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Vit D3 (cholecalciferol) and osteoporosis (risk of falls and fractures)

A recent report in JAMA¹ has highlighted a potential problem with very high dose oral cholecalciferol in elderly people - “A double-blind, placebo-controlled trial of 2256 community-dwelling women, aged 70 years or older, considered to be at high risk of fracture were recruited from June 2003 to June 2005 and were randomly assigned to receive cholecalciferol or placebo each autumn to winter for 3 to 5 years. The study concluded in 2008.”

The participants received a single oral dose of 500,000 IU of cholecalciferol or placebo.

“...participants receiving annual high-dose oral cholecalciferol experienced 15% more falls and 26% more fractures than the placebo group. Women not only experienced excess fractures after more frequent falls but also experienced more fractures that were not associated with a fall.

A post hoc analysis (*analysis done after the experiment finished, not part of the original trial design and statistics*) found that the increased likelihood of falls in the vitamin D group was exacerbated in the 3-month period immediately following the annual dose and a similar temporal trend was observed for fractures.”

This is quite alarming and raises several questions:

- Is there a difference in the baseline characteristics between the placebo and treatment group that could account for this or some of this?
 - The baseline characteristics were assessed by questionnaire and pre-trial Vit D levels were assessed in a subset. So the baseline data may not be accurate.
 - Broken bone since age 50 - Vit D: 384 (36.5%) Placebo: 343 (32.7%)
 - Ever used walking aid - Vit D: 294 (26.0) Placebo: 275 (24.4)
 - PTH, pmol/L – Vit D: 4.3 (2.9-7.0) Placebo: 5.0 (3.7-6.6)
 - D3 levels nmol/L – Vit D: 53 (40-65) Placebo: 45 (40-57)

Approx 40 more women in the treatment group had experienced fractures pre-trial compared to the placebo group. Interestingly, approx 40 more women in the treatment group during the trial had fractures compared to the placebo group. Were these the same women? The data is not included in the trial report so there is no way for us to know. But they were certainly in the same group.

Also interestingly, the treatment group had higher baseline Vit D levels but significantly lower PTH levels compared to the placebo group.

- Given the size of the study (n = 2256) **it is very odd that there would be such a difference in the baseline characteristics between the two groups.** Why has the randomisation not evened this out pre-intervention?
- Did falls lead to fractures or did fractures lead to falls?



- A pathological fracture of the spine, pelvis, hip (or any other part of the total leg) can lead to a fall. Are there enough of these in the treatment group compared to the placebo group to account for the increased number of falls in the treatment group? The sheer numbers of lower body fractures do not account for the increase in the treatment group, however it is common to break upper body bones as a result of the fall from a pathological fracture in the lower body. So this is possible. The specific data are not included, so it is not possible to investigate this.
- Are there other studies that show increased risk of fractures or falls with high dose vitamin D?
 - Falls no, fractures yes (maybe).

“Only 1 other study has reported an increase in fracture associated with vitamin D treatment. Participants (4354 men, 5086 women) 75 years or older received an annual injection of 300 000 IU vitamin D2 as ergocalciferol or placebo. In men, treatment had no effect on fractures. However women treated with vitamin D had increased risk of nonvertebral (HR, 1.21), hip/femur (HR, 1.80), and hip/femur/wrist/forearm fractures.”ⁱ

The increase in risk in the above quoted studyⁱⁱ was small, and the authors state in the published paper “that these observations are likeliest due to chance”, i.e. they do not believe the results are related to Vitamin D.

- Are there reviews about fractures/falls with vitamin D supplementation in various forms?
 - Yes, but like all complex situations, the results are complex and various. Bone remodelling is a complex process, several hormones and nutrients interact and the role of weight bearing on bones is also important.

Also, these studies/reviews do not include information about very high doses.

“Doses of 700 IU to 1000 IU supplemental vitamin D a day could reduce falls by 19% or by up to 26% with vitamin D3. This benefit may not depend on additional calcium supplementation, was significant within 2-5 months of treatment, and extended beyond 12 months of treatment. Conversely, our results do not support the clinical use of vitamin D doses below 700 IU a day for the prevention of falls among older individuals. A 25(OH)D concentration of at least 60 nmol/l is required for fall prevention; therefore, a daily intake of at least 700 IU supplemental vitamin D is warranted in all individuals age 65 and older. Notably, good adherence is essential as the effect of vitamin D on falls will not be proportional below 700 IU a day. Furthermore, it is possible that greater benefits may be achieved with the use of vitamin D3 instead of vitamin D2. Finally, active forms of vitamin D do not appear to be more effective than 700-1000 IU of supplemental vitamin D for fall prevention in older persons.”ⁱⁱⁱ

“Vitamin D has direct effects on muscle strength modulated by specific vitamin D receptors present in human muscle tissue. Myopathy from severe vitamin D deficiency presents as muscle weakness and pain, but is reversible with vitamin D supplementation. In several trials of older individuals at risk for vitamin D deficiency, vitamin D supplementation improved strength, function, and balance in a dose-related pattern. Most importantly, these benefits translated into a reduction in falls.”ⁱⁱⁱ

- Would we expect very high doses of cholecalciferol to improve bone mineral density (BMD)?
 - Based on available evidence the answer is probably no.

A recent study in Australia looked at vitamin D concentrations and bone mineral density following biliopancreatic diversion surgery after a 600,000 IU i.m. dose of cholecalciferol^{IV}.

“VitD concentrations (mean±SD) were significantly increased from baseline values (61.5±18.8nmol/L) at 1.5 months (92.4±21.5, p<0.001), 3 months (100.5±24.4, p<0.001) and 6 months (79.1±20.9, p=0.014) post-injection, with non-significant elevations at 9 months (73.3±15.1, p=0.248) and 12 months (73.4±17.3, p=0.278). The proportion of patients with ‘normalised’ VitD levels was significantly higher at all post-injection time points (range: 93-100%) compared with baseline (71.4%)(p<0.01). Ionised calcium and ALP remained within normal levels at baseline and all follow-up time-points, although ionized calcium decreased by 3.4% (p=0.015) and ALP increased by 14.6% (p=0.021) at 12 months compared with baseline. **No significant change in PTH, NTX or BMD was observed.**”

“Once-yearly injection of VitD (600,000IU), as an adjunct to regular oral VitD supplementation, is a safe and effective means of improving serum VitD concentrations for a period 12 months in patients having undergone BPD. However, while maintained, this therapy did not significantly increase BMD in the year following commencement of treatment.”

- What is the state of safety data about very high doses of cholecalciferol?
 - From Einarsdóttir et al (600,000IU i.m):

“We found no side effects of the VitD injection, which is in line with previous findings. Diamond et al. studied the safety and efficacy of 600,000IU cholecalciferol intramuscular injection in 50 patients with VitD deficiency. No patient in their study reported serious adverse events, but one patient developed a localised erythematous reaction at the injection site. None of the participants in our study reported any such events.”

- From Diamond et al^V (600,000IU i.m.):

“In our study, a single annual intramuscular injection of 600000IU cholecalciferol was administered to 50 vitamin D-deficient participants. The therapy was effective, with normalisation of serum 25OHD levels and maintenance of a level well above 50nmol/L at 12 months. This result was achieved with very little change in serum calcium levels and no deterioration in renal function...”

- For further information about high dose Vitamin D3, see the newsletter “High Dose Vitamin D3 (Cholecalciferol) – some clinical questions answered”

So, where are we? Significant literature exists where cholecalciferol is used in doses up to 600,000 IU (oral or i.m.). So far the JAMA study (Sanders et al.) is the only high dose cholecalciferol study to report significantly negative findings. But there are enough questions about this study, in particular about the differences in baseline characteristics between the treatment and placebo groups, to warrant further explanation and further study.

Is it reasonable to expect that cholecalciferol could increase the risk of falls and fractures? Is there any plausible explanation as to why this could happen?

Active vitamin D hormone will raise blood calcium – including from the kidneys, GIT and bone. But cholecalciferol is not active without double conversion (to calcidiol then to calcitriol).



To affect bone, Vitamin D3 must be in the calcitriol form (1,25(OH)₂D₃). Calcidiol does have some effect but it is very weak, approx 80 times weaker than the active form^{vi}. Paradoxically, Vitamin D per se does NOT induce bone formation, though this is an often quoted misconception. This is why very large doses of Vitamin D do NOT dramatically increase BMD. Active vitamin D DOES stimulate bone resorption via stimulation of osteoclasts. As a hormone, its purpose (in Ca metabolism) is to RAISE BLOOD CALCIUM. In order for significant pathological stimulation of resorption to occur, active vitamin D levels need to be approx 10 times higher than normal physiological levels^{vi}.

Are the levels in any of the women who participated in the JAMA study high enough to produce frank toxicity? The peak blood calcidiol levels (measured vitamin D) were approx 3 times higher in the treatment group vs. the placebo group 1 month after the 500,000 IU dose but for most of the time were approx. double. Were the women with the highest levels the ones who had the fractures? We don't know because the data are not included. For the women in this study, there is NO WAY that the levels of active hormone were anything like this, since the intermediate form (calcidiol) only achieved typically double the level of the placebo group (who were deficient anyway). So, based on current understanding, it is not physiologically reasonable to conclude that the levels of Vit D in the treated women could have contributed to their osteoporosis. This understanding may change since it has not been extensively studied in humans. Since Vitamin D has no known direct influence on bone formation, but does potentially have an influence on bone resorption, it is prudent to ensure that all nutritional requirements for bone formation are in place prior to high dose Vit D administration.

For a proper evaluation of the Sanders et al study, it would be prudent to repeat the study with identical baseline groups. It is not expected that Vit D at very high doses will add benefit to fracture risk above the typical lower doses used currently. However, the high doses are cheap, typically administered by a physician and effective at maintaining calcidiol concentrations.

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ⁱ Sanders KM, Stuart AL, Williamson EJ, Simpson JA, Kotowicz MA, Young D, Nicholson GC. Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial. JAMA. 2010 May 12;303(18):1815-22. Erratum in: JAMA. 2010 Jun 16;303(23):2357. PubMed PMID: 20460620

ⁱⁱ Smith H, Anderson F, Raphael H, Maslin P, Crozier S, Cooper C. Effect of annual intramuscular vitamin D on fracture risk in elderly men and women -- a population-based, randomized, double-blind, placebo-controlled trial. Rheumatology (Oxford). 2007 ec;46(12):1852-7. Epub 2007 Nov 12. PubMed PMID: 17998225

ⁱⁱⁱ Bischoff-Ferrari HA, Dawson-Hughes B, Staehelin HB, Orav JE, Stuck AE, Theiler R, Wong JB, Egli A, Kiel DP, Henschkowski J. Fall prevention with supplemental and active forms of vitamin D: a meta-analysis of randomised controlled trials. BMJ. 2009 Oct 1;339:b3692. doi: 10.1136/bmj.b3692. Review. PubMed PMID: 19797342; PubMed Central PMCID: PMC2755728

^{iv} Kristjana Einarsdóttir, David B. Preen, Timothy D. Clay, Laura Kiely, C. D'Arcy J. Holman, Leon D Cohen. Effect of a single 'megadose' intramuscular vitamin D (600,000 IU) injection on vitamin D concentrations and bone mineral density following biliopancreatic diversion surgery. (unpublished?)

^v Diamond TH, Ho KW, Rohl PG, Meerkin M. Annual intramuscular injection of a megadose of cholecalciferol for treatment of vitamin D deficiency: efficacy and safety data. Med J Aust. 2005 Jul 4;183(1):10-2. PMID: 15992330

^{vi} Suda, Vitamin D and Bone. Proc Japan Acad Sci 2004