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Randomized, Blinded Trial of Vitamin D₃ for Treating Aromatase Inhibitor-Associated Musculoskeletal Symptoms (AIMSS)

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Abstract

Purpose—To evaluate the efficacy and safety of vitamin D₃ at 4,000 IU/day as a treatment option for aromatase inhibitor-associated musculoskeletal symptoms (AIMSS) when compared with the usual care dose of 600 IU D₃.

Methods—Single site randomized, double-blind, phase 3 clinical trial in women with AIMSS comparing change in symptoms, reproductive hormones and AI pharmacokinetics. Postmenopausal women 18 years with stage I-III breast cancer, taking AI and experiencing AIMSS (Breast Cancer Prevention Trial Symptom Scale-Musculoskeletal Subscale 1.5 (BCPT-MS)) were admitted. Following randomization, 116 patients had a run-in period of 1 month on 600 IU D₃, then began the randomized assignment to either 600 IU D₃ (n=56) or 4,000 IU D₃ (n=57)

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The study was registered in ClinicalTrials.gov (NCT01509070) and conducted under IND #114046.

Compliance with Ethical Standards

No conflicts of interest reported by any of the authors.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent was obtained from all individual participants for whom identifying information is included in this article.

daily for 6 months. The primary endpoint was change in AIMSS from baseline (after 1 month run-in) on the BCPT-MS (general musculoskeletal pain; joint pain; muscle stiffness; range for each question: 0=not at all to 4=extremely).

Results—Groups had no statistically significant differences demographically or clinically. There were no discernable differences between the randomly allocated treatment groups at 6 months in measures of AIMSS, pharmacokinetics of anastrozole and letrozole, serum levels of reproductive hormones, or adverse events.

Conclusions—We found no significant changes in AIMSS measures between women who took 4000 IU D₃ daily compared with 600 IU D₃. The 4000 IU D₃ did not adversely affect reproductive hormone levels or the steady state pharmacokinetics of anastrozole or letrozole. In both groups, serum 25(OH)D remained in the recommended range for bone health (≥ 30 ng/mL) and safety (<50 ng/mL).

Keywords

arthragias; vitamin D₃; aromatase inhibitors; breast cancer

INTRODUCTION

Vitamin D₃ has emerged as a potential treatment for aromatase inhibitor (AI)–associated musculoskeletal symptoms (AIMSS).[1–6] AIMSS is characterized by a cluster of musculoskeletal symptoms that includes bone, muscle and joint pain, muscle stiffness, carpal tunnel syndrome, tenosynovitis and allodynia.[7–13] These symptoms are also common in vitamin D deficiency.[14,15]

Vitamin D (D) has a role in maintaining the integrity of the collagen-rich osteoid surface of the skeleton. In D insufficiency a demineralization of this matrix beneath the periosteum may contribute to pressure and pain.[14,16,17] The active hormone 1α,25-dihydroxyvitamin D₃ promotes muscle cell growth, which may lead to improved muscle function[18,19] and a decrease in skeletal pain, thus providing biological rationale for the efficacy of D₃ in treating AIMSS. Supplemental vitamin D is prescribed for woman with AIMSS, often in doses exceeding the IOM and NCCN guidelines.[20,21] However, caution is warranted with use of high dose D₃ in oncology patients due to negative outcomes reported with dietary supplement use.[22,23] Specific to D₃, a U-shaped outcome response curve indicates a narrow range of serum 25(OH)D levels that corresponds to good clinical outcomes.[24–26]

To inform clinical practice, we conducted a randomized, double-blind, controlled clinical trial in women with AIMSS, comparing the IOM tolerable upper intake levels (high-dose D₃ 4,000 IU/day) to the recommended dietary allowance (RDA-600 IU/day) as set by the Institute of Medicine.[20] Safety was assessed by examining the effects of D₃ on AI drug metabolism (letrozole and anastrozole) and on reproductive hormone levels.

METHODS

Study Design

This was a randomized, double-blind, single-site, phase 3 clinical trial conducted at Fraumshuh Cancer Center (FRCC), a community-based oncology practice of Park Nicollet Health Services in Minneapolis, MN.

Study Participants

The study was approved by the Institutional Review Boards at Park Nicollet Institute and the University of Minnesota. Informed consent was obtained before any study procedures.

Participants were enrolled between March 2012 and March 2014 and were randomly assigned (1:1) to the usual care dose of 600 IU D₃ or high-dose of 4,000 IU D₃, plus 1,000 mg calcium carbonate. Once enrolled, participants began a 4-week run-in period with 600 IU D₃ to allow serum levels to begin to normalize. After the run-in period, participants began in randomized groups and treatment duration was 6 months. Cholecalciferol (D₃) supplements were encapsulated and coded bottles prepared at Daily Manufacturing, Inc. (Rockwell, NC). Stability was tested at the beginning of the study and yearly thereafter. The un-blinded biostatistician assigned coded bottles according to a blocked-randomization design in SAS v9.3 (2011; Cary, North Carolina). All study participants, their providers and research staff remained blinded throughout the study.

The primary study endpoint was the change in musculoskeletal symptoms (MS) between groups from baseline to 6 months. Secondary aims included an assessment of drug-nutrient interactions between D₃ and anastrozole and letrozole, AI adherence, and the effects of D₃ on reproductive hormone levels.

This study was open to post-menopausal women >18 years of age, with stage I-III breast cancer, being treated with anastrozole, letrozole or exemestane for at least 30 days and experiencing AIMSS at enrollment (prior to the run-in period). AIMSS were considered present and clinically significant if participants had a score of ≥1.5 on the Breast Cancer Prevention Symptom Scales-MS subscale (BCPT-MS), regardless of temporal association with the start of AI therapy. This cut off of 1.5 was based on our previous study.[27] Patients were excluded if they had received previous AI treatment, had a history of rheumatoid arthritis, hypercalcemia or were taking excluded medications (see Figure 1). Patients unwilling to discontinue other oral supplements containing D₃ and/or calcium were also excluded. Patients with osteoporosis were admitted if fracture risk was low as determined by a research rheumatologist, based on age, densitometry, and other bone mineral density-independent risk factors according to the WHO Fracture Risk Assessment tool (FRAX).[28]

Adherence

Adherence to assigned D₃ supplements was determined by pill counts at each in-person study visit. Medication adherence to AI was monitored through weekly diaries.

AIMSS Measures

The BCPT-MS, and the physical function subscales on the Australian/Canadian Osteoarthritis Hand Index Version 3.1 (AUSCAN)[29,30] and the Western Ontario and McMaster Osteoarthritis Index Version 3.1 (WOMAC)[31] are responsive to changes in AIMSS and the description and rationale for the use of these symptom scales in evaluating AIMSS interventions has been previously reported.[27] Higher scores on these measures represent worse symptoms. Measures of musculoskeletal pain, both general and pain specific to hands, knees and hip joints, and physical functioning were collected at baseline and 6 months. Change in scores from baseline (following run-in with 600 IU D₃) and after 6 months were compared. Assessments included The BCPT-MS,[27,32] the Patient-Reported Outcomes Measurement Information System (PROMIS) Physical Functioning Short Form[33] (higher scores reflect better physical functioning) and the maximum handgrip strength test (HGST) on the dominant hand (lower scores represent worse symptoms) (Jamar Hydraulic Hand Dynamometer (Sammons Preston Rolyan, Bolingbrook, IL).[34] The AUSCAN and WOMAC were later added to the study schedule.

Biological Measures

Serum 25(OH)D was measured by chemiluminescent immunoassay (Liaison/Liaison XL analyzer, DiaSorin, Stillwater, MN) at baseline and 6 months and safety assessments at 1.5 and 3 months. Park Nicollet Methodist Hospital Laboratory participates in CAP external proficiency testing. The lowest concentration that can be reported is 4 ng/mL. Assay imprecision (CVs) are 8.9% and 7.7% at 15 and 50 ng/mL, with intra-assay precisions of 1.6% and 3.1% respectively over the course of the study. Free 25(OH)D levels were measured by the Free 25(OH)D Vitamin D ELISA, a quantitative immunoassay measuring the concentration of free, bioavailable 25(OH)D in serum (Future Diagnostics Solutions B.V. Wijchen, Netherlands). The limit of detection is 1.9 pg/mL and CVs are 10.2%, 7.6%, and 5.5% at 6, 10.9, and 24.9 pg/mL.

Pharmacokinetic studies were performed on plasma samples collected from heparinized tubes at baseline and 6 months and stored at -70 C until analyzed. Three samples were drawn from each patient at each occasion: fasting, then 2 and 4 hours after AI dose. Steady State was assumed for all studies. The plasma concentrations of anastrozole and letrozole were determined using validated liquid chromatography tandem mass spectrometry methods.[35] The lower limits of quantitation were 0.05 ng/mL.

Serum hormone levels were measured using available serum or plasma samples that were stored at -70 C until analyzed. Estrone, estradiol and testosterone were quantified using organic solvent extraction and Celite column partition chromatography followed by radioimmunoassay.[36,37] The assay sensitivities were 2 pg/mL for estrone, 1 pg/mL for estradiol and 15pg/mL for testosterone. Sex hormone binding globulin was measured on an Immulite Analyzer (Siemens Healthcare Diagnostics, Deerfield, IL) with a sensitivity of 1 nM. Free testosterone was calculated using a validated algorithm.[38–40] The intra-assay CVs range between 4.0% and 7.5% for all the compounds, while the inter-assay CVs range between 8.0% and 13%.

Analgesic Use

The use of analgesics was recorded for each of the 7 days before AIMSS measures (baseline and 6-month visits). Analgesics were defined as any medication (including over-the-counter) or dietary supplements used to decrease any pain or discomfort in muscles or joints (e.g., NSAIDs, aspirin, prescription anti-inflammatory, opioid and non-opioid analgesics, glucosamine/chondroitin).

Sun Exposure, Exercise and Physical/Occupational Therapy

Sun exposure was ascertained with questions modified from Glanz et al[41] for exposure for 7 days before the baseline and 6-month visits, trips to sunny locations and the use of protective clothing and sunscreen over the 6-month study period. Participants reported exercise using the exercise questionnaire grid from the Harvard Nurses' Health Study II converted into weekly metabolic equivalent hours[42] for the month before the baseline and 6 months visits. Physical and occupational therapy visits (PT/OT) at baseline and 6 months were verified via electronic medical records.

Sample Size

Sample size calculations were based on a change in BCPT-MS score of 0.62. We have previously demonstrated the BCPT-MS is sensitive to detect changes in AIMSS over a 6-month period and that a change of 0.62 in this symptom scale represents a clinically significant change.[27] Assuming a two-tailed test with $\alpha=0.05$, power=80%, and standard deviation of 1.18, sample size of 116 (58 per group) would detect a difference of 0.62 in mean scores (moderate effect size of 0.525).

Statistical Analyses

All statistical analyses were intent-to-treat using SAS v9.3 (2011; Cary, North Carolina). Baseline characteristics were compared between groups using independent t-tests for continuous variables and chi-square for categorical variables. For variables that were not normally distributed, log transformations were successfully used to achieve normality in the analyses.

Analysis of covariance (ANCOVA) was used to determine if the change in AIMSS from baseline to 6 months differed between the two groups. The 6-month AIMSS scores were the dependent variables. Independent variables used in the models were group assignment and baseline AIMSS scores. Covariates that affect AIMSS were entered into the models and included months on AI (< 6 months/ 6 months), chemotherapy (y/n), taxane use (y/n), musculoskeletal comorbidities (y/n), medications that affect AIMSS (statins, NSAIDs, SSRIs, pain medications), and season of blood draws (Spring-Summer April 1st to September 30th or Fall-Winter October 1st to March 31st). Interactions of these covariates, sun exposure, exercise and PT/OT utilization with treatment group were assessed but no interactions were found and they were not included in the final model.

A one-compartment model was fitted to the plasma concentration-time profiles of anastrozole and letrozole by means of nonlinear mixed-effects modeling using NONMEM 7.2 (ICON Development Solutions, Ellicott City, MD, USA). Steady state concentrations

(C_{ss}) of anastrozole and letrozole were calculated by the following equation: $C_{ss} = \text{Dose} / (\text{dosing interval} * CL / F_{\text{individual}})$. [43]

Vitamin D₃ dose, serum total and free 25(OH)D concentrations were tested as covariates on AI C_{ss}, and the statistical significance was determined by the likelihood ratio test (LRT).

Hormone determinations were reported as geometric means with 95% confidence intervals. Additionally hormone levels at 6 months were log transformed and analyzed using ANCOVA, with baseline level as a covariate.

We conducted secondary analyses to explore associations between 25(OH)D levels (both total and free), BCPT-MS scores and estradiol levels within each treatment group using Pearson correlation coefficients.

RESULTS

There were 906 patients on AIs assessed for study eligibility. Of those screened, 426 (47%) had musculoskeletal symptoms (BCPT-MS score ≥ 1.5) and 116 patients were randomly assigned to either the usual care group receiving 600 IU D₃/day plus 1000 mg calcium (n=59) or the high-dose group receiving 4000 IU D₃/day plus 1000 mg calcium (n=57) (Figure 1).

Patient demographics and disease characteristics were not statistically different between groups (Table 1). At baseline, 55 (48%) patients were taking letrozole, 47 (41%) were taking anastrozole, and 11 (9%) were taking exemestane. Patients had been on AI treatment for 19.9 ± 17.0 months (mean $\pm$ SD), and 54% (n=61) of patients had received prior chemotherapy, completed more than 33 months before enrollment. Among all study patients, 32% had prior taxane as part of their treatment, and this did not differ between groups. Approximately 43% (n=49) of participants enrolled had musculoskeletal comorbidities at study entry. There were no differences between groups on any of the baseline AIMSS measures.

Medication adherence for AIs was $>97\%$ over the course of the study and Adherence to the vitamin D intervention was $>95\%$ at each study time point.

After the run-in period, the mean baseline serum total 25(OH)D level for all participants was 36.6 ± 13.0 ng/mL (mean $\pm$ SD), and free serum 25(OH)D was 8.0 ± 3.2 pg/mL (mean $\pm$ SD). Five participants in the high dose group and 4 participants in the usual care group had insufficient 25(OH)D levels of ≤ 20 ng/mL and no participants were vitamin D deficient. At 6 months, all participants were vitamin D sufficient. Table 2 and Figure 2 show the serum 25(OH)D concentrations by group. After 6 months of supplementation, there was a statistically significant difference in the change in serum 25(OH)D between groups (a decrease of 2.6 ± 7.6 ng/mL in usual care vs an increase of 9.3 ± 10.4 in the high-dose group; $p < 0.0001$). In the high-dose group, serum levels of both total and free 25(OH)D increased from baseline to 6 months (total: 37.0 ± 14 ng/mL to 46.3 ± 11 ng/mL, $p < 0.0001$; free: 8.1 ± 3.9 pg/mL to 11.2 ± 3.2 pg/mL, $p < 0.0001$). In the usual care group, total 25(OH)D levels decreased at 6 months, from 36.4 ± 12.1 ng/mL at baseline to 33.7 ± 8.7 at 6 months; $p < 0.02$.

Sun exposure and exercise did not differ between groups and thus did not affect 25(OH)D levels.

Table 3 summarizes the AIMSS measures by group, for participants who had both baseline and 6-month measurements. Following the run-in period, BCPT-MS scores were similar in both groups (2.4 ± 0.7 in usual care group vs 2.3 ± 0.6 in the high-dose group; mean $\pm$ SD). After 6 months in the assigned groups, there were no statistically significant differences in the change in BCPT-MS scores between groups (change of -0.5 ± 0.9 in usual care group vs -0.2 ± 0.7 in the high-dose group; $p > 0.37$ for differences between groups). The subscales for pain, stiffness, and physical function on the AUSCAN, WOMAC, PROMIS and the HGST did not show any differences between groups for the change from baseline to 6 months. There were no differences in exercise or PT/OT utilization between groups and these did not affect AIMSS measures.

Secondary, exploratory analyses within each group did not show clinically significant correlations between free or total serum 25(OH)D and BCPT-MS scores, hand-grip strength or estradiol concentrations.

Figure 3 shows the steady-state concentrations (C_{ss}) of anastrozole and letrozole in individual patients by group at baseline and 6 months. C_{ss} for exemestane were not assayed. The high-dose vitamin D₃ did not affect C_{ss} (LRT, $p = 0.1$). Neither serum total nor free 25(OH)D was significantly associated with C_{ss} ($p = 0.16$).

There were no significant differences in the change in reproductive hormone concentrations for estrone, estradiol, testosterone (free and total) and sex-hormone binding globulin between groups from baseline to 6 months (Table 4).

The most frequent adverse events according to CTCAE v. 4.0 were musculoskeletal (18%) and gastrointestinal (17%) in nature and these did not differ between groups.

DISCUSSION

This randomized trial comparing a high dose of 4,000 IU D₃ to the usual care dose of 600 IU found no difference in musculoskeletal symptoms after 6 months. This was observed in the setting of a significant change in both total and free serum 25(OH)D levels (decrease in usual care group and increase in high-dose group). There was no effect of Vitamin D₃ supplementation on AI clearance (drug/nutrient interaction) or on reproductive hormone levels.

Our findings differ from other trials on vitamin D and AIMSS. A randomized trial in 147 women initiating letrozole treatment observed a higher proportion of musculoskeletal events in women taking 600 IU D₃ plus calcium compared with those given an additional single weekly dose of 30,000 IU D₃ for 6 months ($p < 0.008$) This study compared AIMSS measures taken before AI initiation to those following 6 months of supplementation.[1] A smaller, single-arm pilot study ($n = 60$) found less joint pain and joint disability in women who achieved serum levels of 25(OH)D > 66 ng/mL with D₃ supplementation for 12 weeks. [5] Because baseline 25(OH)D levels in both of these trials were measured before D

supplementation, serum levels were lower than in our study in which baseline values reflect 4-week run-in on 600 IU D₃. This might contribute to the discrepancy in our results.

Rastelli et al[2] conducted a small randomized trial in 60 women with 25(OH)D <30 ng/mL who were experiencing AIMSS while on anastrozole. Patients were stratified according to their baseline 25(OH)D and all received 400 IU D₃ plus calcium and an additional dose of 50,000 IU of ergocalciferol (D₂) weekly or monthly for 8 or 16 weeks, depending on their serum levels. There was a significant decrease in self-reported pain after 2 months; however, this decrease in pain was not sustained at 4 or 6 months.

Others have suggested that there is a threshold for 25(OH)D levels to achieve positive effects of D₃ on AIMSS. An improvement in joint pain has been reported in women on AIs when serum 25(OH)D levels of 40 ng/mL were achieved.[3,4] In our study, the high-dose vitamin D group achieved a mean total 25(OH)D concentration of 46.3 ± 11 ng/mL at 6 months with no observed differences in AIMSS.

Similar to our findings, a prospective study found no association between 25(OH)D levels and AIMSS in women initiating AI when compared with a cancer-free group.[44] Similarly, the IBIS-II cancer prevention trial also reported that low serum levels of 25(OH)D did not predict AIMSS in postmenopausal women taking anastrozole.[45]

Hand disability and hand-grip strength are reported to be associated with tenosynovial changes in the hands and wrist in women on AIs[12,46] and hand disability is seen in the general population with low 25(OH)D levels.[47] After 6 months of supplementation, we found no differences in changes in hand disability or hand strength between groups.

While a supplemental dose of vitamin D₃ of 4,000 IU/day is the safe upper limit,[20] *in vitro* studies indicate that the active form, 1 α ,25(OH)D₃ can affect reproductive hormone levels in a tissue-specific manner[48–53] and in patients on AIs, serum estradiol has been positively associated with 25(OH)D levels.[54] Here we report that 4,000 IU D₃ did not abrogate the estrogen-suppressing action of AIs nor the steady state levels of anastrozole or letrozole.

Research continues into identifying risk factors and strategies to manage AIMSS symptoms. Patients and their physicians often treat AIMSS with non-steroidal anti-inflammatory medication and acetaminophen, with antidepressants and anticonvulsants as with other chronic pain disorders, various other over-the-counter supplements, as well as non-pharmacologic approaches. Recently studied approaches include exercise,[55] Tai Chi,[56] yoga,[57] and glucosamine with chondroitin.[58] Acupuncture has demonstrated efficacy in some but not all studies.[59–61] Others have failed to find significant benefit from omega-3 fatty acids.[62] Other strategies include switching AIs,[63] or treatment of underlying and potentially exacerbating factors such as insomnia and fear of recurrence.[64,65] Some approaches currently under investigation include duloxetine (SWOG#) and traditional Chinese medicines.[66]

This study has several strengths. First, the BCPT-MS has a low respondent burden and we previously demonstrated the ability of the BCPT-MS to identify and measure AIMSS prospectively [27]. Second, we accounted for effect modifiers that can influence AIMSS and

25(OH)D: percent body fat, sun exposure, exercise, bisphosphonate use, years since menopause, prior taxane exposure, pre-existing musculoskeletal co-morbidities, physical/occupational therapy, and medications that can affect both arthralgia and/or vitamin D levels. These did not differ between groups at baseline or after 6 months and therefore do not account for our results. Third, to our knowledge, this is the first report of the relationship of free, bioavailable 25(OH)D with AIMSS, thus eliminating the possible variation in vitamin D-binding protein.[67] Finally, while there is little data from controlled trials to support exceeding the current recommendations of 600 IU D₃/day for those aged 1 to 70 years or >800 IU for those older than 71 years, research does support 800 IU to prevent fractures for those older than 65.[49,68] Our findings support recommendations that women on AI might be advised to take a daily supplement 600–800 IU D₃ daily, which appears safe and would support bone health.

This study has limitations. The run-in period was designed to accommodate the prevailing use of D supplementation in women on AIs.[69] It is possible that vitamin D has a role in altering AIMSS in women with low 25(OH)D (<30 ng/mL). Although our data cannot address this due to the run-in period, D insufficiency does not currently appear as prevalent in this population. Previous reports of D insufficiency[70,71] have resulted in a high rate of D₃ use among breast cancer survivors.[69]

Second, higher doses of D₃ may yield different results but caution is warranted. The correlation between serum 25(OH)D levels and outcomes appears to have a U or J shaped relationship, suggesting benefit at the middle range of serum 25(OH)D levels and negative health outcomes at both lower and higher levels.[24,72] Third, this was a single site study with 93% of the participants Caucasian, limiting the generalizability of the findings.

In summary, we found no significant changes in AIMSS measures between women who took 4000 IU D₃ daily compared with 600 IU D₃. However, we did not document any harm from vitamin D supplementation in this study; the high-dose vitamin D₃ used in this study did not adversely affect reproductive hormone levels or the steady state pharmacokinetics of anastrozole or letrozole. In both groups, serum 25(OH)D remained in the recommended range for bone health (30 ng/mL)[68] and safety (<50 ng/mL).[20]

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Participation Flow Through the Study

Figure 1.
Participation flow through the study

Figure 2.
Serum 25(OH)D by treatment group (mean±sd)

Figure 3.
Steady-state concentrations (C_{ss}) of anastrozole and letrozole in individual patients by group at baseline and 6 months (horizontal bars represent the mean C_{ss} in each group)

Table 1

Baseline Characteristics of Trial Participants by Treatment Arm

Characteristic	All Enrolled Patients (N = 113)	600 IU D ₃ Control (N = 56)	4000 IU D ₃ Experimental (N = 57)
Age, years Mean (SD)	60.9 (8.8)	60.3 (9.3)	61.4 (8.4)
Weight, kg Mean (SD)	77.5 (14.5)	76.4 (14.1)	78.6 (14.9)
BMI, kg/m ² Mean (SD)	29.0 (5.4)	28.7 (5.2)	29.3 (5.7)
Time from menopause (years) Mean (SD)	12.7 (9.8)	12.7 (9.5)	13.0 (10.2)
Stage of Disease, n (%)			
I	53 (46.9%)	29 (51.8%)	24 (42.1%)
II	45 (39.8%)	19 (33.9%)	26 (45.6%)
IIIA	15 (13.3%)	8 (14.3%)	7 (12.3%)
Chemotherapy, n (%)			
Yes	61 (54.0%)	31 (55.4%)	30 (52.6%)
No	52 (46.0%)	25 (44.6%)	27 (47.4%)
Chemotherapy drug, n (%)			
Adriamycin/Cytosan	6 (9.8%)	4 (12.9%)	2 (6.7%)
AC + Taxane	36 (59.0%)	17 (54.8%)	19 (63.3%)
Other	19 (31.2%)	10 (32.3%)	9 (30.0%)
Months since end of chemotherapy Mean (SD)	33.3 (24.2)	32.7 (22.9)	34.0 (25.8)
Radiation therapy n (%)			
Yes	71 (62.8%)	32 (57.1%)	39 (68.4%)
No	42 (37.2%)	24 (42.9%)	18 (31.6%)
AI drug, n (%)			
Anastrozole	47 (41.6%)	23 (41.1%)	24 (42.1%)
Exemestane	11 (9.7%)	4 (7.1%)	7 (12.3%)
Letrozole	55 (48.7%)	29 (51.8%)	26 (45.6%)
Months on AI Mean (SD)	19.9 (17.0)	17.9 (16.4)	20.0 (17.7)
Bisphosphonate, n (%)			
Yes	19 (16.8%)	11 (19.3%)	8 (14.3%)
No	94 (83.2%)	46 (80.7%)	48 (85.7%)
Previous Tamoxifen, n (%)			
Yes	20 (17.7%)	10 (17.5%)	10 (17.9%)

Characteristic	All Enrolled Patients (N = 113)	600 IU D ₃ Control (N = 56)	4000 IU D ₃ Experimental (N = 57)
No	93 (82.3%)	47 (82.5%)	46 (82.1%)
MS comorbidity* n (%)			
Yes	49 (43.4%)	29 (50.9%)	20 (35.7%)
No	64 (56.6%)	28 (49.1%)	36 (64.3%)
TOTAL Serum 25(OH)D, ng/mL Mean (SD)	36.6 (13.0)	36.2 (12.0)	37.0 (14.0)
Free Serum 25(OH)D, pg/mL Mean (SD)	8.0 (3.2)	7.8 (2.4)	8.1 (3.9)
Physical Activity, met hrs/wk Mean (SD)	16.7 (16.6)	17.2 (16.6)	16.2 (16.8)
BCPT-MS subscale Mean (SD)	2.34 (0.65)	2.41 (0.66)	2.28 (0.64)
WOMAC	N = 74	N = 37	N = 37
Pain—Mean (SD)	10.7 (3.5)	10.5 (3.9)	10.8 (3.0)
Stiffness—Mean (SD)	5.5 (1.7)	5.5 (1.8)	5.5 (1.5)
Physical function— Mean (SD)	34.6 (10.6)	34.7 (11.5)	34.6 (9.8)
AUSCAN	N = 77	N = 38	N = 39
Pain—Mean (SD)	9.8 (3.9)	9.8 (4.1)	9.9 (3.9)
Stiffness—Mean (SD)	2.3 (1.0)	2.3 (1.1)	2.3 (0.9)
Physical function—Mean (SD)	17.2 (6.3)	17.1 (6.5)	17.4 (6.1)
PROMIS Mean (SD)	45.0 (6.4)	44.7 (5.9)	45.3 (6.9)
Handgrip strength, max lbs Mean (SD)	48.0 (12.7)	48.1 (12.4)	48.0 (13.2)

* MS comorbidity = “Yes” if participant had any of the following: fibromyalgia, osteoarthritis (general), knee osteoarthritis, hip osteoarthritis, spine osteoarthritis or low back pain.

Table 2

Total and Free, bioavailable 25-hydroxyvitamin D [25(OH)D] by Treatment Arm

		600 IU D ₃ Control					4,000 IU D ₃				Experimental	
		Baseline		6 months			Baseline		6 Months			
	n	Mean	SD	Mean	SD	(sd)	n	Mean	SD	Mean	SD	
25(OH)D												
Total Vitamin D (ng/mL)	54	36.4	12.1	33.7	8.7	-2.6 (7.6)	57	37.0	1.4	46.3	11	9.3 (10.4)
Free Vitamin D (pg/mL)	53	7.9	2.4	7.4	1.4	-0.5 (1.6)	57	8.1	3.9	11.2	3.2	3.1 (2.5)
												P-value for differences between groups
												<0.0001
												<0.0001

P-value for differences between groups from GLM.
Total Vitamin D: For difference from baseline to 6 months for control group, p value=0.0141; for experimental group, p value=<0.0001.
Free Vitamin D: For difference from baseline to 6 months for control group, p value=0.0155; for experimental group, p-value=<0.0001.

Table 3

Mean, SD, and Change of AIMSS Measures of Trial Participants by Treatment Arm of D₃ Supplementation

		600 IU D ₃ Control						4,000 IU D ₃ Experimental					
		Baseline			6 months			Baseline			6 Months		
Measure	n	Mean	SD	Mean	SD	(sd)	n	Mean	SD	Mean	SD	(sd)	P-value for differences between groups*
BCPT-MS	55	2.4	0.7	1.9	0.9	-0.5 (0.9)	57	2.3	0.6	2.0	0.9	-0.2 (0.7)	0.38
Pain													
WOMAC	36	10.5	3.9	9.9	3.8	-0.6 (3.8)	39	10.8	3.0	9.6	3.2	-1.2 (3.8)	0.40
AUSCAN	37	9.8	4.1	9.5	4.0	-0.2 (3.3)	39	9.9	3.9	9.0	4.3	-0.9 (3.3)	0.21
Stiffness													
WOMAC	36	5.5	1.8	5	1.9	-0.5 (2.0)	39	5.5	1.5	4.9	1.7	-0.5 (1.7)	0.72
AUSCAN	37	2.3	1.1	2.2	1	-0.1 (1.0)	39	2.3	0.9	2.2	1	-0.1 (0.9)	0.91
Physical Function													
WOMAC	35	34.5	11.9	33.3	12.5	-1.2 (11.2)	37	34.6	9.8	30.6	10.3	-4.0 (10.1)	0.20
AUSCAN	38	17.1	6.5	16.4	5.4	-0.7 (3.8)	39	17.4	6.1	16.3	6.2	-1.1 (4.7)	0.52
PROMIS	55	45.4	6.9	47.1	8.2	1.7 (6.9)	57	44.6	5.9	45.3	6.7	0.6 (4.9)	0.39
Hand Grip	53	47.2	12.1	48.2	10.7	1.0 (7.6)	54	47.8	12.6	49.6	12.1	1.8 (10.6)	0.30

P value for change in BCPT-MS within group: control group, p=0.0004 for baseline to 6 months; experimental group, p=0.01 for baseline to 6 months

P value for change in WOMAC Physical Function within group: experimental group, p=0.02 for baseline to 6 months

Hand grip measured in pounds is maximum strength on dominant hand.

P values for between-group differences are from ANCOVA, controlling for musculoskeletal comorbidities (y/n), months on AI (<6 months/ 6 months), on meds that affect AIMSS (y/n), taxane use (y/n), season, and had chemotherapy (y/n).

Mean and SD of Hormone Determinations in Trial Participants by Treatment Arm at Baseline and 6 Months of D₃ Supplementation

Table 4

		600 IU D ₃ Usual Care Control							4,000 IU D ₃ Experimental						
		Baseline			6 Months				Baseline			6 Months			
Hormone	n	Geometric Mean	SE	95% CI	Geometric Mean	SE	95% CI	n	Geometric Mean	SE	95% CI	Geometric Mean	SE	95% CI	P-value for differences between groups*
Estrone	53	5.25	0.28	4.72, 5.84	5.47	0.36	4.78, 6.25	54	5.78	0.32	5.17, 6.45	6.14	0.43	5.33, 7.08	0.67
Estradiol	50	2.77	0.1	2.58, 2.98	3.00	0.12	2.76, 3.25	52	2.83	0.1	2.63, 3.04	2.94	0.16	2.64, 3.27	0.63
Testosterone	54	22.98	1.46	20.24, 26.10	23.43	1.47	2.67, 26.57	57	22.73	1.5	19.92, 25.93	22.65	1.45	19.92, 25.75	0.48
Free testosterone	54	4.25	0.29	3.71, 4.88	4.27	0.28	3.74, 4.88	57	4.34	0.28	3.82, 4.93	4.35	0.30	3.79, 4.99	0.95
SHBG	55	46.32	3.05	40.59, 52.85	47.28	3.3	41.11, 54.37	57	42.23	3.31	36.09, 49.41	41.76	3.26	35.71, 48.83	0.44