



Vitamin D and bone—the search for the optimal dose

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Since the discovery that cod liver oil cured rickets back in 1918, bone disease has been the hallmark of vitamin D deficiency. Still, hundreds year later, we do not know the optimal vitamin D intake or levels for our skeleton. As for most nutrients, the effects of vitamin D intake in the body follow a U-shaped pattern—with an increased risk of detrimental effects at both very low and very high intakes, with a broad range of intakes in between regarded safe and sufficient (1). What the thresholds for too little and too much should be for vitamin D, are still not clarified.

Intervention studies using vitamin D are often heterogeneous in designs, which make them difficult to compare. Dosing regimens vary a lot, regarding frequency of dosing (daily, weekly, monthly or yearly), the dose used, the use of ergocalciferol versus cholecalciferol, and per OS versus intramuscular administration. In addition, some researchers co-supplement with calcium, while others don't. This heterogeneity must be considered as a reflection of the lack of knowledge of the optimal design.

Also confounding the results, is that the majority of studies have not used low 25(OH)D levels as an inclusion criteria. Thus, many studies have been performed in vitamin D sufficient participants, where the relation between 25(OH)D and the clinical outcome—in this case bone mineral density (BMD)—must be expected to be quite flat (1).

Not surprisingly, therefore, intervention studies on bone and vitamin D have yielded inconsistent results. A systematic review and meta-analysis from 2014, including the results from 23 studies and more than 4,000 participants, reported a small, but significant positive effect on BMD in the femoral neck only, with a large

heterogeneity of the results (2). Thus, the majority of the studies reported null-findings, six reported positive effects, and two detrimental effects on BMD. After this review was published, several other randomized controlled trials (RCTs) have reported BMD results after vitamin D intervention, many using higher doses. This includes one Norwegian study using cholecalciferol 20,000 IU/w for 5 years which resulted in increased BMD at the femoral neck, but not other measurement sites in males, but not females (3). Also, in the VIDA study in New Zealand, 2 years intervention with a monthly dose of 100,000 IU cholecalciferol, resulted in significantly less bone loss at the hip in the active as compared to the control group, although of doubtful clinical significance (0.5% difference between the groups). However, there was a significant interaction with baseline 25(OH)D levels, so that those with levels below 30 nmol/L ended up with a difference between the groups of 2% in favor of vitamin D (4).

However, most of the studies performed have compared one dose of vitamin D with placebo, with or without calcium co-supplementation. Only a few included in the review and meta-analysis from 2014 have compared different dosing regimens (2). In addition, a recent Scottish study in postmenopausal women with low 25(OH)D levels (mean 33 nmol/L) at baseline, reported that a dose of 1,000 IU/d cholecalciferol attenuated bone loss at the hip, but not other measurement sites, as compared to a dose of 400 IU/d or placebo (5). In contrast, in a US study of postmenopausal women with baseline 25(OH)D levels around 50 nmol/L, no differences in BMD was seen after treatment with cholecalciferol 800 IU/d, 50,000 IU/month or placebo,

although a small increment in calcium absorption was observed in the high-dose group (6).

The study of Rahme and coauthors published in *Journal of Bone and Mineral Research* in July this year, therefore provides additional insight into this topic (7). The study included 257 elderly and overweight participants with a mean age of 71 years and a BMI of 30, and a baseline serum 25(OH)D level of around 50 nmol/L. All of them received 600 IU of cholecalciferol and 1,000 mg of calcium per day. In addition, the participants were randomized to receive either two capsules containing 11,000 IU of cholecalciferol to be taken once a week, or similar looking placebo pills. This resulted in an average daily cholecalciferol dose of 3,750 IU in the high-dose arm as compared to 600 IU in the low-dose arm. BMD and bone markers were measured at baseline and after 12 months, with complete data for final analyses in 222 participants. After one year, the authors reported small increments in BMD in the range of 0.5–1.6% for both treatment arms, with no significant differences between the two groups except for sub-total (whole-body less head) BMD, where the increase was significantly higher in the high-dose group. Bone markers (parathyroid hormone, osteocalcin and cross-laps) were reduced in both arms, but without significant differences between the groups. The authors concluded that there was little additional benefit in vitamin D supplementation at a dose exceeding the IOM recommendation of 600 IU/day on BMD and bone markers in overweight elderly individuals.

The results from the study of Rahme can be compared with the results from a very similar study in 297 postmenopausal women with osteopenia (T-score in lumbar spine or hip ≤ -2.0), treated for 1 year with a daily dose of 1,000 mg calcium and 800 IU of cholecalciferol (8). In addition, half of the participants were randomized to receive capsules of cholecalciferol containing 20,000 IU to be taken twice a week, while the other half received placebo capsules. This resulted in an average dose of 6,500 IU/day in the high dose group, as compared to 800 IU in the standard dose group. Baseline 25(OH)D levels were 64 nmol/L (9). Similar to the results in Rahme's study, this resulted in very modest improvements in BMD of the hip of 0.3–0.6%, without any significant differences between the groups. However, while the levels of 1,25-dihydroxyvitamin D [$1,25(\text{OH})_2\text{D}$] remained unchanged or decreased in both the 600, 800 and 3,750 IU groups, the levels increased significantly in the 6,500 IU group. This is an important point, as too much $1,25(\text{OH})_2\text{D}$ may have detrimental effects in bone through stimulation of

bone turnover and suppression of bone mineralization (10). Also, the bone turnover marker serum P1NP were significantly more reduced in the 800 IU group than in the 6,500 IU group (8), whereas there were no significant differences in bone marker suppression (osteocalcin and cross-laps) between the 600 and 3,750 IU groups (7).

Comparisons of serum 25(OH)D levels between studies have been challenging due to the range of different laboratory assays, yielding very different results (11). During the last years, much effort have been put into the standardization of laboratory methods through the Vitamin D Standardization Program (VDSP) (12). This work makes such comparisons possible, and is also a necessary requisite for setting thresholds for vitamin D sufficiency. Fortunately, both these studies have analysed their sera using this approach. Thus, if we compare the serum 25(OH)D levels achieved in these two trials, the 3,750 IU/d intervention resulted in an average final 25(OH)D levels of 90 nmol/L (7), whereas the 6,500 IU/d group ended up with 163 nmol/L (9). One could therefore argue that these results together provide support for daily doses not to exceed 3,750 IU/day—alternatively that a level of around 160 nmol/L is above the optimal range for bone health. This suits well with the IOM recommendations from 2011 which settled the safe upper tolerable limit for vitamin D intake to 4,000 IU/d (13). It is therefore of concern that a recent study from the US reported an increase in use of higher supplemental doses. Thus, in 2013–2014, the prevalence of self-reported daily use of 4,000 IU vitamin D or more was 3.2%, increasing from 0.2% in 2007 (14).

As two independent and adequately powered RCTs now both have demonstrated similar results, it seems timely to conclude that there is no extra benefit of using high-dose (3,750–6,500 IU/d) cholecalciferol for improvement of BMD in populations without vitamin D deficiency. Moreover, the optimal 25(OH)D level for bone health is probably well below 160 nmol/L, and above 30 nmol/L. To further narrow this quite wide range, RCTs with inclusion of vitamin D deficient subjects with low BMD have to be performed. Furthermore, not only BMD but also bone biopsies should be included to evaluate more subtle changes (15). And finally, the use of standardized 25(OH)D analyses should be implemented in all future vitamin D studies.

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