Editorials

Vitamin D:

too much of a good thing?

THE STORY SO FAR

Vitamin D is increasingly recognised as an important sterol hormone, with some suggesting that it should be renamed 'hormone D'.[1] Vitamin D receptors are widely expressed throughout the body accounting for its regulatory role beyond the confines of the skeleton, including the immune system, pancreas, brain, and cardiovascular system.[2] Consequently, vitamin D deficiency is implicated in diseases such as diabetes, multiple sclerosis, cardiovascular disease, and increased mortality.[2] Research interest in vitamin D has grown by more than 250% in a decade and publications in 2012 almost equalled the research output for vitamins A, B, C, and E combined.

Vitamin D deficiency is highly prevalent among the UK population; 35% of otherwise healthy Scottish adults are severely deficient and a further 29% are at high risk of deficiency,[3] with northerly latitude, poor summers, reduced sun exposure, increasing use of sun protection, and an ageing population being contributory. The benefits of treating deficiency are revealed in meta-analyses showing reduced risk of fractures and falls in older people,[4] as well as reduced cardiovascular and overall mortality.[5] The joint letter from the Chief Medical Officers (CMOs) to UK health professionals[6] supports the importance of vitamin D sufficiency as a public health priority by advocating treatment for young, pregnant, and older adults. As a consequence there has been an unprecedented increase in vitamin D prescribing.

Since 2008, vitamin D monotherapy in primary care in England has increased exponentially in terms of both quantity and cost: 124 000 prescriptions for vitamin D are issued each month at a net ingredient cost of £2.18 million, with colecalciferol accounting for 97% and 89% of prescriptions in terms of quantity prescribed and cost respectively.

CONTROVERSY SURROUNDING VITAMIN D PRESCRIPTION

Some argue that there is no evidence to support treatment of vitamin D deficiency[7] particularly as symptoms may be subtle. However, subtle symptoms are typical of many hormonal disorders including hypothyroidism, yet the importance of hormonal replacement is unquestioned. The growing evidence for the skeletal benefits of supplementation is supported by our understanding of the pathological effects of deficiency, which contributes to reduced bone mineralisation, fragility, and fractures.[8] Such morbidity is particularly problematic in childhood, pregnancy, and in older people.

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Data on the efficacy of vitamin D supplementation offer mixed messages and a certain degree of 'fatigue'; there are more published meta-analyses of trials of vitamin D and fracture risk (>20) than there are individual trials. The negative results of recent meta-analyses of vitamin D and fracture risk seem to be supported by a similar lack of improvement in bone mineralisation, leading some to conclude that widespread use of vitamin D for fracture prevention in adults without specific risk factors for deficiency is inappropriate. Interpretation of these data requires an appreciation of their detail. The statistical power of aggregate data (AD) meta-analysis (the most common method) is much lower than that of equivalent meta-analysis of pooled individual patient data (IPD). Only when large numbers of large trials are available, can AD meta-analysis detect differential treatment effects between risk groups with any consistency. When interest lies in investigating whether patient characteristics are related to treatment effect, IPD meta-analysis will generally be necessary. In their IPD meta-analysis of 11 double-blind, randomised, controlled trials, Bischoff-Ferrari *et al*[4] demonstrated that high-dose vitamin D supplementation (≥800 IU daily) reduced both the risk of hip fracture by 30% and the risk of any non-vertebral fracture by 14% in adults aged ≥65 years. These benefits were consistent across subgroups defined by age group, type of dwelling, baseline 25-hydroxyvitamin D level, and additional calcium intake. Analyses that include trials that administered daily vitamin D doses ≤800 IU, or those that recruited younger subjects are unlikely to demonstrate a positive effect. Low fracture rates in younger adult populations would make powering such intervention studies adequately very difficult. Data on bone mineral density (BMD) are particularly difficult to interpret given that changes in bone mineralisation take years to develop following intervention when studied with dual-energy X-ray absorptiometry. Thus studies assessing BMD over too short a timeframe could be confounding.

Other data suggest that vitamin D positively impacts on aetiologies contributory to fracture risk such as falling. The joint guidelines from the American and British Geriatrics Societies now recommend vitamin D therapy at doses of at least 800 IU daily in older adults at risk of vitamin D deficiency, for the prevention of falls;[9] a view endorsed by the US Preventative Task Force (USPTF), which concluded that the number needed to treat (NNT) to prevent one fall is 10, in comparison with a NNT of 16 for physical therapy.[10] Such conclusions are consistent with the association between vitamin D deficiencies as manifest by osteomalacia where symptoms including proximal myopathy improve with supplementation.

"Another problem facing the adequate replacement of vitamin D is the issue of quality of available vitamin D preparations."

Table 1. Comparison of current monthly prescribing (March 2013) for 'low dose' oral solid-dosage forms of colecalciferol in primary care England

IUs/unit	Scripts/ month	NIC/ month, £	NIC/ script, £	IUs/month	NIC/IU, pence	Minimum equivalent NIC/month, £	Monthly saving, £
400	5240	105 386	20.11	129 774 000	0.081	19 465	85 920
600	105	7434	70.80	4 352 400	0.171	653	6781
800	32 534	212 640	6.54	1 417 647 200	0.015	–	–
1000	28 118	526 956	18.74	1 747 390 000	0.030	262 100	264 857
Total							**357 558**

NIC = net ingredient cost.

Another problem facing adequate replacement of vitamin D is the issue of quality of available vitamin D preparations. There are consistent inaccuracies in stated dosing among over-the-counter (OTC) supplements, not only between batches but also between pills from the same pack.[11] The Medicines and Healthcare Products Regulatory Agency stipulates that unlicensed products should not be used in the presence of equivalent licensed preparations. With guidelines suggesting that repeat measurement of serum 25-hydroxy-colecalciferol (25OHD) is unwarranted following specific dosing regimens,[12] it is important to ensure the accuracy of doses used, in order to avoid unnecessary investigation and repetitive testing.

Despite the availability of licensed colecalciferol products in the UK, prescription cost analysis shows that they account for only one-quarter of all prescriptions dispensed in primary care, the rationale for which is unclear. The same data reveal that the average prescription cost of unlicensed preparations is more than three times greater than for licensed products (£19.90 versus £6.53 respectively). Licensed forms account for only 11% of the total cost of colecalciferol prescribing. Unit dose among the solid oral dosage preparations varies widely from 400 IU to 50 000 IU, representing alternative therapeutic intentions of maintenance therapy and treatment of deficiency.[12] However, there is considerable variation in the cost of comparable dosage forms. For lower-dose preparations of 1000 IU per unit dose and under, the cost per IU varies from 0.015 pence to 0.171 pence (Table 1). Such discrepancies are not explained by the quantity prescribed. If the NHS were to purchase all low-dose preparations at a uniform cost per IU, the NHS in England would save approximately £375 000 per month at current prescribing levels.

As research evidence for the deleterious effects of vitamin D deficiency grows, the case for medical intervention warrants scrutiny. When appropriate, prescribed therapy should be favoured over OTC preparations, not just on the grounds of assuring quality but also as a means of improving patient compliance with treatment. Given the growth in vitamin D prescribing, the NHS budget impact must be more carefully managed by purchasing authorities and prescribers alike. Such widespread prescription should be met at the lowest reasonable cost with the highest guarantee of quality. Licensed preparations meet both criteria and therefore should be the first choice for the maintenance treatment of vitamin D deficiency.

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