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Effects of Supplemental Vitamin D on Bone Health Outcomes in Women and Men in the VITamin D and OmegA-3 TriaL (VITAL)

Meryl S. LeBoff, M.D.[a,b], **Sharon H. Chou, M.D.**[a], **Elle M. Murata, B.A.**[a], **Catherine M. Donlon, B.S.**[a], **Nancy R. Cook, Sc.D.**[b,c,d], **Samia Mora, M.D.**[b,c,e], **I-Min Lee, Sc.D.**[c,d], **Gregory Kotler, Ph.D.**[c], **Vadim Bubes, Ph.D.**[c], **Julie E. Buring, Sc.D.**[b,c,d], **JoAnn E. Manson, M.D., Dr.P.H.**[b,c,d]

[a]Division of Endocrinology, Diabetes and Hypertension, Department of Medicine, Brigham and Women's Hospital Boston, MA 02115, United States

[b]Harvard Medical School, Boston, MA 02115, United States

[c]Division of Preventive Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02215, United States

[d]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA 02115, United States

[e]Division of Cardiovascular Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, United States

Abstract

Although supplemental vitamin D is used to promote bone health in the general population, data from randomized controlled trials (RCTs) have been inconsistent. We determined whether daily, vitamin D_3 supplementation improves bone mineral density (BMD) and/or structure. VITamin D and OmegA-3 TriaL (VITAL) is a double-blind, placebo-controlled RCT of supplemental vitamin D_3 (2,000 IU/day) and/or omega-3 fatty acids (1 g/day) in 25,871 adults nationwide. This ancillary study included a subcohort of 771 participants (men ≥50 and women ≥55 years; not taking bone active medications) evaluated at baseline and 2-years follow-up (89% retention). Total 25(OH)D levels were measured by liquid chromatography tandem mass spectrometry (Quest Diagnostics, CA). Free 25(OH)D (FVD) levels were measured using the ELISA assay by Future Diagnostics Solutions B.V. (Wijchen Netherlands). Primary endpoints were 2-year changes in areal (a)BMD at the spine, hip, and whole body determined by dual-energy X-ray absorptiometry. Secondary endpoints were 2-year changes in volumetric (v)BMD and cortical thickness at the radius and tibia assessed by peripheral quantitative computed tomography. Supplemental vitamin D_3 vs. placebo had no effect on 2-year changes in aBMD at the spine (0.33% vs. 0.17%; p=0.55), femoral neck (−0.27% vs. −0.68%; p=0.16), total hip (−0.76% vs. −0.95%; p=0.23), or whole body (−0.22% vs. −0.15%; p=0.60), or on measures of bone structure. Effects did not vary by sex, race/ethnicity, BMI, or 25(OH)D levels. Among participants with baseline FVD levels below the median (<14.2

Corresponding author and person to who reprint requests should be addressed Meryl S. LeBoff, MD, Chief of the Calcium and Bone Section, Professor of Medicine, Harvard Medical School, Division of Endocrinology, Diabetes and Hypertension, Department of Medicine, Brigham and Women's Hospital, 221 Longwood Avenue, Boston, MA 02115, Phone: (617) 732-6155, Fax: (617) 264-5220, mleboff@bwh.harvard.edu.

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pmol/L), there was a slight increase in spine aBMD (0.75% vs. 0%; p=0.043) and attenuation in loss of total hip aBMD (−0.42% vs. −0.98%; p=0.044) with vitamin D_3. Whether baseline FVD levels help to identify those more likely to benefit from supplementation warrants further study. Supplemental vitamin D_3 vs. placebo for two years in general healthy adults not selected for vitamin D insufficiency did not improve BMD or structure.

Keywords

DXA; Bone QCT; PTH/VitD/ FGF23; General population studies; Osteoporosis

Introduction

Osteoporosis is a major health problem and primary prevention strategies are needed. Vitamin D supplements are widely recommended and prescribed in the general population to promote bone health. In the past decade, vitamin D supplement use has increased four-fold.[1] Mechanisms by which vitamin D may support skeletal health include improved mineralization of bone through increased intestinal calcium absorption, prevention of secondary hyperparathyroidism, and direct effects on osteoblast formation.[2–6] Observational studies have indicated that high 25-hydroxyvitamin D [25-(OH)D] levels are positively associated with areal bone mineral density (aBMD).[7–10] Data from large meta-analyses and systematic reviews that support use of supplemental vitamin D alone (without calcium) to benefit bone are lacking.[11–15] The few randomized controlled trials (RCTs) of vitamin D alone vs. placebo have not shown significant changes in aBMD at the spine, but showed small benefits at the femoral neck and/or a level of total 25(OH) D below which supplemental vitamin D increased spine and hip aBMD.[16–18] While RCTs provide the highest quality data, most previous RCTs of vitamin D vs. placebo on aBMD were limited by design, including bolus dosing,[17,19,20] short duration,[21,22] small sample sizes,[21,22] participants selected for vitamin D insufficiency,[20] and/or inability to separate effects of supplemental vitamin D from calcium.[23–25]

Bone strength depends on bone density and quality. Components of bone quality include cortical and trabecular structure, which can be assessed using peripheral quantitative computed tomography (pQCT). Some but not other studies suggest an association of 25(OH)D levels with improved bone structure, though there are no large, long-term RCTs of supplemental vitamin D vs. placebo on bone structure.[26,27] A recent study from Canada raised concerns that high doses (4,000 IU/day or 10,000 IU/day) vs. a low dose of vitamin D (400 IU/day) resulted in loss of volumetric bone density at the radius and tibia.[28]

Recent estimates of vitamin D status among U.S. middle-age to older adults show that approximately 20% have 25(OH)D levels <50 nmol/L.[29] Higher proportions of vitamin D insufficiency or deficiency have been reported among black adults (reduced cutaneous vitamin D synthesis),[30] obese individuals (vitamin D sequestration in fat tissue),[31] and older adults.[32]

While serum 25(OH)D levels have been considered the clinical biomarker for vitamin D status, vitamin D circulates primarily bound to vitamin D binding protein. It is the free

25(OH) vitamin D (FVD) that may exert biological effects on bone.[33–37] At present, there is no consensus on the optimal circulating total 25(OH)D or FVD level for bone, and it is unclear whether FVD may better predict effects of supplemental vitamin D on BMD and structure. The ancillary study, *VITamin D and OmegA-3 TriaL (VITAL): Effects on Bone Structure and Architecture,* addresses these knowledge gaps, evaluating whether vitamin D_3 supplementation (2,000 IU/day), compared with placebo in the generally healthy population not selected for vitamin D insufficiency, produces small increases or reduces bone loss in spine, hip, and whole body aBMD or improves volumetric (v)BMD and bone strength measures at the radius and tibia. We also examined whether intervention effects were modified by baseline levels of total 25(OH)D and FVD.

Materials and Methods

Trial Design and Oversight

VITAL is a randomized, placebo-controlled trial with a two-by-two factorial design investigating effects of vitamin D_3 (cholecalciferol 2,000 IU/day) and/or omega-3 fatty acids (1 g/day) supplements in the primary prevention of cancer and cardiovascular disease. Calendar packs with trial capsules were mailed to the participants. This study included men ≥50 and women ≥55 years from 50 U.S. states and had a median follow-up of 5.3 years. To ensure compliance, participants completed a 3-month placebo run-in phase and personal use of vitamin D_3 was limited to 800 IU/day (U.S. Recommended Dietary Allowance for older adults).[38] More comprehensive protocol details have been reported.[39,40]

The VITAL study was a hybrid design with the overall cohort of 25,871 participants and a subcohort of 1,054 participants who lived within driving distance of the Harvard Clinical and Translational Science Center (CTSC) in Boston. Participants were eligible for this ancillary study if they were not on bisphosphonates within the past 2 years or other bone active agents (Appendix) within the past year. Of the CTSC participants, 771 completed assessments for bone and body composition at baseline, exceeding the enrollment goal of 600.[41,42] Participants received annual questionnaires evaluating risk factors for bone loss and fragility fractures, falls, medication/supplement use, and physical activity. Fasting blood samples were collected at baseline and year 2, matched by season, and levels of calcium, albumin, total 25(OH)D, and plasma phospholipid omega-3 fatty acids were assayed by Quest Diagnostics (San Juan Capistrano, CA). Total 25(OH)D, including both $25(OH)D_2$ and $25(OH)D_3$, and plasma phospholipid omega-3 fatty acids levels were measured by liquid chromatography tandem mass spectrometry. Total 25(OH)D was calibrated to Centers for Disease Control and Prevention (CDC) standards. FVD levels, including both $25(OH)D_2$ and $25(OH)D_3$, were measured using the new ELISA assay by Future Diagnostics Solutions B.V. (Wijchen Netherlands). See Appendix for serum measurement methods. The study was approved by the Institutional Review Board of Partners HealthCare–Brigham and Women's Hospital (BWH).

Ancillary Study End Points

In 771 participants at baseline and 687 at 2-year follow-up (89% retention), aBMD was assessed by dual-energy X-ray absorptiometry (DXA; Discovery W, APEX Software

Version 4.2, Hologic, Bedford, MA). If participants were found to have osteoporosis on DXA scans, they were sent letters indicating they had osteoporosis and recommending follow-up with their health care providers. Participants who started treatment with bone active agents were not eligible to complete the 2-year DXA scan and were excluded from 2-year analyses. Primary end points were 2-year changes in aBMD at the lumbar spine (L1-L4), non-dominant hip (total, femoral neck), and whole body. Least significant change at BWH is 0.024 g/cm^2 at the spine, 0.021 g/cm^2 at the femoral neck, 0.017 g/cm^2 at the total hip, and 0.008 g/cm^2 for males and 0.010 g/cm^2 for females at the whole body. Guidelines from Hologic and the International Society for Clinical Densitometry were followed for all DXA scans. Detailed descriptions of the DXA protocol and reproducibility have been published.[41] Inclusion and exclusion criteria for DXA scans are described in the Appendix.

In 677 participants at baseline and in 600 at 2-year follow-up (89%), pQCT scans were performed on the non-dominant radius and tibia. Secondary end points included 2-year changes in total, trabecular, and cortical vBMD, cortical thickness, and bone strength measures as assessed by pQCT (XCT 3000; Stratec Medizintechnik GmbH). At our site, precision (%CV) ranges from 0.02% to 2.87% at the radius and tibia.[43] Details of pQCT measures are in the Appendix.

Statistical Analysis

The intention-to-treat principle was used to analyze treatment effects between vitamin D_3 and placebo groups. This ancillary study was designed to have 80% power to detect differences of 1.03, 1.22, and 0.42% in spine, femoral neck, and whole body aBMD, respectively, with a planned sample size of 600 and 10% loss to follow-up.[24] By exceeding this planned enrollment to 771 participants, detectable differences were reduced to 0.91, 1.08, and 0.37%, respectively. To assess whether balance was achieved by randomization among this subcohort, baseline characteristics were compared by treatment assignment. Continuous variables were first examined for normality. Means (standard deviation) or median (25th, 75th percentiles) are reported as appropriate. We used t-tests and analysis of variance (or the Wilcoxon rank sum and Kruskal Wallis tests) to compare continuous variables across randomized groups. Chi-square tests were used to compare proportions, using trend tests for ordinal data.

The primary analysis compared the effects of vitamin D_3 vs. placebo on changes in bone health measures, adjusted for the omega-3 fatty acids intervention, age, sex and race/ethnicity. Tests of significance for treatment effects were based on time by treatment interactions in repeated measures analyses. Thus, those with no follow-up data were considered missing at random given their observed baseline data. Differences in treatment effects according to sex, race/ethnicity, BMI, fat mass index (FMI), baseline and achieved total 25(OH)D and FVD level were specified a priori. Adherence-based and other analyses were performed as secondary analyses. All analyses were generated using SAS. Results were considered statistically significant when $p<0.05$. There was no control for multiple hypothesis testing, and no formal adjustment was made to the p-values. Thus, results regarding secondary, subgroup and exploratory end points should be interpreted with caution.

Results

Ancillary Study Participants

The parent trial randomized 25,871 participants into 4 treatment groups (vitamin D_3, omega-3 fatty acids, both agents, or both placebos) between November 2011 and March 2014. A subcohort of 771 participants in the Boston area had detailed in-person assessments at baseline. Testing at 2-year follow-up was completed by 687 participants (89% retention; Figure 1). Follow-up scans were not conducted for 19 participants who started taking bone active medications between baseline and 2-year follow-up. Other reasons for study discontinuation include lost to follow up, withdrawal of consent, subjects moved, did not want to drive back to Boston, were to busy, or did not want to return for a follow-up visit.

Among participants answering the compliance question by questionnaire, 94.3% in the vitamin D group and 93.2% in the placebo group reported adherence to study pills at year 1. At 2 years, 93.0% of the vitamin D group and 92.1% of the placebo group reported study pill adherence (Appendix Table 5).

Table 1 shows baseline characteristics of the bone health subcohort; most characteristics were balanced between the two groups. Of the 771 participants, 46.7% were women and 53.3% were men. The mean age was 63.8 years. At baseline, 42.3% were taking supplemental vitamin D (≤800 IU/day) and 17.1% were taking supplemental calcium (≤1200 mg/day). At baseline, 7.9% of participants had a history of fracture. A total of eighty participants had osteoporosis defined as a T-score ≤−2.5 at the spine or non-dominant hip (n=75) and/or reporting a fragility fracture at the hip, spine, forearm or shoulder at baseline (n=16). A total of 19 participants elected to start treatment for osteoporosis and were not included in the 2-year follow-up analyses. There were 402 participants who had osteopenia defined as a T-score between −1 and −2.5 at the spine or non-dominant hip. The vitamin D_3 group had a slightly lower total 25(OH)D level at baseline (67.4 vs. 71.1 nmol/L, p=0.025).

Compared to the overall VITAL cohort of 25,871 participants,[39] the bone health subcohort was slightly younger (mean age 63.8 vs. 67.1 years) and healthier with fewer participants with obesity, hypertension, or diabetes. While the overall cohort included an oversampling of black participants (20.2%), only 8.9% of the bone health subcohort was black given regional demographics of New England.[41]

At baseline, the mean serum total 25(OH)D level was 69.1 nmol/L, and 18.0% of participants had total 25(OH)D levels <50 nmol/L (n=770). In the vitamin D_3 group, mean total 25(OH)D levels increased by 46.2% to 98.6 nmol/L (n=359). The total 25(OH)D level in the placebo group was similar at baseline and 2-year follow-up (71.1 nmol/L and 70.6 nmol/L, respectively; n=354). Mean FVD level was 14.6 pmol/L at baseline (n=770). FVD increased by 55.5% to 22.3 pmol/L at year 2 in the vitamin D_3 group (n=359). Calcium levels did not change in either group between baseline and year 2 (p=0.27).

There were no increased incidences of hypercalcemia, kidney stones, or other adverse effects in the vitamin D_3 vs. placebo groups.[39]

Primary Outcome: aBMD Measures

Daily supplemental vitamin D_3 did not increase aBMD or reduce bone loss at the spine, femoral neck, total hip, or whole body, compared to placebo (Figure 2, Appendix). Overall, 2-year changes in aBMD at all sites were minimal at <1%.

Secondary Outcomes: pQCT Measures

There were no effects of daily supplemental vitamin D_3 on pQCT outcomes at the radius or tibia. Changes in bone structure (total, cortical, and trabecular vBMD, cortical thickness) and bone strength indices (polar stress strength index, bone strength index) were similar for the vitamin D_3 and placebo groups (Table 3).

Subgroup analyses of aBMD on primary outcomes

Subgroup analyses are presented in Table 2 and the Appendix. The effect of vitamin D_3 supplementation vs. placebo on 2-year changes in aBMD at all sites did not significantly differ by race/ethnicity, BMI, FMI, or baseline use of supplemental vitamin D (≤800 IU/day). In pre-specified analyses, when stratified by sex, vitamin D_3 supplementation vs. placebo in women resulted in a trend for smaller decreases in aBMD at the spine (p=0.062; p for interaction=0.067). In exploratory analyses, we did not find any significant differences in response to vitamin D_3 supplementation, compared to placebo, in those with osteopenia or osteoporosis vs. those with normal aBMD. In participants taking calcium supplements (≤1,200 IU/day) at baseline, there was attenuation of femoral neck aBMD loss with vitamin D_3 supplementation vs. placebo (p=0.029); however, there was no significant interaction (p=0.10; Appendix).

The vitamin D_3 intervention had a slight benefit on spine and total hip aBMD among participants with baseline FVD levels below the median (14.2 pmol/L; prespecified) with significant interaction at both sites (p=0.026 and 0.047, respectively). There were small increases in spine aBMD (0.75% vs. 0.00%; p=0.043) and smaller decreases in total hip aBMD (−0.42% vs. −0.98%; p=0.044) with vitamin D_3 compared to placebo in those with low FVD. In participants with baseline total 25(OH)D levels below the median (69.9 nmol/L; prespecified), there was a trend for greater attenuation of aBMD loss at the spine (p=0.066) and total hip (p=0.065) with vitamin D_3 supplementation vs. placebo. Using thresholds that were not pre-specified (<75, <50, <37 or <30 nmol/L), there were no differences in changes in aBMD between the vitamin D3 and placebo groups (Table 2). Only 24 participants had 25(OH)D levels <30 nmol/L.

In exploratory analyses (Appendix), among participants in the vitamin D_3 group, there was no beneficial effect on aBMD at any site between those who achieved 25(OH)D levels above vs. below the median (97.3 nmol/L) or FVD levels above or below the median (21.3 pmol/L) at 2 years.

Discussion

Supplemental vitamin D_3 (2,000 IU/day for two years) without calcium, compared with placebo, did not significantly benefit bone density or structure in this large VITAL ancillary

study. In contrast to our hypotheses, supplemental vitamin D_3 did not increase aBMD or prevent bone loss at the spine, hip, or whole body. Vitamin D_3 also did not improve or adversely affect total, trabecular, or cortical vBMD, cortical thickness, or bone strength at the radius or tibia compared to placebo. These effects were not modified by baseline BMI, FMI, age, race/ethnicity, or personal use of vitamin D supplements.

This VITAL ancillary study makes significant contributions to the literature as it is different than prior studies. This is the largest randomized, placebo-controlled study that assessed effects of daily, supplemental vitamin D on bone density and structure in the general U.S. population unselected for vitamin D insufficiency, and it is the first large RCT that measured FVD levels at baseline and 2-years follow-up.

RCTs of daily supplemental vitamin D on aBMD in the general population have shown either no benefits of vitamin D on aBMD or small improvements that have been interpreted as not clinically meaningful, consistent with our findings from our placebo-controlled VITAL ancillary study. A meta-analysis of RCTs found minimal differences (ranging 0.16% −0.76%) in aBMD between vitamin D and placebo groups at the spine, total hip, and femoral neck with no differences at the whole body.[15] Another meta-analysis also did not support vitamin D supplementation for primary prevention of osteoporosis in healthy adults.[14] In the New Zealand Vitamin D Assessment (ViDA) trial, bolus vitamin D supplementation of 100,000 IU/month vs. placebo for 2 years in community-dwelling older adults [baseline 25(OH)D ~55 nmol/L] attenuated bone loss at the hip by 0.5%.[17] In a 1-year RCT among postmenopausal women in Scotland [baseline 25(OH)D 33.7 nmol/L], 1,000 IU/day, but not 400 IU/day, of vitamin D prevented bone loss of ~0.6% at the hip but not at the spine.[44] However, two additional studies found no effect of vitamin D supplements on aBMD.[20,45]

A larger benefit may be seen in those with high fracture risk. While we found no benefit of vitamin D_3 supplementation in participants with osteopenia or osteoporosis, most were mildly osteopenic. Jennings et al. showed that vitamin D_3 supplementation (400 IU/day) had no effect on aBMD but, in exploratory analyses, attenuated femoral neck bone loss only in those with osteoporosis.[46] In a U.K. study in elderly women after osteoporotic hip fractures, vitamin D_3 supplementation vs. placebo also improved aBMD at the femoral neck by 1.1–3.3% and at the total hip by 2.1–4.6%.[47] In a RCT in the Netherlands of 348 elderly women at high fracture risk [mean age 80 years; baseline 25(OH)D ~26.0 nmol/L], 400 IU/day of vitamin D_3 vs. placebo improved femoral neck aBMD by 1.9% over two years.[16,48]

There may be a total 25(OH)D threshold below which vitamin D supplementation benefits bone health, but this level is debated. While the Institute of Medicine recommends 25(OH)D levels ≥50 nmol/L for 97.5% of the population and suggests <30 nmol/L as deficient,[49] the Endocrine Society and National Osteoporosis Foundation have recommended 25(OH)D levels >75 nmol/L and define 52–75 nmol/L as insufficient, particularly in those with osteoporosis.[50–54] Total 25(OH)D levels <25 nmol/L are associated with osteomalacia, reduced bone mineralization, low aBMD, and secondary hyperparathyroidism.[3,4] The ViDA trial found that among participants with low baseline 25(OH)D ≤30 nmol/L (n=25),

the placebo group had significant spine and femoral neck aBMD loss (~2%), compared to stable aBMD in the vitamin D_3 group; there was no difference in aBMD in participants with baseline 25(OH)D >30 nmol/L.[17] Post-hoc analyses of a United Kingdom (U.K.) trial in those with baseline total 25(OH)D levels ≤ 30 nmol/L, vitamin D supplements had a small treatment effect on spine and hip aBMD (0.6%).[44] In contrast to the studies in New Zealand and the U.K., in our VITAL ancillary study, we were unable to identify a vitamin D threshold for bone health using baseline total 25(OH)D levels of <30, <50 or <75 nmol/L. It is possible that our participants may have already reached the vitamin D level needed for bone health. The mean baseline 25(OH)D level of participants in this VITAL ancillary study was 69.1 nmol/L, 18.0% had 25(OH)D levels <50 nmol/L, and 3.1% <30 nmol/L (n=25). This is consistent with recent U.S. National Health and Nutrition Examination Survey data (2011–2014) showing that 2.9% of the population ≥60 years have 25(OH)D levels <30 nmol/L.[29] Since a small percentage of older U.S. adults have profound vitamin D deficiency,[29] it would be neither ethical nor feasible to perform a supplemental vitamin D_3 placebo-controlled study in this population.

There is limited research investigating the relationship between FVD levels and effects of supplemental vitamin D on aBMD. In a vitamin D dose-ranging study in 273 older women in the U.S. with low baseline total 25(OH)D levels ≤50 nmol/L, aBMD changes were not associated with baseline total 25(OH)D or FVD levels; however, the study was not powered to detect changes in aBMD with each of the 7 tested vitamin D doses.[55] We found that baseline FVD levels, compared to total 25(OH)D levels, may better predict improvements in aBMD at the spine and total hip, though changes were small (0.56–0.75%). Whether baseline FVD levels help to identify those more likely to benefit from supplementation warrants further study. Given multiple comparisons, these results should be interpreted with caution.

This VITAL ancillary study evaluated the surrogate mechanisms through which supplemental vitamin D affects bone health and potential fracture risk. Other factors such as poor physical performance or balance, certain medical conditions (poor vision, cognitive impairment, neurological diseases, hypotension, diabetes, among others) or other intrinsic and environmental factors that contribute to falls can impact the risk of fractures.[56–58] In a parallel ancillary study, we are adjudicating incident fractures in the overall VITAL cohort (n=25,871) for a median of 5.3 years to determine whether long-term vitamin D_3 supplementation reduces fracture risk in men and women nationwide.

This ancillary study to VITAL has many strengths, including being the largest RCT of supplemental vitamin D_3 on aBMD at the spine and hip, and vBMD, structure, and strength measures at the radius and tibia. This study had high retention (89%) and adherence (~92%) and power to detect small effects on aBMD, the primary outcome. This study also evaluated effects of vitamin D_3 supplementation vs. placebo on bone health measures and analyzed outcomes according to FVD levels. Additionally, the vitamin D assays were calibrated to CDC standards. There were also limitations. The timeline for the bone density and structure outcomes was limited to 2-years of follow-up. The results were not adjusted for multiple hypothesis testing, so the findings from the secondary and subgroup analyses should be interpreted as exploratory. These results do not generally apply to younger people or adults

with osteoporosis or those with profound vitamin D deficiency, who otherwise warrant treatment.

In summary, this placebo-controlled RCT found that daily vitamin D_3 supplementation for 2 years did not improve bone density or structure in the general population of older adults in the U.S. not selected for vitamin D insufficiency.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Potential conflicts of interest:

• Dr. LeBoff reports grants from NIH, during the conduct of the study.

• Dr. Chou has nothing to disclose.

• Ms. Murata has nothing to disclose.

• Ms. Donlon has nothing to disclose.

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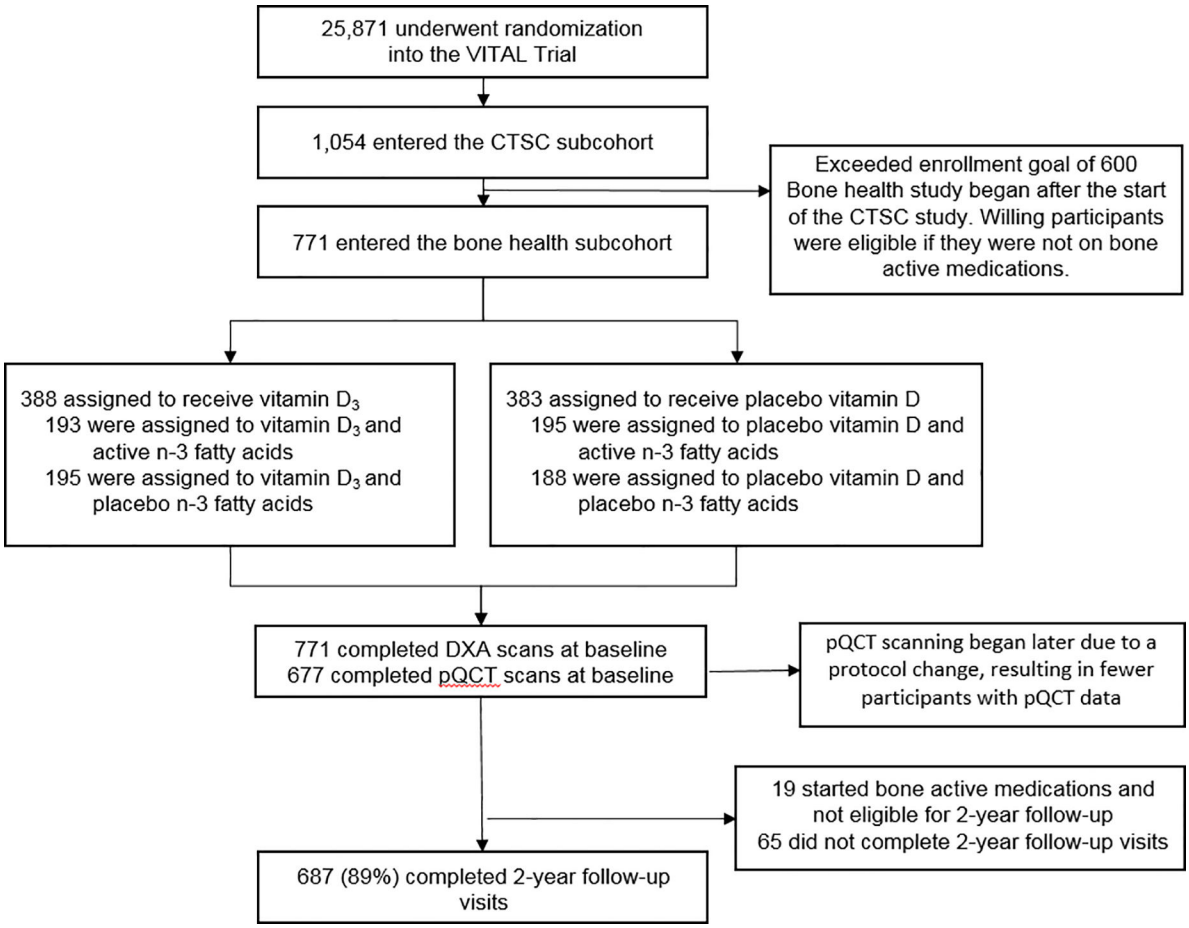

Figure 1.
Randomization and Follow-up of Participants

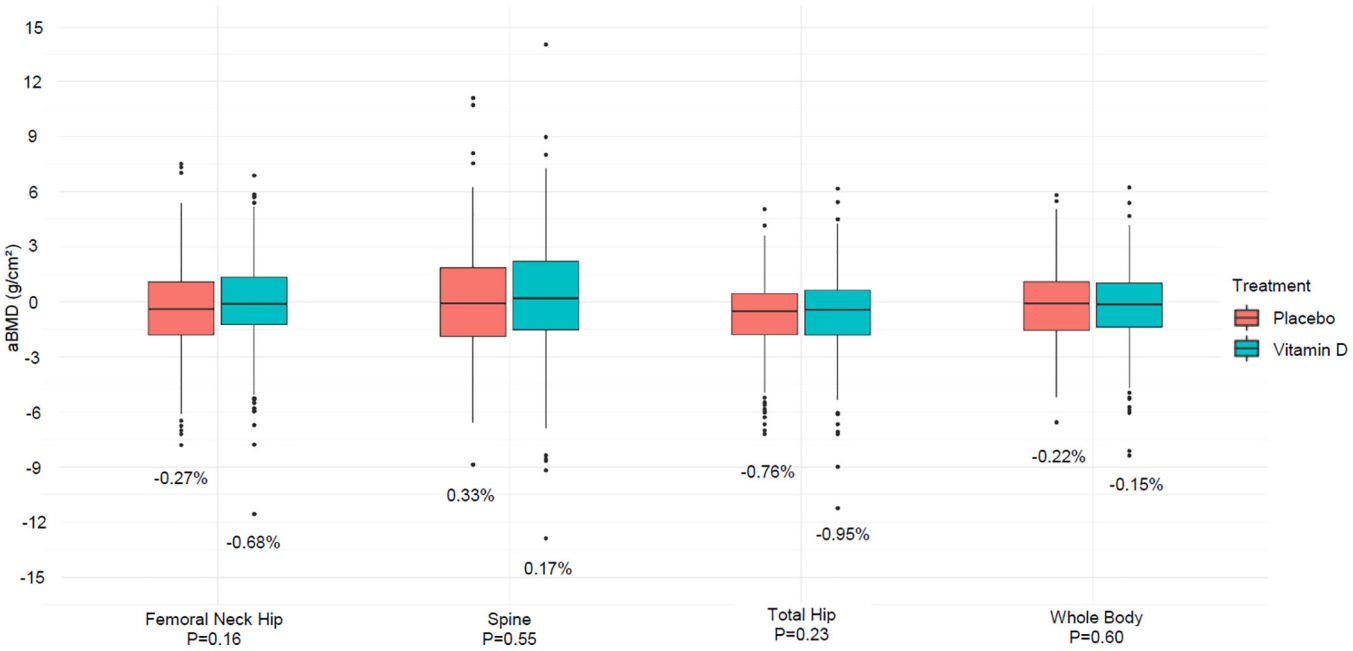

Figure 2.

Mean absolute changes in aBMD from baseline to 2 years in the vitamin D_3 and placebo groups. Percentages represent the percent change in aBMD over 2 years. All analyses adjusted for age, sex and race.

Table 1.

Characteristics of the Bone Health Subcohort at Baseline According to Randomized Assignment to Vitamin D_3 vs. Placebo Groups

Characteristic	Total (N=771)	Vitamin D_3 Group (N=388)	Placebo Group (N=383)	P-value
Female sex – no. (%) N=771	360 (46.7%)	179 (46.1%)	181 (47.3%)	0.76
Age – mean (SD) N=771	63.8 (6.1)	63.7 (6.0)	63.9 (6.3)	0.53
Race or ethnic group * – no. (%)	755 (97.9%)			0.28
Non-Hispanic white	630 (83.4%)	317 (82.8%)	313 (84.1%)	
Black	67 (8.9%)	35 (9.1%)	32 (8.6%)	
Nonblack Hispanic	26 (3.4%)	11 (2.9%)	15 (4.0%)	
Asian	15 (2.0%)	9 (2.4%)	6 (1.6%)	
Native American or Alaskan native	5 (0.7%)	2 (0.5%)	3 (0.8%)	
Other or unknown	12 (1.6%)	9 (2.4%)	3 (0.8%)	
Body mass index – mean (SD) kg/m^2 N=771	27.2 (4.8)	27.2 (4.7)	27.3 (4.8)	0.91
Fat mass index – mean (SD) kg/m^2 N=767	10.27 (3.89)	10.26 (4.03)	10.28 (3.74)	0.94
Leisure time physical activity – median (Interquartile Range) MET- hours/week N= 767	21.47 (7.86 – 37.11)	21.61 (7.86 – 37.80)	20.99 (7.97 – 36.00)	0.62
Diabetes history – no. (%) N= 770	84 (10.9%)	44 (11.4%)	40 (10.4%)	0.68
Current smoking – no. (%) N=766	48 (6.3%)	26 (6.8%)	22 (5.8%)	0.33
Any Fracture History † – no. (%) N=771	61 (7.9%)	32 (8.3%)	29 (7.6%)	0.73
Parental history of hip fracture – no. (%) N=733	102 (13.9%)	54 (14.8%)	48 (13.0%)	0.49
Baseline Calcium Supplement Use ‡ – no. (%) N=771	132 (17.1%)	69 (17.8%)	63 (16.5%)	0.62
Baseline Vitamin D Supplement Use ‡ – no. (%) N=771	326 (42.3%)	157 (40.5%)	169 (44.1%)	0.30
Baseline Total 25(OH)D § –mean (SD) nmol/L N=770	69.1 (22.7)	67.4 (22.2)	71.1 (23.2)	0.025
Baseline FVD – mean (SD) pmol/L N=770	14.6 (4.7)	14.4 (4.5)	14.8 (4.8)	0.21

* Race and ethnic groups self-reported by participants

† Of those who reported fractures, 16 had a history of a fragility fracture (hip, spine, shoulder and/or forearm fracture)

‡ Calcium supplement intake ≤1200 mg/day, Vitamin D intake ≤800 IU/day

§ To convert values of 25(OH)D to ng/ml, multiply by 0.4

Table 2.

Absolute 2-year Change in aBMD according to Subgroup, Comparing the Vitamin D_3 Group with the Placebo group

Subgroup	Spine aBMD					
	Vitamin D_3 Group		Placebo Group		P-value	P-value for Interaction
	N	Absolute Change (SD) g/cm^2	N	Absolute Change (SD) g/cm^2		
Sex						0.067
Female	149	−0.001 (0.036)	133	−0.008 (0.033)	P=0.062	
Male	177	0.007 (0.036)	174	0.010 (0.035)	P= 0.46	
Low Bone Density						**0.040**
Normal	110	0.002 (0.038)	114	0.009 (0.039)	P= 0.17	
Osteopenia/ Osteoporosis	209	0.003 (0.035)	192	−0.003 (0.032)	P= 0.067	
Race						0.83
Non-Hispanic White	267	0.003 (0.036)	248	0.002 (0.036)	P= 0.79	
Black	28	0.004 (0.044)	28	0.005 (0.035)	P= 0.89	
BMI (median)						0.13
< Median (26.45 kg/m^2)	165	0.000 (0.038)	152	−0.006 (0.032)	P= 0.12	
≥ Median (26.45 kg/m^2)	161	0.006 (0.034)	155	0.009 (0.037)	P= 0.52	
FMI						0.90
< Median (9.42 kg/m^2)	175	0.002 (0.036)	149	−0.001 (0.033)	P= 0.50	
≥ Median (9.42 kg/m^2)	149	0.006 (0.038)	158	0.004 (0.037)	P= 0.74	
Vitamin D supplement use at baseline ≤800 IU/day						0.88
Yes	134	0.003 (0.031)	138	0.000 (0.034)	P= 0.56	
No	192	0.004 (0.040)	169	0.003 (0.037)	P= 0.76	
Calcium supplement use at baseline ≤1200 mg/day						0.40
Yes	58	0.001 (0.033)	51	−0.007 (0.033)	P= 0.28	
No	268	0.004 (0.037)	256	0.003 (0.035)	P= 0.83	
Baseline Total 25(OH)D Level						0.09
< 75 nmol/L	209	0.006 (0.037)	165	0.000 (0.037)	P=0.10	
≥ 75 nmol/L	116	−0.001 (0.036)	142	0.004 (0.034)	P=0.24	
Baseline Total 25(OH)D Level						0.061
< Median (70 nmol/L)	179	0.006 (0.038)	138	−0.001 (0.035)	P= 0.066	
≥ Median (70 nmol/L)	146	0.001 (0.035)	169	0.004 (0.035)	P= 0.30	
Baseline Total 25(OH)D Level						0.42
<50 nmol/L	60	0.002 (0.040)	57	0.005 (0.036)	P= 0.76	
≥50 nmol/L	265	0.004 (0.036)	250	0.001 (0.035)	P= 0.39	
Baseline Total 25(OH)D Level						0.92

<37 nmol/L	29	0.005 (0.040)	20	0.005 (0.045)	P= 0.77	
≥37 nmol/L	296	0.003 (0.036)	287	0.002 (0.035)	P= 0.59	
Baseline Total 25(OH)D Level						0.14
<30 nmol/L	12	−0.014 (0.052)	10	0.017 (0.051)	P=0.17	
≥30 nmol/L	313	0.004 (0.036)	297	0.001 (0.035)	P=0.30	
Baseline FVD						**0.026**
< Median 14.2 pmol/L	171	0.008 (0.040)	149	−0.000 (0.034)	**P= 0.043**	
≥ Median 14.2 pmol/L	154	−0.001 (0.032)	158	0.003 (0.036)	P= 0.170	
Subgroup	**Total Hip aBMD**					
	Vitamin D_3 Group		**Placebo Group**		**LSmean, (95% CI), P-value**	**P-value for Interaction**
	N	**Absolute Change (SD) g/cm^2**	**N**	**Absolute Change (SD) g/cm^2**		
Sex						0.48
Female	152	−0.012 (0.024)	150	−0.016 (0.022)	P= 0.20	
Male	188	−0.003 (0.023)	189	−0.004 (0.020)	P= 0.684	
Low Bone Density						0.32
Normal	112	−0.003 (0.025)	118	−0.007 (0.021)	P= 0.12	
Osteopenia/ Osteoporosis	214	−0.009 (0.023)	206	−0.010 (0.022)	P= 0.73	
Race						0.81
Non-Hispanic White	282	−0.008 (0.024)	277	−0.009 (0.021)	P= 0.44	
Black	27	−0.003 (0.022)	28	−0.006 (0.018)	P= 0.56	
BMI (median)						0.31
< Median (26.45 kg/m^2)	173	−0.007 (0.020)	166	−0.007 (0.018)	P= 0.96	
≥ Median (26.45 kg/m^2)	167	−0.007 (0.027)	173	−0.010 (0.024)	P= 0.13	
FMI						0.52
< Median (9.42 kg/m^2)	183	−0.005 (0.021)	161	−0.006 (0.019)	P= 0.84	
≥ Median (9.42 kg/m^2)	154	−0.009 (0.027)	178	−0.012 (0.023)	P= 0.19	
Vitamin D supplement use at baseline ≤800 IU/day						0.79
Yes	141	−0.008 (0.024)	148	−0.009 (0.020)	P= 0.67	
No	199	−0.007 (0.024)	191	−0.009 (0.022)	P= 0.24	
Calcium supplement use at baseline ≤1200 mg/day						0.73
Yes	59	−0.009 (0.027)	54	−0.012 (0.019)	P= 0.46	
No	281	−0.007 (0.023)	285	−0.008 (0.022)	P= 0.32	
Baseline Total 25(OH)D Level						0.09
< 75 nmol/L	216	−0.005 (0.026)	183	−0.009 (0.023)	P=0.09	
≥ 75 nmol/L	123	−0.010 (0.020)	156	−0.008 (0.020)	P=0.59	
Baseline Total 25(OH)D Level						0.064
< Median (70 nmol/L)	185	−0.005 (0.025)	148	−0.010 (0.022)	P= 0.065	
≥ Median (70 nmol/L)	154	−0.010 (0.022)	191	−0.008 (0.021)	P= 0.68	

Baseline Total 25(OH)D Level						0.18
<50 nmol/L	62	−0.003 (0.029)	60	−0.011 (0.022)	P= 0.12	
≥50 nmol/L	277	−0.008 (0.023)	279	−0.008 (0.021)	P= 0.61	
Baseline Total 25(OH)D Level						0.12
<37 nmol/L	30	0.000 (0.028)	20	−0.013 (0.024)	P= 0.096	
≥37 nmol/L	309	−0.008 (0.024)	319	−0.009 (0.021)	P= 0.49	
Baseline Total 25(OH)D Level						0.36
<30 nmol/L	13	0.002 (0.026)	10	−0.010 (0.028)	P=0.29	
≥30 nmol/L	326	−0.007 (0.024)	329	−0.009 (0.021)	P=0.33	
Baseline FVD						**0.047**
< Median 14.2 pmol/L	175	−0.004 (0.024)	159	−0.009 (0.023)	**P= 0.044**	
≥ Median 14.2 pmol/L	164	−0.010 (0.024)	180	−0.008 (0.020)	P= 0.62	

All analyses adjusted for age, sex, and race

Table 3.

2-year Changes in pQCT Measurements

	Vitamin D_3 Group		Placebo Group		
pQCT Measurements	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**P-value**
Radius					
Total vBMD (mg/cm^3)					
Baseline	326	369.678 (69.484)	321	373.903 (72.498)	
Year 2	282	376.236 (74.480)	278	382.252 (71.676)	
% Change	277	2.16%	269	1.23%	P=0.31
Trabecular vBMD (mg/cm^3)					
Baseline	326	196.447 (43.156)	321	202.796 (46.074)	
Year 2	282	199.563 (44.647)	278	205.112 (46.019)	
% Change	277	0.59%	269	−0.21%	P=0.099
Bone Strength Index (mg*mm)					
Baseline	326	46.429 (19.223)	321	46.160 (18.378)	
Year 2	282	47.066 (19.627)	278	47.722 (18.932)	
% Change	277	1.48%	269	0.76%	P=0.44
Cortical vBMD (mg/cm^3)					
Baseline	311	1197.75 (31.572)	308	1196.98 (30.816)	
Year 2	258	1199.41 (33.686)	257	1201.55 (30.098)	
% Change	246	0.16%	239	0.22%	P=0.49
Cortical Thickness (mm)					
Baseline	311	3.271 (0.584)	308	3.221 (0.595)	
Year 2	258	3.248 (0.605)	257	3.200 (0.603)	
% Change	246	−1.59%	239	−1.64%	P=0.997
Polar Stress Strength Index (mm^3)					
Baseline	311	291.559 (98.278)	308	277.702 (91.069)	
Year 2	258	297.382 (103.180)	257	280.804 (94.408)	
% Change	246	0.23%	239	0.18%	P=0.94
Tibia					
Total vBMD (mg/cm^3)					
Baseline	331	295.291 (48.045)	330	299.232 (49.285)	
Year 2	294	296.756 (49.312)	284	303.213 (48.755)	
% Change	291	0.05%	283	0.26%	P=0.30
Trabecular vBMD (mg/cm^3)					
Baseline	331	246.626 (40.741)	330	250.139 (42.283)	
Year 2	294	249.300 (41.539)	284	254.067 (42.019)	
% Change	291	0.47%	283	0.42%	P=0.76
Bone Strength Index (mg*mm)					

	Vitamin D_3 Group		Placebo Group		
pQCT Measurements	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**P-value**
Baseline	331	105.338 (38.119)	330	106.355 (38.763)	
Year 2	294	106.951 (39.314)	284	109.583 (39.621)	
% Change	291	0.26%	283	0.48%	P=0.56
Cortical vBMD (mg/cm^3)					
Baseline	322	1167.39 (32.258)	329	1162.02 (30.375)	
Year 2	294	1169.98 (32.739)	285	1166.38 (30.624)	
% Change	283	0.24%	285	0.25%	P=0.92
Cortical Thickness (mm)					
Baseline	322	5.670 (0.881)	329	5.648 (0.907)	
Year 2	294	5.645 (0.914)	285	5.659 (0.905)	
% Change	283	−0.74%	285	−0.56%	P=0.24
Polar Stress Strength Index (mm^3)					
Baseline	322	1922.60 (542.988)	329	1867.05 (520.903)	
Year 2	294	1948.58 (557.398)	285	1904.76 (529.863)	
% Change	283	0.42%	285	0.41%	P=0.65

All analyses adjusted for age, sex, and race