



Are we overrating the extra-skeletal benefits of oral vitamin D supplementation?

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Vitamin D (Vit D) is a fat-soluble hormone poorly present in food, which is endogenously produced mainly through the biological conversion of its precursors into the biologically active form (1,25-dihydroxy-cholecalciferol) triggered by ultraviolet radiation exposure from either sunlight or, less frequently, indoor tanning (1). According to the Endocrine Society recommendations, Vit D3 deficiency can be diagnosed when serum 25-hydroxyvitamin D (25OHD) concentration falls below 20 ng/mL (i.e., ≤ 50 nmol/L), whilst Vit D3 insufficiency is conventionally defined as a serum 25OHD concentration between 21–29 ng/mL (i.e., 52.5–75.0 nmol/L) (2). Although severe forms of Vit D3 deficiency are relative rare and mainly manifest as rickets (3), the current worldwide burden of Vit D3 deficiency and insufficiency is alarming, being recently estimated at around 20% and 50%, respectively (4). This evidence has paved the way to widespread serum Vit D3 testing (5), enhanced oral Vit D3 supplementation (6) and even food fortification in several countries around the world, such as Canada, United States, Finland and India (7). For example, the Endocrine Society currently recommends that at least 600 IU/day of oral Vit D3 are needed in the adulthood to optimize bone health and muscle function (2).

Beside its well-recognized role in calcium homeostasis, Vit D3 may exert a variety of other potential pleiotropic effects (8,9), so that major emphasis is accumulating that oral supplementation might be a promising ‘policy’ for enhancing global health (10). Nevertheless, a contradictory picture emerges from the analysis of large, randomized, placebo-controlled trials, which have very recently explored

the effect of oral Vit D3 supplementation on prevention of common chronic diseases.

Manson *et al.* carried out a nationwide randomized, placebo-controlled trial, in which 25,871 United States middle-aged individuals free of cardiovascular disease and cancer at the baseline were randomly assigned to receive either 2,000 IU daily of Vit D3 (cholecalciferol) (n=12,927) or placebo (n=12,944) (11). No significant differences were observed between the supplemented and placebo groups in incidence of major cardiovascular events [hazard ratio (HR), 0.97; 95% confidence interval (95% CI), 0.85–1.12] or of any type of cancer (HR, 0.96; 95% CI, 0.88–1.06) during a median follow-up of 5.3 years. A subgroup analysis, focused on different types of cardiovascular disorders or cancers, showed virtually identical results, whereby the incidence of myocardial infarction (HR, 0.96; 95% CI, 0.78–1.19), stroke (HR, 0.95; 95% CI, 0.76–1.20), breast cancer (HR, 1.02; 95% CI, 0.79–1.31), prostate cancer (HR, 0.88; 95% CI, 0.72–1.07) and colorectal cancer (HR, 1.09; 95% CI, 0.73–1.62) were comparable between the two groups.

As regards diabetes, Pittas *et al.* randomly assigned 2,423 adults at high risk for diabetes to receive 4,000 IU daily of Vit D3 (n=1,211) or placebo (n=1,212), regardless of the baseline serum 25OHD level (12). Although the mean serum 25OHD levels nearly doubled in the Vit D3 supplemented group, the primary outcome of incident type 2 diabetes occurred similarly in the Vit D and placebo groups (HR, 0.88; 95% CI, 0.75–1.04; P=0.12) during a median follow-up of 2.5 years.

In another recent placebo-controlled trial, Roth

Table 1 Summary of recent randomized, placebo-controlled trials investigating the effect of oral vitamin D3 supplementation for preventing common chronic diseases

Authors, year (ref)	Outcome variable	Study design	Oral Vit D3 dose (IU/day)	Follow-up (mean)	Change in serum 25OHD levels (ng/mL)	Main results (Vit D vs. placebo) ¹
Manson <i>et al.</i> , 2019 (11)	Cardiovascular disease	Randomization to vitamin D (n=12,927) or placebo (n=12,944)	2,000	5.3 years	From 29.8 to 41.8	0.97 (95% CI, 0.85–1.12)
Manson <i>et al.</i> , 2019 (11)	Cancer	Randomization to vitamin D (n=12,927) or placebo (n=12,944)	2,000	5.3 years	From 29.8 to 41.8	0.96 (95% CI, 0.88–1.06)
Pittas <i>et al.</i> , 2019 (12)	Diabetes	Randomization to vitamin D (n=1,211) or placebo (n=1,212)	4,000	2.5 years	From 27.7 to 54.3	0.88 (95% CI, 0.75–1.04)
Roth <i>et al.</i> , 2018 (13)	Anthropometric parameters in newborns	Randomization of pregnant women to vitamin D (600 IU/day, n=260; 2,400/day, n=259; 4,000 IU daily, n=260; 4,000 IU/day +4,000 IU/day post-partum, n=260) or placebo (n=260)	From 600 to 4,000	1 year after birth	From 26.6–27.4 to 69.7–113.6	No difference in live birth, gestational age at birth or anthropometric parameters
Bischoff-Ferrari <i>et al.</i> , 2012 (14)	Hip and non-vertebral fractures	Randomization to vitamin D (n=15,527) or placebo (n=15,495)	From 360 to 2,000	N/A	Baseline level 16.4–21.6	0.90 (95% CI, 0.50–1.01) for hip fractures and 0.93 (95% CI, 0.87–0.99) for non-vertebral fractures

¹, data are expressed as hazard ratio and 95% confidence intervals. N/A, non-available; Vit D, vitamin D; 25OHD, 25-hydroxyvitamin D.

et al. randomly assigned 1,298 pregnant women to receive either oral Vit D3 supplementation from 17 to 24 weeks of gestation until birth (600 IU daily, n=260; 2,400 IU daily, n=259; 4,000 IU daily, n=260; 4,000 IU daily plus 4,000 IU daily post-partum, n=260) or placebo (n=260) (13). Among the 1,164 infants who could be evaluated at 1 year of age, live birth, gestational age at birth and multiple anthropometric parameters did not significantly differ among groups of infants whose mothers had received or not Vit D3 supplementation.

Notably, the benefit of oral Vit D3 supplementation for reducing bone fractures has also been questioned by the findings of the meta-analysis of Bischoff-Ferrari *et al.*, who pooled participant-level data involving a total of 31,022 individuals 65 years of age or older from 11 different double-blind, randomized, controlled trials (Vit D3 dosages between 360–2,000 IU daily) (14). A total number of 1,111 incident hip fractures and 3,770 non-vertebral fractures were recorded over the follow-up period. The authors found that risk reduction of hip fractures was non-significantly different in participants randomly assigned to

receive either oral Vit D3 (n=15,527) or placebo (n=15,495) (HR, 0.90; 95% CI, 0.50–1.01), whilst a modest risk reduction of non-vertebral fractures was noted in the Vit D3 group (HR, 0.93; 95% CI, 0.87–0.99). Treatment-dose analysis revealed that a beneficial effect on risk of hip and non-vertebral fractures could be obtained only in subjects supplemented with higher doses of oral Vit D3 (>800 IU/day). However, this finding is not really surprising, whereby similar results have been also reported by Aspray *et al.*, who showed that oral Vit D3 supplementation had negligible effects on bone health in the elderly (15).

Collectively, the current evidence from large randomized placebo-controlled trials would lead us to raise reasonable doubts that oral Vit D3 supplementation, at least at conventional daily doses (i.e., between 400–2,000 IU/day), would produce major health benefits, or that it would be able to significantly reduce the incidence and the adverse consequences of the most common chronic diseases (as summarized in *Table 1*). On the other hand,

recent evidence has been also published that the upper level of Vit D3 supplementation, recommended by the Endocrine Society, may increase by nearly 4-fold the risk of hypercalciuria, especially when combined with oral calcium supplementation (16), thus possibly increasing the risk of developing kidney stones in predisposed individuals, as recently emphasized by Letavernier and Daudon (17). It is also worthwhile mentioning here that Vit D3 supplementation shall not be considered completely safe, whereby overtreatment may generate some toxic effects (18), whilst widespread oral vit D3 supplementation may also impose a remarkable economic burden on healthcare budget.

One essential aspect that shall be highlighted, however, is that the vast majority of randomized placebo-controlled trials that have been published so far included subjects at the lower end of the distribution of serum 25OHD concentration, but only a limited number of subjects with real Vit D3 deficiency (*Table 1*). This leads the way to planning future tailored studies aimed at establishing whether public health actions based on vit D3 supplementation or food fortification will really be effective for reducing the risk of acute or chronic diseases in subjects with Vit D3 deficiency, whose number is exponentially increasing around the world (19). Additional efforts shall also be made for eliminating or lowering the impact of many important confounders of Vit D3 status in future epidemiological investigations (20).

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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