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Effects of vitamin D_3 supplementation on lean mass, muscle strength and bone mineral density during weight loss: A double-blind randomized controlled trial

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Abstract

Objectives—To compare 12 months of vitamin D_3 supplementation versus placebo on lean mass, bone mineral density and muscle strength in overweight or obese postmenopausal women completing a structured weight-loss program.

Design—Double-blind, placebo-controlled randomized clinical trial.

Setting—Fred Hutchinson Cancer Research Center, Seattle, WA.

Participants—218 postmenopausal (50-75 y) women, BMI ≥25 kg/m^2, with serum 25-hydroxyvitamin D (25(OH)D) concentrations ≥10 −<32 ng/mL (i.e. insufficient).

Intervention—2000 IU/day oral vitamin D_3 or placebo in combination with a lifestyle-based weight loss intervention consisting of 500-1000 kcal/day reduction and 225 mins/week of moderate-to-vigorous intensity aerobic exercise.

Measurements—Serum 25(OH)D, body composition and muscle strength were measured pre-randomization (baseline) and at 12 months. Mean changes were compared between groups (intent-to-treat) using generalized estimating equations.

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Results—Change in 25(OH)D was significantly different between vitamin D and placebo groups at 12 months (+13.6 vs −1.3 ng/mL, p<0.0001); however, no differences in change in lean mass (Vit D:−0.8 kg vs P:−1.1 kg, p=0.53), bone mineral density of the spine (Vit D:−0.01 g/cm^2 vs P: 0.0 g/cm^2, p=0.82) or right femoral neck (both −0.01 g/cm^2, p=0.49) were detected between groups. Leg strength decreased significantly in the vitamin D group compared to placebo (Vit D: −2.6 lbs vs P:+1.8 lbs, p=0.03). Among women randomized to vitamin D, achieving repletion (25(OH)D ≥32 ng/mL) did not alter results.

Conclusion—Vitamin D_3 supplementation during weight-loss decreased leg strength but did not alter changes in lean mass or bone mineral density compared to placebo among postmenopausal women with vitamin D insufficiency.

Keywords

25-hydroxyvitamin D; caloric restriction; exercise; obesity; strength

INTRODUCTION

The benefit of weight loss for chronic disease prevention among older obese adults is controversial because of concerns over the potentially deleterious loss of muscle and bone mass, leading to greater frailty and increased risk of fracture.[1-3] Greater bone loss has been observed in postmenopausal women undergoing caloric restriction compared to women on a weight maintenance diet,[4, 5] with some evidence that changes in bone mineral density during weight reduction may differ between predominantly trabecular (e.g. vertebrae) and cortical bones.[4, 6, 7] Moreover, decreases in bone density associated with diet-induced weight loss in postmenopausal women do not correct to pre-weight loss levels with weight regain.[8]

Some studies have suggested that exercise may help prevent weight-loss-related muscle and bone loss.[9, 10] However, in a randomized trial of postmenopausal women undergoing weight loss, women randomized to a diet + aerobic exercise program (which yielded a mean 11% weight loss), experienced a significant reduction in bone mass compared to control women (−2.2% vs 0.3%, p=0.03) despite completing a mean 171.7 (± 62.7) mins/week of moderate to vigorous exercise.[11]

Low serum vitamin D [routinely measured by the major circulating vitamin D metabolite, 25-hydroxyvitamin D (25(OH)D)], is more prevalent among obese individuals than normal weight peers,[12] potentially compounding the health risks associated with obesity. Recent population prevalence estimates of vitamin D insufficiency (25(OH)D <30 ng/mL) based on meta-analysis were 69.5% and 86.4% among US and European adults, respectively.[13] Low serum 25(OH)D is associated with muscle weakness, poor physical function and frailty,[14-16] as well as with an increased risk of falls among older adults.[17]

Vitamin D has direct effects on bone and muscle function including calcium absorption, direct bone mineralization, and suppression of bone turnover.[18,19, 20]. Randomized, placebo-controlled trials have demonstrated that vitamin D supplementation can reduce rates of bone loss,[21, 22] and reduce risk of falls in older adults.[23]. Vitamin D receptors are also present in human skeletal muscle,[24, 25] and vitamin D_3 administration has been shown to increase

muscle strength in women deficient in vitamin D, if provided in doses similar to those in this study,[26, 27] but not in low doses.[28]. However, the mechanisms underlying these observed associations remain incompletely understood[26, 27, 29] and whether vitamin D supplementation can attenuate any deleterious effects of weight loss on these outcomes remains unknown.

The purpose of this study was to investigate the effects of 12 months of oral vitamin D_3 supplementation (2000 IU/day) versus placebo on changes in lean mass, muscle strength and bone mineral density (BMD) during a structured behavioral weight loss program among overweight or obese postmenopausal women with insufficient levels of circulating vitamin D (serum 25(OH)D ≥10 − <32 ng/mL). We hypothesized that women randomized to 2000 IU vitamin D_3 compared to placebo would experience a smaller loss in lean mass, greater improvements in muscle strength and an attenuated reduction in BMD in response to weight loss.

METHODS & PROCEDURES

The Vitamin D, Diet and Activity (ViDA) study, conducted from September, 2010 to August 2012 in Seattle, WA, was a 12-month double-blind, placebo-controlled randomized clinical trial testing oral vitamin D_3 supplementation (cholecalciferol, 2000 IU/day) vs. placebo on weight and related biomarkers in overweight and obese postmenopausal women. A dose of 2000 IU was chosen because at the time of trial initiation the Institute of Medicine recommended an upper limit of 2000 IU/day for vitamin D supplements.[30] The primary outcome was weight loss. Secondary outcomes included changes in body composition and serum biomarkers (insulin, C-reactive protein).[31] All study procedures were reviewed and approved by the Fred Hutchinson Cancer Research Center Institutional Review Board in Seattle, WA, and all participants provided signed Informed Consent.

Participant Recruitment, Inclusion and Exclusion Criteria

The target population for the ViDA study included postmenopausal women, aged 50-75 years, who were overweight or obese (body mass index (BMI) ≥25 kg/m^2, or ≥23 kg/m^2 for Asian-American women) with serum 25(OH)D concentrations ≥10 ng/mL and <32 ng/mL (“insufficient”). Exclusion criteria included: currently taking >400 IU vitamin D from supplemental sources; diagnosed osteoporosis or a T score of −2.5 SD or less as measured by dual energy X-ray absorptiometry (DXA); renal disease or history of kidney stones; diagnosed diabetes; severe congestive heart failure; history of breast cancer or other invasive cancer excluding non-melanoma skin cancer; use of hormone replacement therapy within the past 6 months; alcohol intake in excess of 2 drinks/day; current smoking; contraindication to taking 2000 IU vitamin D_3/day; history of bariatric surgery; use of weight loss medications; and additional factors that might interfere with measurement of outcomes or with the success of the intervention (e.g. inability to attend facility-based sessions).

Study Design and Randomization

Recruitment, randomization and study procedures have been previously described.[31] Briefly, of 498 women who met initial eligibility criteria and were invited for vitamin D screening, 310 were eligible based on study 25(OH)D criteria, 264 underwent a clinic screening interview, and 218 women were randomized into the study.

Following baseline data collection, eligible women were randomized in a 1:1 ratio by permuted blocks into either: i) lifestyle-based weight loss program + 2000 IU/day oral vitamin D_3 (n=109) or ii) lifestyle-based weight loss program + daily placebo (n=109). The random assignment was generated by a computerized program, stratified according to BMI (<30 kg/m^2 or ≥30 kg/m^2) and consent for optional subcutaneous fat biopsies. All study staff except statisticians were blinded to randomization status. The number of women randomized to each arm did not differ by season (Chi-square test p>0.999).

Vitamin D Preparation and Dose

The vitamin D_3 preparation (2000 IU cholecalciferol) and matching placebo (sunflower oil) gel capsules were created and bottled in unmarked containers by J.R. Carlson Laboratories, Inc. (Arlington, IL). Two matching bottles, each containing a 6-month supply of capsules, were prepared for each participant. Quality assurance protocols verified that the contents of the study capsules matched the assigned content provided by the lab in a 10% subsample.

Weight Loss Intervention

The ViDA weight loss program included both a diet and exercise component, adapted from a successful intervention based on the Diabetes Prevention Program and Look Ahead lifestyle change weight loss programs[32, 33] that we have used in a similar population of overweight and obese postmenopausal women.[34] The intervention has been previously described in detail.[31]

The goals of the diet program were: total daily energy intake of 1200-2000 kcal/day based on baseline weight, less than 30% daily energy intake from fat, and a 10% reduction in body weight by 6 months with maintenance thereafter to 12 months. Diets were not supplemented with calcium but women were advised on how to obtain sufficient calcium in their diets. The nutrition program, led by behaviorally-trained registered dieticians, was delivered in groups and individual sessions.

The goal of the exercise program was: ≥45 minutes of moderate-to-vigorous intensity exercise, 5 days per week (225 min/week) for 12 months. Women attended two sessions per week at our study facility where they were supervised by an exercise physiologist, and performed their remaining sessions at home. Facility-based exercise consisted of treadmill walking or jogging, stationary bicycling, and use of other aerobic machines, while a variety of home exercises were encouraged including walking/hiking, aerobics, and bicycling.

Study Measures and Data Collection

All measures were taken at baseline (pre-randomization) and at 12 months. Participants completed a series of questionnaires to assess demographic information, medical history,

health habits, reproductive and body weight history, dietary intake (via 120-item self-administered food frequency questionnaire)[35] and supplement use, and physical activity patterns via the International Physical Activity Questionnaire (IPAQ).[36] Habitual sun exposure was assessed by a series of questions for which categorical response options were provided.[37] Participants also wore pedometers (H215-S, Bestek Electronics, Taiwan) while awake for 7 consecutive days at baseline and 12 months in order to determine an average daily step count.

Anthropometric measures were taken using standard methods and BMI (kg/m^2) was calculated. Waist circumference, measured at the iliac crest using a fiberglass tape and rounded to the nearest 0.5 cm, was taken in duplicate and averaged. Lean mass, appendicular lean mass (upper and lower limb muscular mass), and BMD of the spine (posterior-anterior L1-L4 vertebrae) and right femoral neck (lowest value from the proximal femur, femoral neck or trochanter)[38] were measured using a dual x-ray absorptiometry (DXA) whole-body scanner (GE Lunar, Madison, WI) with participants in a supine position. T-scores (number of standard deviations below the average BMD for a young adult reference population at peak bone density) were provided by the manufacturer, and a skeletal muscle index [SMI=appendicular lean mas (kg)/ height $(m)^2$] was calculated to determine the prevalence of sarcopenia (SMI ≤ 5.67 kg/m^2) according to consensus recommendations.[39]

One repetition-maximum (1 RM) strength testing was performed by a trained exercise physiologist according to the guidelines of the American College of Sports Medicine.[40] One-RM tests are the standard for dynamic strength assessment and the protocol includes basic familiarization and practice sessions immediately prior to the test in order to reduce any possibility of injury. A chest press (upper-body) and leg press (lower-body) were performed by each participant unless there was contraindication to doing so.

Serum 25(OH)D

Serum vitamin D was measured as previously described[31] from blood collected at baseline and at 12 months, after 12 hours fasting, 24 hours without exercise, and 48 hours without alcohol. Blood was processed within 1 hour and serum stored at −70°C until analysis. Assays were performed using DiaSorin LIAISON 25-OH Vitamin D Total assay.[41, 42] The inter- and intra-assay coefficients of variability (CVs) for this assay were 11.2 % and 8.1%, respectively.

Study Medication Adherence

At randomization, participants received a 6-month supply of study medications. Medication bottles were returned at 6 months; remaining capsules were counted before a second 6-month supply was provided. At 12 months, the second bottle and any remaining capsules were returned and counted.

Safety/Adverse Effects

All women were interviewed after 1, 3, 6, 9 and 12 months of study participation for any signs or symptoms of vitamin D toxicity or other adverse events. Reports were reviewed by a physician's assistant with appropriate follow-up as necessary. Summary data were

reviewed according to study group by an independent Data and Safety Monitoring Committee at 6-month intervals. No serious adverse events were reported.

Statistical Analysis

Age-adjusted partial correlation coefficients were calculated between baseline measures of body composition, strength and serum 25(OH)D. Mean changes in 25(OH)D, muscle strength, lean mass and BMD from baseline to 12 months, stratified by study arm, were computed. The intervention effect on these variables was examined based on the assigned treatment at randomization, regardless of adherence or study retention (i.e. intent-to-treat).

Mean 12-month changes in the vitamin D group were compared to controls (placebo) using the generalized estimating equations (GEE) modification of linear regression to account for intra-individual correlation over time. Models were initially unadjusted, and subsequently adjusted for age, race/ethnicity (white, other), baseline BMI, baseline serum 25(OH)D, season of randomization, average sun exposure, vitamin D intake (diet + non-study supplements), calcium intake (diet + supplements), and protein intake. The GEE approach for mixed-model regression using the available data was applied to address missing data. Additional analyses were based on post-hoc analyses of specific subgroups. No women were taking bisphosphonates, selective estrogen receptor modulators, or other prescription osteoporosis treatment drugs. One participant reported taking prednisone during the study period. We found no effect of excluding her data from analyses; therefore, her data were retained for all analyses.

Among women randomized to receive vitamin D, changes in the outcome measures were also compared according to 12-month change in serum 25(OH)D (median split), and in women who did vs. did not become replete (≥32 ng/mL). Other subgroup analyses compared changes in outcomes in women with and without complete pill counts, in women with serum 25(OH)D <20 ng/mL at baseline, and in women who did vs. did not meet the criteria for sarcopenia (SMI ≤5.67 kg/m^2). These analyses also considered potential confounders as listed above.

All analyses were performed using SAS software version 9.2 (SAS Institute Inc., Cary, NC).

RESULTS

Participants

The baseline characteristics of women randomized to the study are shown in **Table 1**; their mean age and BMI were 59.6 ± 5.1 years and 32.4 ± 5.8 kg/m^2, respectively. The majority were non-Hispanic White (86%) and college graduates (76%). At 12 months, 182 women (83%) underwent a DXA scan and 170 (78%) completed a test of muscle strength; 30 (14%) did not complete the study. There was no significant change in average sun exposure over 12 months between study arms (p=0.11).[31]

Adherence to Interventions

No significant differences in adherence to the weight loss program were detected between study arms. Women randomized to vitamin D attended a mean 56.1% of all diet counseling

sessions and completed a mean (SD) 138 (147) mins/wk of moderate-to-vigorous physical activity while women in the placebo arm attended a mean 59.5% of diet sessions and completed a mean (SD) 147 (140) mins/wk of physical activity. The 12-month change in vitamin D intake from dietary sources and supplements did not differ between study arms (p=0.60), nor did any other major component of dietary intake, with the exceptions of dietary protein (Vit D:1.5 vs. P: 0.3 g/d, p=0.006) and omega-3 fatty acids (Vit D: −0.4 vs. P: −0.1 g/d, p=0.02).

Serum 25(OH)D increased a mean 13.6 ng/mL in the vitamin D arm and decreased a mean 1.3 ng/mL in the placebo arm over 12 months (p<0.0001). Complete (6 and 12 month) study medication counts were obtained for 120 women (Vit D: N=59 (54%); P: N=61 (56%)). Among those with medication counts, vitamin D medication adherence was 97.9%; placebo adherence was 95.8%.

Baseline Associations

At baseline, serum 25(OH)D concentration was positively associated with total vitamin D intake (r=0.20, p=0.02) but not significantly associated with BMI (r= −0.09, p=0.21), waist circumference (r= −0.13, p=0.07), or % lean mass (r= 0.11, p=0.12), after adjusting for age. Serum 25(OH)D was not significantly associated with muscle strength of the chest or legs, or with BMD of the spine or right femoral neck (all p>0.47).

Intervention Effects

At 12 months, no significant differences were detected between groups for total weight loss (Vit D: −8.2% vs P: −8.4%, p=0.66), change in lean mass (Vit D: −0.8 kg vs P: −1.1 kg, p=0.53) or appendicular lean mass (both groups: −0.1 kg, p=0.11) (**Table 2**). No between-group differences were detected with respect to the 12-month change in upper-body muscle strength (Vit D: −0.9 lbs vs P: −3.6 lbs), while leg strength significantly decreased in the vitamin D group compared to placebo (Vit D:−2.6 lbs vs P:+1.8 lbs, p=0.03). Changes in BMD of the spine and femoral neck were small and not significantly different between groups. The intervention effects on fat mass, insulin and c-reactive protein have been previously published.[31]

Although a greater magnitude of change in serum 25(OH)D was significantly associated with greater weight loss in the vitamin D group (p=0.03), a greater increase in 25(OH)D was not significantly associated with an attenuated loss of lean mass, BMD, or muscle strength after adjustment for potential confounders (**Table 3**).

Among women randomized to vitamin D supplementation, no significant differences in outcomes were detected between women whose serum 25(OH)D remained below 32 ng/mL compared to women who became replete (≥32 ng/mL) (**Table 4**). In a subsample of women with more severe vitamin D insufficiency (i.e., serum 25(OH)D <20 ng/mL) at baseline (n=87), we observed no significant differences in any outcome except spine BMD where there was a greater 12-month loss in bone density in the placebo group compared to women receiving vitamin D (−0.02 g/cm^2 vs. −0.01 g/cm^2, p=0.01); however group sizes were

small. (**Supplemental Table S1**). No significant effect modification by either age (≥65 y vs. <65 y) or % weight loss (≥7% vs. <7%) was detected (results not shown).

In the small subsample of women (n=57, 26%) who met the criteria for sarcopenia at baseline, no significant differences between study arms were detected; however, sarcopenic women receiving vitamin D (n=34) did show modestly more favorable changes in lean mass (Vit D:−0.24 kg vs P:−0.34 kg), appendicular lean mass (Vit D:0.51 kg vs P:0.34 kg), right femoral neck BMD (Vit D:0.01 g/cm^2 vs P:−0.02 g/cm^2), and upper body strength (Vit D: −1.97 lbs vs P:−5.33 lbs) compared to women receiving placebo [data not shown, all p>0.05].

Analyses limited to women with complete study medication pill counts (n=120, 55%), among whom adherence was 97%, showed similar results to the overall study sample; only a significant difference in change in leg strength was detected between groups (vitamin D: −10.7 lbs vs placebo: +7.3 lbs, p<0.01) (**Table 5**).

DISCUSSION

Previous studies have demonstrated that vitamin D supplementation can reduce rates of bone loss[22] and improve muscle strength in vitamin D–deficient women.[26, 27] However, in this randomized controlled trial, 12 months of daily 2000 IU oral vitamin D_3 supplementation did not alter changes in lean mass or BMD compared to placebo among women participating in a diet + exercise weight loss program.

Contrary to our hypothesis, women receiving vitamin D experienced a significant decrease in leg muscle strength compared with those receiving placebo, with three women in the placebo group and six women receiving vitamin D exhibiting large decreases in leg strength (60-100 lbs) over 12 months that skewed the findings in the overall and subgroup analyses. It is not clear whether this is by chance or causally related to vitamin D supplementation. A recent study in 107 frail, obese older adults demonstrated that a multi-component exercise program consisting of flexibility exercises, progressive resistance training, and aerobic exercise added to caloric restriction that resulted in 9% weight loss attenuated the loss of thigh muscle volume and total hip BMD compared to participants in a diet-alone condition.[43] Moreover, the participants completing the diet + exercise program experienced an increase in knee flexion and extension strength, despite a modest decrease in thigh muscle volume.[43] All participants received 1,500 mg calcium + 1,000 IU vitamin D supplementation/day throughout the 12-month study, resulting in a mean increase in 25(OH)D of approximately 5 ng/mL (from 20.9 to 25.6 ng/mL in the diet + exercise arm); thus, any independent effect of vitamin D supplementation could not be determined.

One potential explanation for the decreased leg strength observed in our study is the use of a maximal strength test (1-RM) protocol in this sample of older women and the possibility that some women may have been less inclined to exert maximal effort at the end of the study compared to pre-randomization. Maximal strength protocols have been used in other studies of older adults;[29, 44] however, substantial differences in measures of muscular strength may explain, in part, the heterogeneity of findings with respect to the effect of vitamin D on

muscle strength.[29, 45, 46]. Previous studies of vitamin D supplementation have demonstrated changes in strength using measures such as hand and lower limb maximal isometric voluntary contraction strength with computerized dynamometers and maximal leg extension power [29]. Careful attention to the selection of muscular strength measures in future studies is warranted in order to be appropriate for the study population as well as the nature and duration of the intervention, and to best allow comparison with existing research.

Previous weight loss studies in older adults have shown similar reductions in lean mass and BMD as what we observed in this study. For example, Villareal et al.[44] reported a mean (SD) −1.8 ± 1.7 kg change in lean mass and −0.011 ± 0.026 g/cm^2 change in BMD of the total hip in adults ≥65 years who were randomized to a diet + exercise weight loss program that resulted in a mean total weight loss of 8.6 ± 3.8 kg over 12 months. However, to our knowledge, no other studies have examined the potential benefits of vitamin D supplementation during a behavioral weight loss program as a potential antidote to the loss of lean mass and BMD. Only one other trial has specifically tested the effect of vitamin D (12 months, 3332 IU daily, N= 138 women aged 18-70 yrs, BMI>27) in combination with a 6-month dietary weight loss program[47] but the assessment of body composition was limited to body fat measured by bioelectrical impedance, therefore we cannot make any direct comparisons to the present study.

A limitation of the current study is the fact that we did not include women with serum 25(OH)D concentrations below 10ng/mL, among whom the effect of vitamin D supplementation on muscle and bone outcomes during weight loss could be more pronounced. We may also have observed stronger effects by excluding women with baseline serum 25(OH)D ≥20 ng/mL or in a sample limited to women who met the criteria for sarcopenia. For example, a recent meta-analysis of 23 randomized trials suggested a small overall benefit of vitamin D supplementation on BMD at the femoral neck with greater positive effects seen in populations with circulating vitamin D <15 ng/mL,[48] while another meta-analysis found that vitamin D supplementation was associated with greater strength gains in people with serum 25(OH)D <12 ng/mL.[29]. Additional limitations include that we tested only one dose of supplementation, did not measure parathyroid hormone or test the independent effects of vitamin D without a weight loss intervention, and had complete study medication counts for only 55% of participants. Finally, our study population was relatively homogeneous, and thus our results may not be generalizable to other racial/ethnic groups or to men. Strengths of our study include its double-blind randomized controlled design, its relatively long duration compared to most other vitamin D supplementation studies, and the use of DXA to measure lean mass and bone density at multiple sites.

Our results suggest that vitamin D repletion in healthy postmenopausal women with insufficient 25(OH)D undergoing behavioral weight loss should conform to standard adult guidelines for vitamin D supplementation,[49] and that loss of lean mass and bone density that results from moderate weight loss cannot be attenuated with 2000 IU vitamin D supplementation. Our small subgroup analysis in women with sarcopenia at baseline showed modest, albeit not significant, favorable changes in lean mass, femoral neck BMD and upper-body strength associated with vitamin D supplementation during weight loss. Thus, the effect of vitamin D supplementation in adults with sarcopenic obesity[50] for whom the

deleterious loss of further muscle and bone mass may be of greater concern warrants future investigation, as does the potential effect of repletion in women with more severe 25(OH)D deficiency.

Other methods to attenuate bone loss and strength reductions in older women undergoing lifestyle change to lose weight should be investigated, such as strength training,[51-53] calcium,[54] and, for women at risk for osteoporotic fractures, medications to reduce bone resorption or increase bone formation.[55, 56]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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List of Abbreviations

25(OH)D	25-Hydroxyvitamin D
BMD	Bone Mineral Density
BMI	Body Mass Index
CI	Confidence Interval
DXA	Dual X-ray Absorptiometry
IPAQ	International Physical Activity Questionnaire
IU	International Units
RM	Repetition Maximum
SD	Standard Deviation
SMI	Skeletal Muscle Index
ViDA	Vitamin D, Diet and Activity

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Table 1

Selected baseline characteristics of study participants.

Variable	N (%) or Mean (SD)		
	All (n=218)	Placebo (n=109)	Vitamin D (n=109)
Age (years)	59.6 (5.1)	59.0 (4.7)	60.3 (5.3)
Weight (kg)	87.7 (16.3)	88.1 (17.1)	87.4 (15.5)
BMI (kg/m^2)	32.4 (5.8)	32.5 (6.1)	32.3 (5.5)
Body Fat (%)	47.4 (4.9)	47.5 (4.5)	47.3 (5.2)
Waist circumference (cm)	100.1 (12.3)	100.3 (13.5)	100.0 (11.0)
Race/Ethnicity [n, (%)]			
Non-Hispanic White	188 (86.2)	94 (86.2)	94 (86.2)
Non-Hispanic Black	13 (6.0)	6 (5.5)	7 (6.4)
Hispanic	5 (2.3)	4 (3.7)	1 (0.9)
Other (American Indian, Asian or Unknown)	12 (5.5)	5 (4.6)	7 (6.4)
College graduate [n, (%)]	161 (73.9)	79 (72.5)	82 (75.2)
Moderate to vigorous physical activity (min/wk)	142.2 (143.2)	146.6 (140.4)	137.9 (146.5)
Energy intake (kcal/d)†	2004 (699.3)	1982 (678)	2025 (722)
Relative % energy from fat	33.0 (6.2)	32.6 (5.7)	33.4 (6.7)
Relative % energy from protein	17.6 (3.2)	17.9 (3.5)	17.2 (2.9)
Relative % energy from carbohydrate	48.3 (7.4)	48.1 (7.1)	48.5 (7.8)
Dietary vitamin D intake (IU)	264 (184)	276 (208)	252 (160)
Vitamin D supplement intake (IU)	280.0 (134.5)	303.6 (125.2)	262.7 (140.5)
Total calcium intake, diet + supplement (mg)	1120 (600)	1170 (633)	1071 (564)
Sun exposure (hrs/wk)‡	2.4 (1.3)	2.2 (1.3)	2.5 (1.3)
Serum 25(OH)D (ng/mL)	21.4 (6.1)	21.4 (6.1)	21.4 (6.2)

†Values derived from FFQ were truncated <600 kcal and >4000 kcal

‡Calculated based on average exposure between 1000 and 1600; reported separately for weekdays and weekends.

Table 2

12-month change in serum 25(OH)D, weight, lean mass, bone mineral density and muscle strength by study arm.

	PLACEBO						VITAMIN D_3							
	N	**Baseline Mean (SD)**	**N**	**12 month Mean (SD)**	**Change**	**%**	**N**	**Baseline Mean (SD)**	**N**	**12 month Mean (SD)**	**Change**	**%**	***p****	***p**†*
Serum 25(OH)D (ng/mL)	109	21.4 (6.1)	94	20.1 (6.7)	−1.3	−6.2	109	21.4 (6.2)	93	35.0 (9.4)	13.6	63.4	<.0001	<.0001
Weight (kg)	109	88.1 (17.1)	94	80.7 (17.6)	−7.4	−8.4	109	87.4 (15.5)	94	80.2 (15.6)	−7.1	−8.2	0.66	0.41
BMI (kg/m^2)	109	32.5 (6.1)	94	29.7 (6.1)	−2.8	−8.8	109	32.3 (5.5)	94	59.5 (5.6)	−2.8	−8.7	0.67	0.58
Body Fat (%)	107	47.5 (4.5)		44.0 (7.0)	−3.5	−7.4	108	47.3 (5.2)	90	43.1 (7.5)	−4.1	−8.7	0.58	0.70
Lean mass (kg)	107	41.5 (6.5)	91	40.4 (6.4)	−1.1	−2.6	108	41.4 (5.0)	90	40.6 (4.7)	−0.8	−2.0	0.86	0.53
Lean mass (%)	107	48.0 (4.5)	91	51.3 (6.8)	3.3	6.9	108	48.4 (5.2)	90	52.3 (7.5)	3.9	8.1	0.60	0.76
Appendicular lean mass	107	16.7 (2.6)	91	16.6 (2.5)	−0.1	−0.2	108	16.8 (2.3)	90	16.7 (2.0)	−0.1	−0.7	0.12	0.11
R femoral neck BMD (g/cm^2)	106	0.97 (0.12)	92	0.96 (0.12)	−0.01	−1.18	106	0.96 (0.11)	88	0.95 (0.10)	−0.01	−1.16	0.77	0.49
R femoral neck BMD T-score	104	−0.3 (1.0)	92	−0.4 (1.0)	−0.1	36.3	106	−0.4 (0.8)	87	−0.5 (0.8)	−0.1	22.1	0.73	0.90
Spine BMD (g/cm^2)	106	1.16 (0.17)	92	1.16 (0.17)	0.0	0.02	108	1.15 (0.14)	90	1.13 (0.14)	−0.01	−1.28	0.62	0.82
Spine BMD T-score	105	−0.2 (1.4)	93	−0.2 (1.4)	0.0	8.9	108	−0.3 (1.2)	89	−0.4 (1.2)	−0.1	53.1	0.81	0.90
Muscle Strength														
1-RM chest press (lbs)	109	56.2 (15.3)	87	52.6 (14.8)	−3.6	−6.3	106	53.8 (13.8)	83	52.9 (15.6)	−0.9	−1.6	0.22	0.42
1 RM leg press (lbs)	106	178 (51.6)	84	180 (48.8)	1.8	1.0	107	176 (42.4)	82	172 (42.6)	−4.0	−2.3	0.03	0.03

BMI=Body Mass Index; BMD=Bone Mineral Density; RM= Repetition Maximum

*GEE model comparing the 12-mo change between vitamin D vs. placebo; all available data, unadjusted

†Adjusted for age, race/ethnicity, season of randomization, baseline serum 25(OH)D, baseline BMI, vitamin D intake (diet + non-study supplement), calcium intake (diet + non-study supplement), protein intake, and average sun exposure

Table 3

Baseline and 12 month outcome measures, stratified by median split* of change in serum 25(OH)D in women receiving 2000 IU/day vitamin D_3.

	Mean (SD)					
	Baseline	**12 month**	**Change**	***p***	***p†***	***p‡***
Weight (kg)						
Placebo	88.1 (17.1)	80.7 (17.6)	−7.4	*ref*		
<12.4 ng/mL	88.6 (16.6)	83.6 (16.8)	−5.0	0.09	*ref*	*ref*
≥12.4 ng/mL	86.2 (13.9)	76.6 (13.7)	−9.6	0.05	0.002	0.03
p_{trend}						
Lean Mass (%)						
Placebo	48.0 (4.5)	51.3 (6.8)	3.3	*ref*		
<12.4 ng/mL	48.96 (5.1)	51.8 (7.3)	2.9	0.45	*ref*	*ref*
≥12.4 ng/mL	48.4 (5.5)	52.9 (7.7)	4.6	0.17	0.06	0.25
p_{trend}						
Lean Mass (kg)						
Placebo	41.5 (6.5)	40.4 (6.4)	−1.1	*ref*		
<12.4 ng/mL	42.3 (4.9)	41.6 (5.1)	−0.7	0.25	*ref*	*ref*
≥12.4 ng/mL	41.1 (4.8)	39.6 (4.1)	−1.4	0.11	0.02	0.07
p_{trend}						
Appendicular Lean Mass (kg)						
Placebo	16.68 (2.6)	16.64 (2.5)	−0.04	*ref*		
<12.4 ng/mL	17.31 (2.0)	17.0 (1.9)	−0.27	0.24	*ref*	*ref*
≥12.4 ng/mL	16.62 (2.5)	16.41 (2.2)	−0.21	0.19	0.87	0.59
p_{trend}				0.15		
Spine BMD (g/cm^2)						
Placebo	1.16 (0.17)	1.16 (0.17)	0.0	*ref*		
<12.4 ng/mL	1.15 (0.13)	1.14 (0.14)	0.0	0.54	*ref*	*ref*
≥12.4 ng/mL	1.11 (0.13)	1.12 (0.14)	0.0	0.76	0.76	0.39
p_{trend}				0.69		
Spine T-score						
Placebo	−0.16 (1.4)	−0.17 (1.4)	−0.01	*ref*		
<12.4 ng/mL	−0.27 (1.1)	−0.30 (1.2)	−0.03	0.66	*ref*	*ref*
≥12.4 ng/mL	−0.54 (1.1)	−0.52 (1.1)	0.02	0.87	0.79	0.26
p_{trend}				0.81		
Right Femoral Neck BMD (g/cm^2)						
Placebo	0.97 (0.12)	0.96 (0.12)	−0.01	*ref*		
<12.4 ng/mL	0.96 (0.10)	0.96 (0.10)	0.0	0.2	*ref*	*ref*
≥12.4 ng/mL	0.95 (0.09)	0.94 (0.09)	−0.01	0.62	0.14	0.12
p_{trend}				0.79		

	Mean (SD)					
	Baseline	**12 month**	**Change**	***p***	***p†***	***p‡***
Right Femoral Neck T-score						
Placebo	−0.26 (1.0)	−0.36 (1.0)	−0.1	*ref*		
<12.4 ng/mL	−0.41 (0.8)	−0.39 (0.8)	0.02	0.33	*ref*	*ref*
≥12.4 ng/mL	−0.48 (0.8)	−0.57 (0.7)	−0.1	0.26	0.08	0.10
p_{trend}				0.36		
Muscle Strength						
1-RM chest press (lbs)						
Placebo	56.2 (15.3)	52.6 (14.8)	−3.6	*ref*		
<12.4 ng/mL	53.1 (15.6)	52.5 (12.3)	−0.7	0.14	*ref*	*ref*
≥12.4 ng/mL	55.5 (13.1)	53.4 (18.6)	−2.2	0.59	0.75	0.92
p_{trend}				0.48		
1-RM leg press (lbs)						
Placebo	177.8 (51.6) 175.7	179.6 (48.8) 174.3	1.8	*ref*		
<12.4 ng/mL	(51.2) 179.1	(49.6) 168.3	−1.40	0.25	*ref*	*ref*
≥12.4 ng/mL	(33.2)	(34.9)	−10.8	0.006	0.33	0.80
p_{trend}				0.01		

BMD=Bone Mineral Density; RM= Repetition Maximum

p=Compared to placebo, unadjusted

$p^{\dagger}$= Compared to lowest median split category of change in 25(OH)D, unadjusted

$p^{\ddagger}$Compared to lowest median split category of change in 25(OH)D, adjusted for age, race-ethnicity, season of randomization, baseline BMI, baseline 25(OH)D, total vitamin D intake (diet + non-study supplements), total calcium intake (diet + supplements), protein intake, average sun exposure

Table 4

Change in lean mass, muscle strength and bone mineral density in women randomized to 2000 IU vitamin D_3/day who did vs. did not become replete (25(OH)D ≥32ng/mL) by 12 months

	25(OH)D <32ng/mL		25(OH)D ≥32ng/mL			
	Baseline Mean (SD)	**Change**	**Baseline Mean (SD)**	**Change**	***p1***	***p2***
Serum 25(OH)D	19.2 (5.5)	7.2	23.5 (5.7)	18.02	<0.001	<0.001
Lean mass (kg)	41.8 (4.6)	2.8	41.7 (5.2)	4.3	0.82	0.83
Lean mass (%)	47.9 (5.3)	−1.2	49.3 (5.3)	−1.1	0.11	0.33
Appendicular lean mass (kg)	17.1 (2.2)	−0.3	16.9 (2.4)	−0.2	0.93	0.98
R femoral neck BMD (g/cm^2)	0.94 (0.09)	0.0	0.96 (0.10)	−0.01	0.44	0.75
R femoral neck BMD T-score	−0.5 (0.8)	0.0	−0.4 (0.8)	−0.1	0.74	0.93
Spine BMD (g/cm^2)	1.14 (0.13)	0.0	1.12 (0.13)	0.0	0.6	0.39
Spine BMD T-score	−0.3 (1.0)	−0.1	−0.5 (1.1)	0.0	0.89	0.49
Muscle Strength						
1-RM chest press (lbs)	50.9 (13.3)	1.4	56.9 (14.8)	−6.0	0.14	0.23
1 RM leg press (lbs)	171.5 (49.1)	2.3	181.7 (37.7)	−10.2	0.09	0.59

BMD=Bone Mineral Density; RM= Repetition Maximum

p1 Unadjusted

p2 Adjusted for age, ethnicity, baseline BMI, baseline serum 25(OH)D, season of randomization, vitamin D intake (diet + supplements), total calcium intake, protein intake (g/day), average sun exposure

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Table 5

12-month change in serum 25(OH)D, weight, lean mass, bone mineral density and muscle strength in women with complete pill counts.

	PLACEBO (n=61)			VITAMIN D_3 (n=59)				
	Baseline Mean (SD)	**12 month Mean (SD)**	**Change**	**Baseline Mean (SD)**	**12 month Mean (SD)**	**Change**	***p* ***	***p* †**
Serum 25(OH)D (ng/mL)	21.4 (6.1)	20.2 (6.8)	−1.1	21.1 (5.6)	36.8 (9.0)	15.7	<0.001	<0.001
Weight (kg)	86.8 (16.9)	79.3 (16.7)	−7.5	85.9 (14.4)	76.7 (13.2)	−9.1	0.23	0.14
Lean mass (kg)	40.1 (5.4)	39.3 (5.2)	−0.8	41.2 (4.8)	40.1 (4.4)	−1.1	0.89	0.79
Lean mass (%)	47.6 (4.4)	51.0 (6.8)	3.4	48.8 (5.6)	53.3 (7.6)	4.6	0.20	0.17
Appendicular lean mass (kg)	16.2 (2.4)	16.2 (2.2)	0.05	16.6 (2.3)	16.5 (2.1)	−0.13	0.45	0.44
R femoral neck BMD (g/cm^2)	0.96 (0.12)	0.95 (0.11)	−0.01	0.94 (0.10)	0.94 (0.10)	−0.01	0.58	0.57
R femoral neck BMD T-score	−0.39 (0.92)	−0.44 (0.90)	−0.05	−0.51 (0.77)	−0.57 (0.75)	−0.06	0.89	0.88
Spine BMD (g/cm^2)	1.14 (0.17)	1.15 (0.17)	0.0	1.13 (0.14)	1.13 (0.15)	0.0	0.38	0.30
Spine BMD T-score	−0.29 (1.42)	−0.27 (1.41)	−7.88	−0.45 (1.16)	−0.42 (1.25)	−6.79	0.5	0.31
Muscle Strength								
1-RM chest press (lbs)	55.9 (15.3)	52.1 (15.3)	−3.8	54.3 (14.9)	50.9 (12.4)	−3.4	0.63	0.90
1 RM leg press (lbs)	170.8 (46.9)	178.2 (49.6)	7.3	182.2 (40.0)	171.5 (45.4)	−10.7	0.001	0.004

BMD=Bone Mineral Density; RM= Repetition Maximum

* GEE model comparing the 12-mo change between vitamin D vs. placebo; all available data, unadjusted.

† Adjusted for age, race/ethnicity, season of randomization, baseline serum 25(OH)D, baseline BMI, vitamin D intake (diet + non-study supplement), calcium intake (diet + non-study supplement), protein intake, and average sun exposure.

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