (2010 prices) but one 25(OH)D assay costs £10.50–£25.³ The costs of modest food fortification would, as for other foods, be passed on to consumers. In Finland, voluntary food fortification with vitamin D has reduced the prevalence of vitamin D deficiency (25(OH)D <50 nmol/l) significantly in most population groups.^{38,39} This approach, already widely used in the USA and enforced by statute in the UK since 1942 (but only for margarine [at 280–350 IU/100G⁴⁰]), requires care to avoid excessive intakes in infants.³ Ultraviolet B (UVB) irradiation of certain vegetables, notably mushrooms and yeast, increases vitamin D content and is used in some countries,³ and may prove more useful than trying to ensure controlled UVB irradiation of the skin. Surveys of representative population groups and checks on food content would be needed to audit the adequacy of provision and its safety at the population level. Such audits and safety checks would be expected to lead to adjustment of fortification levels where necessary.

The many studies of vitamin D status in the UK over recent years have clearly not been acted upon, and this must change.⁴¹ Even modest risk reductions in musculoskeletal vitamin D deficiency disorders, acute neonatal heart failure, rickets, the severity and costs of osteoporosis and its painful complications, and in fragility fractures (in the 25,000 overt vertebral fractures and the 70,000 annual hip fractures in England and Wales which have a falling in-patient mortality but a continuing

mortality of 20% after six months and 30% by one year, with a 50% loss of independence⁴²⁻⁴⁵) would, clearly, be welcome to sufferers and their families and would also reduce NHS costs. At present, the NHS has no recommendations for vitamin D intake levels for those aged between 19 and 64 years old.^{3,37} Compliance with oral supplementation is well known to be poor (reducing to 50% after six months in those being treated for osteoporosis). In the UK supplements on prescription usually contain either calcium (which can cause constipation, reducing compliance and, in supplements, may increase cardiovascular risks⁴⁷) or vitamin A which antagonises vitamin D.^{3,48} It would be helpful, therefore, if the British National Formulary (BNF) included preparations of vitamin D alone, at a range of doses, to facilitate treatment of people presenting clinically with deficiency related disorders. While many pregnant and

nursing women might take supplements, as they do folic acid, others might not use them regularly, even if they could afford them, or even if they were free of charge for all.

Thus, food fortification, adjusted to achieve serum 25(OH)D concentrations across the healthy adult population of at least 50 nmol/l (but ideally <150 nmol/l) would provide a safe, acceptable and cost-effective way of reducing health risks from musculoskeletal disorders known to benefit from improved vitamin D intakes, with reduced fracture risks confirmed in corrected meta-analysis of data for 68,500 patients in seven trials.⁴⁹ This could be introduced while we await the outcomes of large scale RCTs currently in progress on the efficacy and safety of higher doses,⁵⁰⁻⁵¹ before we can judge what is 'not too little and not too much but just right'.⁵²

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Enhanced vitamin D intakes for all? Why we should say ‘no’

MD Witham

It would be easy to assume, given the excited media coverage that vitamin D generates, that the case for universal supplementation was already proven. Vocal lobbying is however no substitute for scientific evidence, and for vitamin D, we do not have the understanding of its biological effects or the required evidence for the efficacy or safety of universal supplementation.

There are several major disease targets that vitamin D supplementation might potentially ameliorate – bone health, cancer, cardiovascular disease, autoimmune disease (including multiple sclerosis and type 1 diabetes) and metabolic disease including type 2 diabetes. What evidence do we have that supplementation at the population level would improve outcomes in these conditions?

Evidence for bone health is probably the strongest. Observational studies suggest that supplementation with low doses of vitamin D reduces the risk of rickets,¹ and in selected older people (particularly those in institutional care), calcium and vitamin D supplements reduce the risk of falls and osteoporotic fracture.² However, these benefits do not appear to extend to community-dwelling older people, even if they have had a previous fracture³, and the Women's Health Initiative (WHI) trial⁴ did not show a significant reduction in hip fracture when supplementing a large, population-based cohort with low-dose vitamin D and calcium.

Although prospective observational data links low 25-hydroxyvitamin D (25[OH]D) levels with an increased risk of cardiovascular events, supplementation trials

devised to specifically reduce the risk of cardiovascular events have not been performed. Meta-analysis of existing osteoporosis trials (which are clearly not representative of the general population) show no reduction in myocardial infarction or stroke,⁵ and the effect of supplementation on cardiovascular risk factors has been variable; some but not all studies show improvement in endothelial function (a powerful marker of cardiovascular risk),⁶⁻⁸ but there appears to be little effect on lipid levels, and blood pressure is modestly reduced only in those with elevated blood pressure at baseline.⁹

Data on cancer outcomes in supplementation trials is even scantier. The WHI trial showed no reduction in colorectal cancer,¹⁰ and the one trial frequently quoted to show an effect of vitamin D on cancer rates (again as a secondary analysis of an osteoporosis trial) actually showed a reduction in new cancers with calcium supplements, but no additional reduction when vitamin D was combined with calcium.¹¹ Observational data are not easy to interpret; although there appears to be a lower cancer incidence with increasing 25(OH)D levels in most studies, a few studies show the opposite, albeit with better cancer *survival* with higher vitamin D levels.

Both type 1 and type 2 diabetes mellitus have been linked with lower 25(OH)D levels, but evidence that vitamin D supplementation can prevent the occurrence of type 1 diabetes is lacking, and the available evidence from randomised controlled trials does not suggest any effect on rates of type 2 diabetes to date.¹² Even in patients with pre-existing diabetes or impaired fasting glucose, vitamin D supplements appear to produce only a small improvement in insulin resistance and fasting glucose – and no improvement in long-term glycaemic control. Once again, robust data from large, long-term trials are lacking.

The evidence base for other health conditions, for example multiple sclerosis, is even flimsier, with no intervention studies to guide practice. Several trials across a variety of populations at risk from a number of infections have now been performed to assess whether vitamin D supplementation can reduce infection rates, especially rates of respiratory tract infection and tuberculosis; results have been mixed at best, as confirmed by a recent systematic review.¹³

No large randomised controlled trials have been conducted to examine the effect of vitamin D supplementation on overall mortality in a general population; meta-analysis of existing trials (mostly for osteoporosis and fracture prevention) suggest either a small effect on mortality (absolute risk reduction of 0.5%)¹⁴ or no effect.⁵ It cannot be assumed that any benefit in a group at such high risk of death as those with osteoporosis will apply to a general population.

What about potential harms? These are of particular importance in any population-level intervention, as large numbers of healthy people (i.e. with little scope for accruing benefits) will receive exposure to the potential harm. It is unlikely that universal supplementation will cause overt toxicity; the doses required for this appear to be very large indeed.¹⁵ However, the WHI trial⁴ showed a 16% higher risk of renal and ureteric stones in the treatment group (who received only 400U of vitamin D3). Observational data point to higher immunoglobulin E (IgE) levels in people with 25(OH)D levels above 135 nmol/l,¹⁶ higher rates of atopic disorders in the offspring of women with 25(OH)D levels >75 nmol/l during pregnancy¹⁷ and two observational studies suggest a slightly higher risk of cardiovascular events in those with the highest 25(OH)D levels,^{18,19} compared with people with moderate 25(OH)D levels. Finally, there is the concern that patients with primary hyperparathyroidism (often undiagnosed until a routine serum calcium level is checked) could suffer from elevated, and therefore potentially symptomatic, hypercalcaemia. Are these potential risks borne out in practice? Do they outweigh potential benefits at a population level? The truth is, we simply don't know, and until we conduct the appropriate large-scale intervention trials, we will not know.

In conclusion, the benefits of universal supplementation are unproved, the risks are unknown, and we require further evidence before committing to such a public health intervention. Observational and *in vitro* studies are a poor guide here; let us not forget how vitamins C, E and beta-carotene moved from early promise to useless (and indeed potentially harmful) interventions;²⁰ witness the failure of B group vitamins to improve vascular outcomes, and compare the current controversy surrounding folate supplementation and cancer risk. What is good for one group may also not be good for all; we need to evaluate and tailor the balance of benefit and risk for each group of people that we care for. To supplement the entire population with vitamin D in the absence of good data that the benefits outweigh the risks for each individual would be poor medicine and an abrogation of our duty of care to individuals.

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