Vitamin D and Health: What are the clinical trials telling us?

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Abstract. An increasing body of evidence from clinical trials supports the presence of thresholds in vitamin D status below which vitamin supplementation has beneficial effects. Beneficial effects from vitamin D supplementation maximal in, or confined to, people with low vitamin D status have been reported for: risk of falls, acute respiratory infections, exacerbations of asthma and chronic obstructive pulmonary disease, and hospital mortality; and also for improved mean bone mineral density, arterial function and lung function. If the presence of vitamin D thresholds for beneficial effects is confirmed by future studies, this would strengthen the need for vitamin D fortification of foods.

Introduction

Randomized controlled trials (RCTs) of vitamin D supplementation are considered the gold-standard for determining whether vitamin D is beneficial for health. The importance of these studies explains the more than 15-fold increase in the number of publications with 'vitamin D supplementation' in their title from 2003-2017. Recent meta-analyses of RCTs have generally concluded that vitamin D supplementation is not beneficial. However, evidence that vitamin D supplementation is beneficial in people with low vitamin D status, as measured by circulating 25-hydroxyvitamin D (25(OH)D concentrations, is starting to emerge and is reviewed below.

Meta-analyses of RCTs

Meta-analyses of RCTs have reported threshold beneficial effects from vitamin D supplementation against falls, respiratory infection and asthma exacerbation.

Falls: a Cochrane meta-analysis found that vitamin D supplementation, compared to placebo, reduced the risk of falls in four studies that selected people with lower vitamin D levels (Gillespie et al. 2012). The 30% reduction in the risk of falls in these studies (relative risk (RR) = 0.70) was significantly lower than in the other nine studies that did not select participants based on vitamin D status (RR=1.00, $P_{interaction}$ <0.01).

Acute respiratory infections: a meta-analysis of individual patient data from 25 trials found that vitamin D supplementation, compared to placebo, significantly reduced the odds of having an acute respiratory infection in participants with baseline 25(OH)D levels <25 nmol/L (odds ratio (OR) = 0.58), more so than in participants with levels ≥25 nmol/L (OR = 0.89, $P_{interaction}$ = 0.01) (Martineau et al. 2017).

Asthma exacerbations: a further meta-analysis of individual patient data from seven trials reported that vitamin D supplementation, when compared with placebo, reduced the incidence rate of exacerbations in asthma patients who had baseline 25(OH)D concentrations <25 nmol/L by 67% (rate ratio = 0.33), but not in those with baseline levels ≥25 nmol/L (Jolliffe et al. 2017).

Individual trials

Several reports from individual RCTs have found beneficial effects in people with low vitamin D levels for the following outcomes.

Exacerbations of chronic obstructive pulmonary disease (COPD): vitamin D supplementation (compared to placebo) reduced the incidence rate of exacerbations over one year in COPD patients by 43% in those with baseline 25(OH)D concentrations <25 nmol/L, more so than in those with higher vitamin D levels ($P_{interaction}$ = 0.027) (Lehouck et al. 2012).

Hospital mortality: a trial in seriously ill patients admitted to intensive care units found that vitamin D supplementation reduced hospital mortality after 6-months by 38% in those who had baseline 25(OH)D levels ≤30 nmol/L (hazard ratio = 0.56), but not in those above this level (HR = 1.12, $P_{interaction}$ = 0.04) (Amrein et al. 2014).

Lung function: a sub-study of the large NZ Vitamin D Assessment (ViDA) trial found that vitamin D supplementation, compared to placebo, increased forced expiratory volume in 1 second (FEV_1) after 12 months, more in participants who had asthma and/or COPD and also had 25(OH)D levels <50 nmol/L, than in other asthma/COPD participants with higher 25(OH)D levels; and in participants who ever smoked tobacco and had 25(OH)D levels <50 nmol/L, than in ever smokers with higher vitamin D levels (Sluyter et al. 2017a). These results are shown in Figure 1.

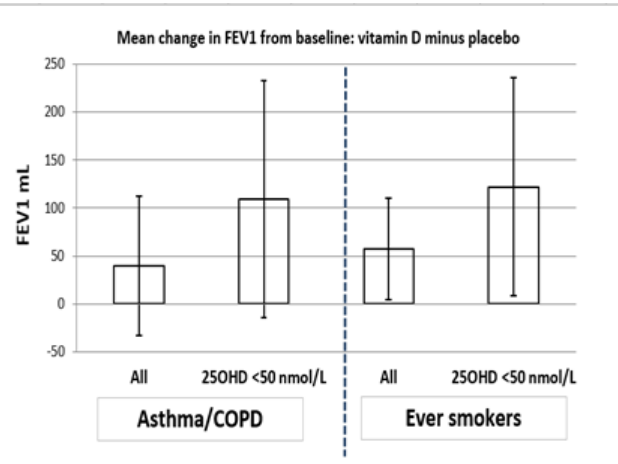

Figure 1. Mean (95% CI) change in forced expiratory volume in 1 second (FEV1) after 12 months in participants supplemented with vitamin D (compared to placebo) – in all participants with asthma/COPD or ever smokers, and those in the same two groups with baseline 25(OH)D < 50 nmol/L.

Arterial function: in another sub-study from the ViDA trial, reductions in arterial waveform parameters that predict increased risk of cardiovascular disease, such as augmentation index and pulse wave velocity, were seen after 12 months of supplementation from vitamin D, compared to placebo, in participants with baseline 25(OH)D <50 nmol/L but not in those above this cut-point ($P_{interaction} < 0.05$) (Sluyter et al. 2017b).

Bone mineral density: in a third sub-study from the ViDA trial, attenuation of bone mineral density loss in the spine and femoral neck after 2 years, from vitamin D supplements compared to placebo, was greater in people with baseline 25(OH)D ≤30 nmol/L than those with higher baseline levels ($P_{interaction} = 0.04$) (Reid et al. 2017).

Discussion

These results suggest that vitamin D supplementation may only be beneficial in people with vitamin D deficiency, and have implications for public health programmes to prevent vitamin D deficiency. The two approaches traditionally used to prevent or correct adverse health situations are the population approach and the high risk approach.

The latter involves screening for vitamin D deficiency, which at the moment can only be done with an expensive blood test (25(OH)D), and then treating those who are deficient by giving them vitamin D supplements. This approach would not be cost-effective in populations where vitamin D deficiency occurs only in a minority, as those who are not deficient would not benefit from taking vitamin D supplements. On the other hand, screening would not be required in communities where vitamin D deficiency is common, such as in South Asians, as the majority would benefit from vitamin D supplementation.

The population approach involves fortifying commonly eaten foods with vitamin D, so that the 25(OH)D level of the whole population is shifted up to the right. This would be a low-cost strategy to minimise the proportion of the population with vitamin D deficiency. More than likely, a combination of both strategies – fortification and supplementation – will be required, and relying only on the latter will not be effective.

The other implication from these results is for the design of clinical trials, which in the future should recruit sufficient numbers of participants with low 25(OH)D concentrations and not give low-dose vitamin D to the placebo arm as is done commonly in US trials, because the 25(OH)D response to vitamin D supplements in people who are deficient is much higher than in those who are vitamin D sufficient.

Conclusions

- Evidence is beginning to emerge of thresholds in vitamin D status for beneficial effects from vitamin D supplementation.
- Future RCTs of vitamin D supplementation should recruit sufficient participants with vitamin D deficiency to confirm the existence of any threshold, and its 25(OH)D level.
- If thresholds of beneficial effects from vitamin D supplementation are confirmed, this would strengthen the need for vitamin D fortification of foods.

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