Effect of High-Dose Vitamin D on Bone Density and Bone Strength[1]

BOTTOM LINE

In healthy older adults with normal serum calcium, serum vitamin D >30 nmol/L, and no osteoporosis, high doses of vitamin D (4,000 units and 10,000 units per day) did not show clinically important improvements in BMD over 400 units of vitamin D per day (although serum vitamin D levels did rise). High doses were associated with an increase in harms (e.g. hypercalcemia, hypercalciuria, and possible worsening of bone mineral density). This study does not support the use of high dose vitamin D in primary prevention of osteoporosis.

BACKGROUND

- As of November 2010, dietary reference intakes (DRI) for vitamin D were reviewed and published by Health Canada.[2] Current DRI's for vitamin D assume minimal sun exposure, and target maintenance of bone health.[2] The recommended dietary allowance for those aged 9-70 years is 600 IU/day, with an upper limit of 4,000 IU/day.[2]
- The most recent preventative vitamin D recommendations from Osteoporosis Canada are as follows:[3]
  - Low risk of vitamin D deficiency = 400-1000 IU daily (grade D evidence)
  - Moderate risk of vitamin D deficiency/adults >50yrs = 800-1,000 IU daily; higher daily doses may be required to achieve optimal serum vitamin D, as such 2,000 IU/day is acceptable (grade C evidence)
- A meta-analysis published in 2014 did not support the use of vitamin D supplements in the prevention of osteoporosis.[4] Another meta-analysis published in 2018, concluded that vitamin D supplements do not reduce the occurrence of fractures, or consistently demonstrate a clinically important impact on BMD measurements.[5]
- High-resolution peripheral quantitative computed tomography (HR-pQCT) is a new type of bone imaging that has the capability of providing information about bone microstructure; this can then be used to generate models of bone strength, a surrogate marker that may approximate fracture risk.[6,7]

TRIAL BACKGROUND[1]

DESIGN: Double-blind, single centre (Calgary, AB, Canada), randomized controlled trial, ITT analysis for BMD changes. Trial conducted from August 2013 – December 2017. Funded by Pure North S'Energy Foundation.

INTERVENTION: 4,000 IU or 10,000 IU vs. 400 IU once daily oral vitamin D x 3 years (Ddrops)
(plus calcium citrate supplementation if dietary intake was less than 1200 mg per day)

INCLUSION: men and women aged 55 to 70, lumbar spine/total hip area BMD T-score greater than -2.5 SD, serum vitamin D between 30-125 nmol/L, and normal serum calcium (2.10-2.55 mmol/L).

EXCLUSION: T-score diagnostic of osteoporosis, serum vitamin D outside the specified range (30-125 nmol/L), serum calcium outside of the normal range, daily vitamin D supplementation > 2000 IU for the last 6 months, kidney stone, or use of bone active medication within 2 years of study, disorders known to impair the metabolism of vitamin D, regular use of tanning beds, high risk FRAX score (≥ 20%).

POPULATION at baseline: n= 311
- mean age 62.2 ± 4.2
- community dwelling adults without osteoporosis ~46% female/54% male, 12.3 ± 6.3 years since menopause, BMI 27.6 ± 4.5, ~96% non-Hispanic white
- ~34% supplemented with vitamin D between 1000-2000 IU
- RA ~1.4%, fracture after 50 yrs ~15%, lumbar spine T-score 0.1 ± 1.4, total hip T-score 0.1 ± 1.1
- estimated GFR 80.4 ml/min/1.73 m^2 ± 11.5, vitamin D 78.8 nmol/L ± 19.8, PTH 21.9 ng/L ± 7.2, calcium 2.4 mmol/L ± 0.1, phosphate 1.0 mmol/L ± 0.2, creatinine 80.2 µmol/L ± 14.5, ALP 68.3 U/L ± 16.8

RESULTS[1]

TABLE 1: EFFICACY						TRIAL LENGTH: 3 YEARS
Clinical Endpoints **Modified ITT analysis**	**Vitamin D 400 IU** n=105	**Vitamin D 4,000 IU** n=97	**Vitamin D 10,000 IU** n=101	**mg HA/cm³ Difference 400 IU vs. 4,000 IU (95% CI)**	**mg HA/cm³ Difference 400 IU vs. 10,000 IU (95% CI)**	**Comments**
CO-PRIMARY ENDPOINTS						
total volumetric BMD at distal radius.	*group x time* interactions: P < 0.001			-3.9 (-6.5 to -1.3)	-7.5 (-10.1 to -5.0)	After 3 years of therapy, there was no difference in BMD between groups. A *group x time* analysis showed statistical significance, but this may not translate to a difference in clinical outcomes. It is therefore difficult to discern how much of a difference in BMD was truly present between each treatment group. The HR-pQCT result (mg HA/cm³) is a volume-based bone density measurement. The endpoint values shown are the difference in mean BMD between the control group and the experimental groups. Larger differences demonstrate greater bone loss.
total volumetric BMD at tibia.	*group x time* interactions: P < 0.001			-1.8 (-3.7 to 0.1)	-4.1 (-6.0 to -2.2)	
bone strength (failure load) at distal radius.	*group x time* interactions: P = 0.06			n/a		
bone strength (failure load) at tibia.	*group x time* interactions: P = 0.12					

TABLE 2: ADDITIONAL OUTCOMES

Clinical Findings	400 IU	4,000 IU	10,000 IU	Comments
mean changes in distal radius BMD from baseline	-1.2%	-2.4%	-3.5%	Mean serum vitamin D 10,000 IU: increase from baseline @ 3 months, increasing again to 200.4 nmol/L @ 18 months, then fell @ 36 months.
mean changes in tibia BMD from baseline	-0.4%	-1.0%	-1.7%	
mean serum vitamin D at baseline	76.3 nmol/L	81.3 nmol/L	78.4 nmol/L	
mean serum vitamin D at 3 months	77.4 nmol/L	115.3 nmol/L	188.0 nmol/L	
mean serum vitamin at 36 months	77.4 nmol/L	132.2 nmol/L	144.4 nmol/L	

TABLE 3: SAFETY

Pre-specified Adverse Events	Vitamin D 400 IU n=109	Vitamin D 4,000 IU n=100	Vitamin D 10,000 IU n=102	4,000 IU NNH/3YRS (vs 400 IU)	10,000 IU NNH/3YRS (vs 400 IU)	Comments
serious adverse events	15%	8%	14%	-	-	No significant differences in adherence to vitamin D supplement between groups; mean adherence 99% (81% to 100%).
hypercalcemia	0%	4%	9%	NNH = 25	NNH = 12	
hypercalciuria	17%	22%	33%	NNH = 20	NNH = 7	
renal dysfunction	1%	2%	2%	-	-	
nephrolithiasis	0%	1%	1%	-	-	
hepatic dysfunction	5%	3%	3%	-	-	Only 2 adverse events were statistically significant between groups; hypercalcemia (P =0.005) and hypercalciuria (P =0.006).
falls	4%	10%	5%	-	-	
low-trauma fractures	4%	2%	5%	-	-	
cancer	1%	3%	5%	-	-	

STRENGTHS, LIMITATIONS, & UNCERTAINTIES

STRENGTHS:
- Groups were evenly distributed by sex; gender can have a significant impact on BMD.
- Mean adherence rate was 99%; indication that vitamin D supplements were well tolerated.
- Calcium intake was controlled; all participants were receiving the recommended daily intake of 1200 mg (calcium citrate supplements were added for those who could not meet this through diet alone).
- Two different block sizes used; reduced risk of unblinding treatment allocation.
- Trial duration of 3 years; adequate time to assess BMD changes.

LIMITATIONS:
- No placebo-controlled group; unable to establish how BMD changes without supplementation.
- Participants were recruited via advertising; volunteer bias present. This may have resulted in participants being different than the general population. Bone health is impacted by general health status; if for example the cohort was less healthy, then this would lead to falsely diminished BMD's.
- Adherence to the supplement was recorded via a daily diary. There is potential for the presence of surveillance bias as participants may have felt they needed to lie about missed doses. Hidden differences in adherence between groups could influence the degree by which BMD changed throughout the study. As the mean rate of adherence was very high (99%), it is possible that these reports were inaccurate.
- Two lots of the 10,000 IU supplement were found to have a decreased potency; the administered dose in this group ranged from 2000 IU to 10,0000 IU between months 18 and 36 of the study. Serum vitamin D levels in the 10,000 unit group fell during this period of the study, although remained higher than the other two groups. This error would have increased similarity between the 10,000 IU and 4,000 IU groups.
- Participants were excluded from the study if they had osteoporosis, thus results of this study can only be applied to those in primary prevention for osteoporosis.
- Alcohol use was not considered in the baseline characteristics.
- Access to HR-pQCT imaging is limited and currently unavailable in Saskatchewan.

UNCERTAINITIES:
- All treatment groups exhibited a dose-dependent reduction in BMD from baseline, though both the statistical and clinical significance of these changes is unclear.
- Would results have been different if studied in people with existing osteoporosis?
- As shown in overlapping confidence intervals between treatment groups, after 3 years of therapy there was no difference in BMD between groups. There was a trend toward a dose-dependent response and *group x time* interactions showed statistical significance; however, the clinical significance of this is uncertain.
- The study was funded by a foundation that stands to benefit from an increased desire for vitamin D supplementation. Pure North S'Energy sells a variety of supplements including vitamin D; however, the results were not in favor of vitamin D supplementation, so the presence of publication bias is unlikely.
- As demonstrated by the manufacturer error, there is uncertainty as to the exact dosage present in over-the-counter vitamin D supplements purchased by the public.

Bottom Line:
- Vitamin D doses above the recommended dietary allowance do not provide additional bone health; further research with a placebo control is needed to determine the degree of BMD changes over time without vitamin D supplementation.
- Vitamin D supplementation demonstrates dose-dependent increases in serum levels.

RxFILES RELATED LINKS

- **Vitamin D Trial Summary Table 2010**: https://www-rxfiles-ca.cyber.usask.ca/RxFiles/uploads/documents/members/Vitamin-D-trial-summary-chart.pdf

- **Vitamin D: Q&A – Oct 2010**: https://www-rxfiles-ca.cyber.usask.ca/RxFiles/uploads/documents/Vitamin-D-Overview-QandA.pdf

References:

1. Burt, L., Billington, E., Raymond, D., Rose, M., Hanley, D., & Boyd, S. (2019). Effect of High-Dose Vitamin D Supplementation on Volumetric Bone Density and Bone Strength: A Randomized Clinical Trial. *JAMA, The Journal of the American Medical Association, 322*(8), 736-745.

2. Government of Canada. Vitamin D and Calcium: Updated Dietary Reference Intakes. https://www.canada.ca/en/health-canada/services/food-nutrition/healthy-eating/vitamins-minerals/vitamin-calcium-updated-dietary-reference-intakes-nutrition.html#a10

3. Papaioannou, A., Morin, S., Cheung, A., Atkinson, S., Brown, J., Feldman, S., . . . Leslie, W. (2010). 2010 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada: Summary. *CMAJ : Canadian Medical Association Journal = Journal De L'Association Medicale Canadienne, 182*(17), 1864-1873.

4. Reid, I., Bolland, M., & Grey, A. (2014). Effects of vitamin D supplements on bone mineral density: A systematic review and meta-analysis. *The Lancet, 383*(9912), 146-155.

5. Bolland, M., Grey, A., & Avenell, A. (2018). Effects of vitamin D supplementation on musculoskeletal health: A systematic review, meta-analysis, and trial sequential analysis. *The Lancet Diabetes & Endocrinology, 6*(11), 847-858.

6. Nishiyama, K., & Shane, K. (2013). Clinical Imaging of Bone Microarchitecture with HR-pQCT. *Current Osteoporosis Reports, 11*(2), 147-155

7. Mayo Clinic (2015). New tools to predict fracture risk. https://www.mayoclinic.org/medical-professionals/endocrinology/news/new-tools-to-predict-fracture-risk/mac-20430573

8. E Colt, M Akram, & F X Pi Sunyer. (2016). Comparison of high-resolution peripheral quantitative computerized tomography with dual-energy X-ray absorptiometry for measuring bone mineral density. *European Journal of Clinical Nutrition, 71*(6), 778-781.

9. Pure North S'Energy Foundation. https://purenorth.ca/