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Baseline characteristics of participants in the VITamin D and OmegA-3 TriaL (VITAL): Effects on Bone Structure and Architecture

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ABSTRACT

Vitamin D supplements are often used to benefit skeletal health, although data on effects of daily high-dose vitamin D alone on bone density and structure are lacking. The ongoing *VITamin D and OmegA-3 TriaL* (VITAL) is a double-blind, randomized, placebo-controlled trial testing effects of high-dose supplemental vitamin D_3 (cholecalciferol; 2000 IU/day) and/or omega-3 fatty acids (FAs; 1 g/day) for the primary prevention of cancer and cardiovascular disease. The study has a mean treatment period of 5 years among 25,874 U.S. men ≥50 years and women ≥55 years old from all 50 states. The ancillary study, *VITAL: Effects on Bone Structure and Architecture*, is testing effects of vitamin D_3 and/or omega-3 FAs on musculoskeletal outcomes and body composition in a subcohort of 771 participants. At in-person visits at the Harvard Catalyst Clinical and Translational Science Center (CTSC), participants completed bone density/architecture, body composition, and physical performance assessments at baseline and two-year follow-up. Baseline characteristics were evenly distributed among treatment groups, suggesting that any uninvestigated confounders will be evenly distributed; sex differences were also analyzed. Future analyses of the two-year follow-up visits will elucidate whether daily high-dose, supplemental vitamin D_3 and/or omega-3 FAs improve musculoskeletal outcomes, helping to advance clinical and public health recommendations.

Clinical trial registration number: NCT01747447.

1. Introduction

There are high prevalences of osteoporosis and vitamin D deficiency in the U.S. Osteoporosis is the most common bone disease and is characterized by reduced bone mass, architectural deterioration, an imbalance in bone turnover, and compromised bone strength, which lead to increased fracture risk. Over 53.6 million Americans have osteoporosis or low bone mass [1]. Additionally, one in two women and one in five men aged 50 years and older will suffer an osteoporotic fracture in their remaining lifetime [2,3]. Structural changes in bone, body composition, and clinical risk factors including vitamin D deficiency contribute to the development of osteoporosis. About 1/3 of individuals living in North America are vitamin D deficient (< 20 ng/mL of 25-hydroxyvitamin D [25(OH)D]) [4]. Vitamin D deficiency is more prevalent in black individuals because of reduced activation of vitamin D after ultraviolet B radiation exposure [5,6]. Overweight individuals are also more likely to be vitamin D deficient because vitamin D is sequestered in fat [7].

In addition to correcting low vitamin D levels, supplemental vitamin D is widely used to promote bone health, reduce fractures, and prevent functional decline. However, clinical trials and meta-analyses show inconsistent results as to whether supplemental vitamin D alone improves musculoskeletal health outcomes [8–29]. While randomized controlled trials (RCTs) provide the highest quality data, available studies are limited by designs that included supplemental calcium combined with vitamin D, vitamin D doses < 1000 IU/day, bolus doses of vitamin D, studies of short duration, and/or failure to measure 25(OH)D levels.

Studies of the effects of omega-3 FAs on bone health are limited. In vitro studies have shown that omega-3 FAs suppress osteoclast formation [30], and animal studies have shown a reduction in bone resorption and some improvements in skeletal health [31–37]. However,

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observational and case-control studies have produced varying results [38–40], and data from large RCTs of omega-3 FAs' effects on bone mineral density (BMD) and structure are sparse and overall do not seem to show a benefit [41–43].

The *VITamin D and OmegA-3 TriaL (VITAL)* is a large, double-blind RCT testing whether high-dose supplemental vitamin D_3 (2000 IU/day) and/or omega-3 FAs (1 g/day) is effective in the primary prevention of cancer and cardiovascular disease [44]. The *VITAL: Effects on Bone Structure and Architecture* study is one of two ancillary studies evaluating effects of supplemental vitamin D alone on musculoskeletal outcomes [45]. In this study, detailed in-person assessments at the Harvard Catalyst CTSC were performed in a subcohort of participants (n = 771) at baseline and two years of follow-up. The study aims to determine whether supplemental vitamin D alone benefits BMD, bone structure, body composition, and physical performance measures. A complementary ancillary study, *VITAL: Effects on Fractures*, is determining effects of these interventions on incident fractures among the 25,874 VITAL participants nationwide. In this article, we present the baseline demographic, bone, body composition, physical performance, health and behavioral characteristics of the VITAL CTSC Bone Health subcohort by randomized treatment groups to assess the distribution among the interventions and whether there are sex differences in these baseline measures.

2. Materials and methods

2.1. Overview of study design

The study design was previously described [45,46]. VITAL is a large, randomized, 2 × 2 factorial, double-blind, placebo-controlled trial testing the risks and benefits of supplemental vitamin D_3 (cholecalciferol, 2000 IU/day) and marine omega-3 FAs (Omacor® fish oil, eicosapentaenoic acid [EPA] + docosahexaenoic acid [DHA]; 1 g/day) on cardiovascular disease and cancer. The mean length of treatment was 5 years, which ended on December 31, 2017. VITAL- Bone Health consists of two ancillary studies, *VITAL: Effects on Fractures* and *VITAL: Effects on Bone Structure and Architecture*, which build upon the resources and design of the parent VITAL study to test effects of supplemental vitamin D_3 and/or omega-3 FAs on skeletal health. In this study, *VITAL: Effects on Bone Structure and Architecture*, a subcohort of participants (n = 771) completed detailed phenotyping, bone health, body composition, and physical performance assessments at baseline and two-year post-randomization at the Harvard Catalyst CTSC in Boston. The baseline visits took place between January 2012 and March 2014, and the two-year follow-up visits occurred between October 2014 and July 2016. The primary aims of this ancillary study are to determine whether supplemental vitamin D_3 and/or omega-3 FAs positively affects areal bone mineral density (aBMD) at the spine, total hip, femoral neck, and whole body as assessed by dual-energy X-ray absorptiometry (DXA), as well as biomarkers of bone remodeling. Blood samples are frozen at −80 °C so that baseline and two-year follow-up bone turnover makers will be measured in the same assay. Levels of 25(OH)D, EPA and DHA will also be measured in these blood samples to assess study pill compliance and to determine the effects of the interventions on study outcomes. The secondary aim of this study is to determine whether supplemental vitamin D_3 and/or omega-3 FAs improves structure and architecture at the radius and tibia as assessed by peripheral quantitative computed tomography (pQCT). High-resolution pQCT (HR-pQCT) was also performed among a subset of participants during the two-year follow-up visits. The tertiary aim is to determine whether supplemental vitamin D_3 and/or omega-3 FAs has beneficial effects on body composition and physical function. Biomarkers of bone remodeling, pQCT, and HR-pQCT measures will be presented in future publications. Studies were approved by the Partners Human Research Committees, the Institutional Review Board of Brigham and Women's Hospital.

2.2. Study population

Women and men were eligible for the parent VITAL study if they were ≥55 years and ≥50 years old, respectively, without previous history of cardiovascular disease or cancer. Safety exclusions included allergy to soy or fish, renal failure, hypercalcemia, hypo- or hyperparathyroidism, severe liver disease, granulomatous disease, or other serious illness. Participants were randomized after they completed a detailed consent form and a 3-month placebo run-in phase. If participants demonstrated good compliance during the placebo run-in phase (took at least 2/3 of their study pills), they were randomized into the trial. Participants agreed to limit their total personal supplemental vitamin D intake to ≤800 IU/day, total supplemental calcium to ≤1200 mg/day, and to refrain from taking supplemental fish oil. A total of 25,874 participants from all 50 states, including 5107 African Americans were randomized into the trial between November 2011 and March 2014. The intervention phase of VITAL ended on December 31, 2017. Follow-up questionnaires will continue for an additional two years after the intervention phase is completed.

A subcohort of VITAL participants who lived within driving distance of Boston were enrolled into the CTSC subcohort (n = 1054). Participants were eligible for the *VITAL: Effects on Bone Structure and Architecture* ancillary study if they met requirements for the parent trial and were not on bisphosphonates within the past two years or other bone active medications including, denosumab, human parathyroid hormone, calcitonin, raloxifene, tamoxifen, or systemic estrogens within the past year. No participants were on aromatase inhibitors in the VITAL CTSC Bone Health subcohort. Of 1054 participants in the CTSC subcohort, 771 completed bone density, body composition, and physical performance assessments.

2.3. Bone measures

Areal BMD at the lumbar spine (L1-L4), right and left hip (total hip and femoral neck), and whole body was measured using DXA (Discovery W, APEX Software Version 4.2, Hologic, Bedford, MA). Guidelines from Hologic and the International Society for Clinical Densitometry (ISCD) were followed for positioning of all DXA scans. Left and right hip measures were averaged in our analyses; when only one hip was available due to metal artifact(s), only the unaffected hip was used. T-scores were generated using the default sex and ethnicity-matched databases in the Hologic APEX Software 4.2. Z-scores were generated using the age, sex, and ethnicity-matched results from the same default databases [47]. In the DXA Hologic system, American Indians and Alaskan Natives were compared to the white database [48] and Hispanic white participants were compared to the Hispanic database [49]. Reproducibility is very good at our site [50]. Least significant change (LSC) 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. Lumbar spine DXA scans were used to generate the Trabecular Bone Score (TBS; Version 2.1, Medimaps Group, Geneva, Switzerland). TBS is a textural analysis that can predict fracture risk independent of BMD [51]. Scores ≥1.350 signify normal microarchitecture, between 1.200 and 1.350 partially degraded microarchitecture, and ≤1.200 degraded microarchitecture [52,53]. The Fracture Risk Assessment Tool (FRAX), included in the APEX Software Version 4.2, predicted 10-year probability for major osteoporotic fractures (MOF) and hip fractures in participants with low bone mass (osteopenia; T-scores from −1.1 to −2.4 at the spine, hip, or femoral neck).

When participants had internal metal (i.e. hip/knee replacements), the bone measures from the unaffected, contralateral side were used to replace the affected side to prevent metal from confounding and increasing the bone density results (n = 62) [54]. When there was not an unaffected contralateral side to represent (i.e. metal in the spine, bilateral hip/knee replacements), bone measures were excluded at that