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ESTABLISHING BENEFIT FROM VITAMIN D SUPPLEMENTATION – ADHERENCE TO DEFINED CRITERIA AND TARGETING OF HIGH-RISK GROUPS ESSENTIAL?

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Abstract: *Background:* Vitamin D is the one of the most common nutritional deficiencies worldwide, and insufficiency or deficiency can be associated with musculoskeletal and non-skeletal conditions such as cancer, cardiovascular disease and diabetes mellitus. *Objective:* Recent data suggests that Vitamin D is relatively safe and toxicity is rarer than previously indicated. However, international guidelines regarding dosage and target plasma levels are conflicting. Moreover multiple well-designed studies of healthy older adults, unselected in terms of Vitamin D status, have revealed largely negative results (with the possible exception of older patients in care homes/hospitals) in terms of improvement in musculoskeletal and non-skeletal conditions to date. *Conclusion:* On that basis, it is suggested that future trials regarding Vitamin D supplementation should be carried out in high-risk groups. The use of published criteria for evaluating the effect of nutrients and targeting of individuals with Vitamin D insufficiency and deficiency for inclusion in such studies is also proposed. The identification of specific subgroups that will benefit from supplementation and replacement, and the establishment of a scientific basis for such therapy, should be possible with this approach.

Key words: Vitamin D, interventional studies, supplementation, benefit, harm.

Introduction

Vitamin D deficiency is the commonest nutritional deficiency globally, however optimal dosage regimens remain uncertain (1). It is estimated that approximately one billion people worldwide have vitamin D deficiency, and vitamin D insufficiency affects nearly 50% (2).

The lack of consensus regarding supplementation has been previously highlighted (3). International guidelines are conflicting; the Institute of Medicine (IOM) recommends a a serum vitamin D (25(OH)D) of 50 nmol/L and defines a 25(OH)D concentration less than 30 nmol/L as deficiency (4), whereas the Endocrine Society recommends a target 25(OH)D of 75 nmol/L and defines deficiency as a 25(OH) D less than 50nmol/L (5). The Scientific Advisory Committee on Nutrition (SACN) also published an independent report in 2016 with recommendations regarding vitamin D and 25nmol/L defined as the "population protection level" (6). Table 1 summarises current guidelines on target levels.

Some authorities have suggested widespread supplementation with daily doses of 2,000 to 4,000 IU of vitamin D and toxicity is probably rare (7). An association of Vitamin D insufficiency with musculoskeletal and non-skeletal conditions such as cancer, cardiovascular disease, and inflammatory bowel disease is widely recognised. Many non-randomised cohort studies have produced misleading and contradictory results, and it is not proposed to dwell on that data in this review. Recent studies from Bolland (8) and Pittas (9) highlight negative results with regard to improving musculoskeletal health and preventing type 2 diabetes mellitus respectively.

This article highlights a review of intervention studies and proposes a more targeted approach to prospective vitamin D intervention research in the future.

Outcomes of Intervention Studies

Almost all major studies of vitamin D therapy have recruited patients unselected for baseline vitamin status. In 2018, Bolland et al. carried out a systematic review and meta-analysis regarding the effects of vitamin D supplementation on musculoskeletal health (8). Eighty-one randomised controlled trials were identified which reported on falls, fractures or bone mineral density. In pooled analyses, vitamin D had no effect on total fracture (36 trials; n=44 790, relative risk 1•00, 95% CI 0•93–1•07), hip fracture (20 trials; n=36 655, 1•11, 0•97–1•26), or falls (37 trials; n=34 144, 0•97, 0•93–1•02). These results were similar in trials comparing high versus low-dose vitamin D, and in subgroup analyses of trials including daily doses exceeding 800IU.

Based on a known association between low serum 25(OH) D levels and the risk of type 2 diabetes, whether vitamin D supplementation lowers the risk of developing diabetes was investigated by Pittas et al (9). Adults with pre-diabetes were randomly assigned to receive either 4000IU per day of vitamin D3 or placebo regardless of baseline serum 25(OH)D levels. The primary outcome was time-to-event analysis of new-onset diabetes. At follow-up at 2.5 years, new-onset diabetes had occurred in 293 participants in the vitamin D group and 323 in the placebo group. It was concluded that in high risk

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Table 1
Current Guidelines

Organisation	Guidelines Process	Scientific Basis of Recommendations	Target Recommendations			
Institute of Medicine (IOM) (4)	14 scientists 8 in-person meetings Open public workshop Two open sessions with scientists Public website for stakeholder input	Two systematic reviews conducted by Agency for Healthcare Research and Quality (AHRQ) Literature review	**Age**	**RDA[a]**	**Serum Vitamin D target (nmol/L)**	**UL[b] (IU)**
			51–70 (M)	600 IU	50	4000
			51–70 (F)	600I U	50	4000
			>70 (M+F)	800 IU	50	4000
Endocrine Society (ENDO) (5)	Chair, additional 6 experts and methodologist Conference calls and emails	Two systematic reviews of literature	**Age**	**Daily requirement**	**Serum Vitamin D target (nmol/L)**	**UL[b] (IU**
			51–70 (M)	1,500-2,000 IU	75	10,000 IU
			51–70 (F)	1,500-2,000 IU	75	10,000 IU
			>70 (M+F)	1,500-2,000 IU	75	10,000 IU
Scientific Advisory Committee on Nutrition (SACN) (6)	Vitamin D Working Group established – Chair and 9 additional experts Met 15 times	Committee on Medical Aspects of Food and Nutrition Policy (COMA) 1991 IOM report 2011 AHRQ update 2014 National Diet and Nutrition Survey, Health Survey for England, Low Income Diet and Nutrition Survey, UK Diet and Nutrition Survey of Infants and Young Children and Scottish Health Survey	**Age**	**RNIc**	**Serum Vitamin D target (nmol/L)**	**UL[b] (IU**
			51–70 (M)	10ug (400 IU)	25	N/A
			51–70 (F)	10ug (400 IU)	25	N/A
			>70 (M+F)	10ug (400 IU)	25	N/A

a. Recommended Dietary Allowances; b. UL indicates level above which there is risk of adverse events. The UL is not intended as a target intake (no consistent evidence of greater benefit at intake levels above the RDA); c. Recommended Nutrient Intake

individuals for new-onset type 2 diabetes mellitus, vitamin D supplementation did not significantly reduce the risk of diabetes compared with placebo.

In 2014 the Women's Health Initiative (WHI) carried out a clinical trial in which over 36,000 healthy postmenopausal women >50 years (regardless of vitamin D status) were randomised to receive calcium carbonate and vitamin D (500 mg and 400 IU). Secondary analysis of this cohort was performed to address the association between vitamin D and lipid levels using a subset of 600 participants (10). In the multivariate regression model, women randomised to calcium/vitamin D had a reduction in LDL cholesterol compared to placebo, but not when Vitamin D levels were included in the analysis. Meanwhile, a small significant improvement in bone density with a trend to reduced fractures was noted in the calcium/vitamin D group in the same study (11).

Sollid et al. also analysed the effect of high-dose vitamin D supplementation on cardiovascular risk factors (and glycaemic status) in people with pre-diabetes using 20,000IU per week or placebo (12). There was a slight, but significant decrease in total and LDL cholesterol in the vitamin D group compared with the placebo group. However there was also a decrease in HDL cholesterol, and the ratio (Total Cholesterol: HDL) did not vary significantly.

The CAPS Trial (Clinical Trial of Vitamin D3 to Reduce Cancer Risk in Postmenopausal Women) randomised over two thousand healthy women >55years (regardless of Vitamin D status) to either placebo or 2000IU vitamin D/1500mg calcium daily over a four year period (13). There was no significant reduction in cancer incidence with vitamin D therapy. The VITAL (VITamin D and omegA-3 triaL) Research Group conducted a similar randomised placebo-controlled trial in men>50 years and women>55 years(again regardless of Vitamin D status)using 2000 IU vitamin D3 and 1g omega-3 fatty acids for the prevention of any cancer (and cardiovascular disease) (14). Again no reduction in cancer or cardiovascular events accrued to the supplementation group.

There are two large population-based ongoing trials at present; the FIND trial and the D-Health trial. Again, these are both unselected for vitamin D status. The FIND trial planned to study vitamin D supplementation in approximately 18,000 of the Finnish population in order to examine the relationships between vitamin D and the primary prevention of cancer and cardiovascular disease (15). Interestingly, due to recruitment and funding difficulties, the original target of 18000 participants has been revised to 2500. The D-Health trial has recruited over 21,000 participants aged between 65-84 years in Australia to receive monthly oral doses of 60,000 IU of cholecalciferol or matching placebo (16). The primary outcome is all-cause mortality. Secondary outcomes are total cancer incidence and colorectal cancer incidence.

Table 2
Adverse Events from Vitamin D Supplementation

Study	Adverse Event	Potential Mechanism of Harm	Study Population	Dosage (IU)
Dawson-Hughes et al. (22)	Higher percentage of falls observed in those receiving 60,000 IU and 24,000 IU of vitamin D/ calcifediol respectively	Possible detrimental effect of a high monthly bolus dose of vitamin D on muscle function and falls but needs further investigation	Home-dwelling men and women 70 years and older with a low-trauma fall in the previous 12 months	24,000 vitamin D3 vs. 60,000 of vitamin D3 vs. 24,000 of vitamin D3 plus 12000 (300 μg) of calcifediol
Sanders et al. (21)	Participants receiving annual high-dose oral cholecalciferol experienced 15% more falls and 26% more fractures than the placebo group	Up-regulation of Cyp24 (with catabolism of 1,25 dihydroxy-vitamin D) resulting in reduced vitamin D activity at organ receptor sites (bone muscle) with large single bolus.	Women 70 years or older residing in southern Victoria, Australia (at higher risk of hip fracture, defined by criteria such as maternal hip fracture, past fracture, or self-reported faller)	Single oral dose of cholecalciferol (vitamin D3) 500 000 or matched placebo
Smith et al. (20)	Increased hip/femur (HR1.49) fractures with bolus treatment v control group	Increased falls following improved mobility/analgesia with normalisation of Vitamin D	Men and women >75 years from General Practice registers	300,000 ergocalciferol (Vitamin D2) annually over 3 years
Malihi et al. (19)	Borderline increased risk for hypercalcemia (RR=1.93;-CI:1.00,3,73;p=0.05)from long-term high-dose vitamin D supplementation	25(OH)D3 or 25(OH)D2 present in increased amounts bind to vitamin D receptor to enhance intestinal calcium absorption and bone mobilization	Meta-analysis – 15 studies	One study gave vitamin D2 (8966 IU/d) for one year, whereas all other studies gave vitamin D3 (mean daily dose 9990 IU/d; range: 2,857-100,000 IU/d)

Toxicity and Adverse Effects of Vitamin D/Calcium

Higher serum vitamin D targets (>75nmol/l) are thought to be associated with reduced falls/fractures, albeit based on somewhat controversial meta-analyses. The lower target of 50nmol/l relates to biochemical data of normalised calcium and parathyroid hormone levels at that level. The concern is raised regarding the possible toxicity of vitamin D and whether caution be exercised when supplementing or replacing it. Recent evidence suggests that concerns regarding adverse effects and toxicity may have been exaggerated.

According to Tebben et al. the definitive prevalence of vitamin D-related hypercalcaemia is unknown (17). The occurrence of vitamin D toxicity and hypercalcaemia was explored in a 16-year retrospective study of all vitamin D samples analysed in a large US teaching hospital. Lee et al. deduced that this was quite rare, with just 4 patients demonstrating clinical evidence of toxicity, one of whom was normocalcaemic (18). Table 2 highlights potential adverse events from vitamin D supplementation. Clearly large bolus therapy is not recommended due to paradoxical increases in falls and fracture rates (19-22). Prolonged excessive daily dosing (2800-100,000 IU/day) with borderline increased risk of hypercalcaemia, as demonstrated by Malihi et al (19), is not advised.

Several studies have indicated potential risk for atherosclerosis and myocardial infarction since Bolland published his meta-analysis indicating significant risk of myocardial infarction with calcium supplementation without vitamin D in 2010 (23). Some of the original cohort studies, including the seminal study of Chapuy in 1992, utilised Vitamin D and high dose calcium supplementation (24). In fact, that particular study reported a significant reduction in fractures in those prescribed that combination. However those patients were noted subsequently to have very low serum calcium, poor calcium intake and low baseline Vitamin D levels, probably not replicated in more independent community dwelling people. Meanwhile the aforementioned WHI study assessed the risk of vascular disease following calcium and vitamin D supplementation and found no increased risk (25). Many reviews showing no correlation or equivocal effects of calcium prescriptions and vascular disease had significant methodological issues (26). Therefore, in order to minimise the risk of promoting atherosclerosis and ischaemic heart disease, supplementary calcium should only be prescribed to those with low dietary calcium intake, which can be assessed with standardised questionnaires.

Suggested approach to prospective vitamin D intervention research

Approach to nutritional research

Suggested criteria for evaluation of nutrient effects have already been published (27). Heaney proposed that basal nutrient status should be measured, used as an inclusion criterion for entry into a study, and recorded in the report of the trial. Then the intervention (i.e., change in nutrient exposure or intake) should be large enough to change nutrient status and the increment quantified by suitable analyses. The hypothesis to be tested should be that a change in nutrient status (not just a change in diet) produces the sought-after effect. Finally co-nutrient status should be optimised in order to ensure that the test nutrient is the only nutrition-related limiting factor in the response.

Vitamin D studies

Translating this framework to studies of the effects of Vitamin D supplementation, baseline plasma Vitamin D

levels should be measured and a sufficient dose to influence plasma levels should be given with confirmation of same by repeat plasma levels. Other deficient dietary factors (e.g. iron deficiency, which may contribute to weakness, falls, etc.) need to be optimised to avoid confounding changes in dietary factors. Ensuring adherence to study regimes and avoiding non-prescribed Vitamin D supplementation by participants is also essential.

Post-hoc analysis of some of the major intervention trials suggests that adoption of this approach a priori may have resulted in uncovering positive beneficial outcomes for participants. For example, when the subgroups which were definitely adherent to Vitamin D supplementation/placebo were analysed in the aforementioned WHI study, the risk of hip fractures was reduced by 29% (HR 0.71, 95% CI 0.52-0.97) (28). A further confounder of the WHI study was the high intake of nutritional supplements containing Vitamin D in both treatment and placebo groups of the largely middle class population studied, thus rendering identification of benefit less likely.

Vitamin D status

Inclusion of participants regardless of vitamin D status similarly compounds the evaluation of benefit from supplementation. Thus targeting of people with Vitamin D deficiency/insufficiency for prospective trials will enhance the ability to identify benefit of replacement therapy. In this regard, it is notable that the subgroup of patients studied by Pittas with Type 2 Diabetes who had documented baseline vitamin D deficiency actually had significantly reduced progression to development of diabetes (9). Moreover such individuals from high risk groups will be more likely to demonstrate benefit than broad-brush community studies of all older subjects which disregard baseline status.

Frail older people

A good example relates to frail, older adults living in institutions. A Cochrane review in 2014 inferred high quality evidence to support vitamin D and calcium as being associated with a statistically significant reduction in the incidence of new non-vertebral fractures (29). A further Cochrane review in 2018 examined interventions to prevent falls in older people in hospitals and care facilities (30). This review demonstrated moderate quality evidence (4512 participants, 4 studies) that vitamin D supplementation probably reduces the rate of falls, but likely makes little difference to the risk of falls. The population included in the analysed studies all had low vitamin D levels. On that basis, Dyer suggested that the recent conclusions by Bolland et al. (8) regarding the lack of benefit of vitamin D supplementation should not be applied to older adults in care facilities. It was further suggested that trials should target interventions to specific older populations, particularly those in long-term care (31). Higher risk individuals for insufficiency/deficiency include those with poor nutrition, inadequate housing, restricted access to outdoors, and/or chronic disease.

Other conditions

Finally, despite extensive investigation, demonstration of clear-cut benefit from vitamin D supplementation in undifferentiated groups of patients with conditions such as inflammatory bowel disease (IBD) and multiple sclerosis (MS) have likewise proved elusive despite well described associations of these conditions with vitamin D deficiency (32, 33). These review articles highlight promising studies with limited power demonstrating potential benefit regarding disease severity and response to anti-TNFs in IBD. Meanwhile possible reduction in soft outcomes like MRI plaque evolution (but not development or progression of disease) has been suggested, but not definitively established in relation to MS. Adherence to the above guidelines for further studies in at-risk individuals may help identify robust evidence of benefit in these conditions also.

Conclusion

In conclusion, future trials regarding vitamin D supplementation should be carried out using defined criteria in high-risk groups particularly with low baseline serum vitamin D levels to fully evaluate its clinical benefit in terms of major health outcomes such as fractures, falls, cancer, diabetes mellitus, cardiovascular risks, etc. Adherence to published guidelines for evaluating the effects of nutrients, including the targeting of those with Vitamin D insufficiency/deficiency for inclusion in studies is also advisable. The need for such an approach is emphasised by the largely negative publications involving studies of the general adult population to date.

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Ethical standards: Not applicable to this type of study.

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