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Vitamin D Insufficiency and Musculoskeletal Symptoms In Breast Cancer Survivors on Aromatase Inhibitor Therapy

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Abstract

Breast cancer survivors on aromatase inhibitor therapy often experience musculoskeletal symptoms (joint pain and stiffness, bone and muscle pain, and muscle weakness), and these musculoskeletal symptoms may be related to low serum levels of vitamin D. The primary purpose of this pilot exploratory study was to determine whether serum levels of 25-hydroxyvitamin D concentration (25 [OH] D) were below normal (<30 ng/ml) in 29 breast cancer survivors (BCS) on aromatase inhibitor therapy (AIs) and if musculoskeletal symptoms were related to these low vitamin D levels. The mean serum 25(OH) D level was 25.62 ± 4.93 ng/mL; 86% (n = 25) had levels below 30 ng/mL. Patients reported muscle pain in the neck and back, and there was a significant inverse correlation between pain intensity and serum 25(OH) D levels ($r = -0.422$; $p < .05$ [2-tailed]). This sample of BCS taking AIs had below normal levels of serum 25(OH) D despite vitamin D supplements. This is one of the few studies to document a significant relationship between vitamin D levels and muscle pain in BCS on AI therapy. Findings from this pilot study can be used to inform future studies examining musculoskeletal symptoms in BCS on AI therapy and relationships with low serum levels of vitamin D.

Introduction

In recent years, there has been a dramatic increase in the use of third generation aromatase inhibitors (AIs) as adjuvant endocrine therapy for postmenopausal breast cancer survivors (BCS) diagnosed with estrogen-receptor positive breast cancer.[1] BCS on AI therapy often experience musculoskeletal symptoms, and these musculoskeletal symptoms may be related to low levels of vitamin D.[2,3]

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Purpose

The purposes of this pilot exploratory study were to: a) determine whether serum levels of 25-hydroxyvitamin D concentration (25[OH] D) were below normal (<30 ng/ml) in a sample of 29 breast cancer survivors (BCS) on aromatase inhibitor therapy (AIs) for at least 2 months; b) describe any musculoskeletal symptoms experienced by these BCS, and c) determine if musculoskeletal symptoms (joint pain and stiffness, bone and muscle pain, and muscle weakness) experienced by these women on AI therapy were related to their vitamin D levels. The serum level of 25(OH)D necessary for promotion of optimal bone health is considered to be 30 ng/mL, because this is the level required to prevent increases in parathyroid hormone (PTH) production.[4, 5]

Background

With the use of AIs, i.e. anastrazole/Arimidex® (AstraZeneca Pharmaceuticals, LP, Wilmington, DE), exemestane/Aromasin® (Pfeizer, Inc., NY, NY), and letrozole/Femara®; (Novartis Pharmaceuticals, East Hanover NJ), recurrence of estrogen-receptor positive breast tumors have been effectively reduced.[6–11] However, women on AIs are also predisposed to bone loss and increased fracture risk, likely due to extremely low circulating estrogen levels.[12–15]

An additional concern reported in women on AI therapy is an increased prevalence of musculoskeletal symptoms. In the ATAC trial of 9366 patients, there was a significant difference in reports of musculoskeletal disorders in patients on anastrazole compared to patients on tamoxifen ($p<0.0001$). Only 21.3% of women on tamoxifen reported musculoskeletal symptoms compared to 27.8% of women on anastrazole[7]. Musculoskeletal symptoms documented in clinical trials of both non-steroidal AIs[9–12] and steroidal AIs[8] include joint pain, joint stiffness (arthralgia), bone pain, muscle pain (myalgia), and muscle weakness. Arthralgia and/or bone pain was reported in 61% of 56 BCS who were taking one of the three AIs in another non-clinical trial.[16] In a cross-sectional study of 200 women taking anastrazole, letrozole, or exemestane for at least 3 months, 47% had new or worsening joint pain and 44% had new or worsening joint stiffness. The most common joints affected were hands, knees and back.[17] Musculoskeletal symptoms can also affect feet, hips, and shoulders and are now considered a class effect of AIs.[13, 17–20]

Prevalence of musculoskeletal symptoms in clinical trials of women on AI therapy has varied from 8.4% to 35.6%. This variation in prevalence rates is most likely due to inconsistent definitions and absence of a validated measure to assess drug-induced musculoskeletal symptoms.[13, 17] The incidence of myalgia and arthralgia has contributed to the premature discontinuation of AI in 20% of patients[16] and may have contributed to adherence rates of less than 80% in19% to 28% of subjects during the first year of AI therapy.[21] Joint pain and stiffness, bone pain, and muscle pain may also interfere with the high impact exercise needed by postmenopausal breast cancer patients to minimize bone loss and prevent fractures. If women discontinue the use of AIs because of the severity of musculoskeletal symptoms, they are at greater risk of cancer recurrence.

Researchers have suggested that the musculoskeletal symptoms BCS on AIs experience may be a result of low levels of vitamin D.[22–24] Patients with serum 25(OH)D levels <30 ng/ml are diagnosed with moderate (20–29 ng/ml) or severe (10–19 ng/ml) vitamin D insufficiency or with vitamin D deficiency (osteomalacia) (<10 ng/ml). Many postmenopausal women have serum 25(OH) D levels lower than 30 ng/ml, especially if they reside at latitudes higher than ~42°N. where exposure to sunlight is not enough to synthesize vitamin D during winter months.[25] In large population-based studies, 62 to 75% of North American postmenopausal women

had insufficient serum levels of vitamin D.[25–27] Low levels of vitamin D were recently documented in 68% of 1,179 postmenopausal rural American women residing at latitude of ~41 43°N., despite the fact that 59% were taking a daily median dose of 400 IU of vitamin D.[27] In another study, 52% of 1,536 postmenopausal North American women (75% residing above 35°N.) who were taking medication for osteoporosis and at least 400 IU vitamin D daily had at least moderate vitamin D insufficiency.[24]

An inadequate serum vitamin D status is commonly seen in elderly women.[28] Mean serum vitamin D levels of 12 ng/mL (range <4 to 31 ng/mL) were reported in 116 homebound elderly subjects from Maryland who had mean daily intakes of vitamin D of 121 IU (standard deviation [SD] ±132 IU).[29] Seventy-four percent of 80 elderly patients (mean age of 77.8 yrs) residing in Colorado had vitamin D insufficiency, and these patients consumed more than the recommended 400 to 600 IU of vitamin D daily.[30] Few studies have reported serum vitamin D levels specifically in BCS. Low levels of vitamin D were reported in 88% of 128 BCS not taking AIs; however, the subjects resided in Norway at latitudes 58° to 70°N.[4]

Theoretical Framework

Vitamin D is a complex nutrient that functions as a hormone to benefit bones, joints, and muscles; and it is an essential nutrient for maintaining calcium and phosphorus homeostasis. Insufficient levels of vitamin D lead to secondary hyperparathyroidism, hypophosphatemia, and phosphaturia. The result is decreased calcium available for bone mineralization.[31]

Osteomalacia (serum vitamin D levels <10 ng/ml) results in a defective bone building process or a softening of the bone. It is important to differentiate between osteomalacia and osteoporosis. In osteoporosis, there is an imbalance or uncoupling in bone remodeling, and the result is that bone loss or resorption exceeds formation. With osteomalacia, bone formation and resorption may be balanced. However, the bone that is formed is not dense or mineralized and is considered soft bone.

In healthy bone and during bone formation, osteoblasts deposit collagen matrices on periosteal surfaces of bone. Calcium is then incorporated into matrices in a process called mineralization. Without mineralization, the collagen matrix becomes soft and rubbery and continues to expand. One explanation for the musculoskeletal pain with soft bone is that the expansion of the collagen matrix results in pressure to periosteal surfaces and to sensory pain fibers.[31] Muscle pain and weakness in vitamin D deficiency may also be related to the hypophosphatemia and phosphaturia caused by increased activity of the parathyroid hormone.[32]

Symptoms of osteomalacia include bone and muscle pain; joint pain and stiffness; muscle weakness; fatigue; and unsteady gait. In 2003, Plotinikoff and Quigley reported on a study of 163 patients, 10 to 65 years of age, who presented to Minnesota Hospital with nonspecific muscle aches and bone pains. More than 90% of these patients had insufficient levels of vitamin D (mean levels of vitamin D, 12.08 ng/mL; 95% confidence interval [CI], 11.18 –12.99 ng/mL).[33]

Other studies have reported relationships between low vitamin D levels, muscle weakness, and falls.[34,35,36] Bischoff et al.(2000) examined the relationship between muscle strength and vitamin D levels in 319 ambulatory elderly persons. Mean age for the 103 women was 74 yrs, mean age for the 216 men was 76 yrs, and muscle strength was measured by leg extension power (LEP). Muscle strength declined with age in both the men and women (female: $r = -.35$; $p = .0005$/male: $r = -.48$; $p < .0001$), and there was a modest, but significant, positive correlation between muscle strength and serum $1,25(OH)_2$ vitamin D levels in both sexes (female: $r = .22$; $p = .034$/male: $r = .14$; $p = .045$)[37]

BCS on AI therapy are believed to have increased requirements for vitamin D because this vitamin is necessary to induce the expression of CYP3A4 genes within the liver. Letrazole and exemestane are both detoxified in the liver by the CYP3A4 system. Anastrazole is metabolized in the liver by dealkylation and hydroxylation. Thus, AIs utilize the CYP34A system for metabolism, and any metabolic utilization of this system increases the body's requirements for vitamin D [2, 38, 39]

Taylor et al. (2004) examined serum vitamin D levels in 233 BCS with musculoskeletal symptoms. Fifty-nine of the 233 BCS were on AI therapy, and 65% of these 59 women had low levels of vitamin D. [2] However, data from the IBIS II breast cancer prevention study of 6000 postmenopausal women at increased risk for breast cancer and receiving anastrozole versus placebo suggested that AI-induced arthralgia was not correlated with 25(OH) vitamin D levels.[40] More studies are needed to determine the prevalence of vitamin D insufficiency in BCS receiving AI therapy and to examine relationships between vitamin D serum levels and intensity of musculoskeletal symptoms in this patient population.

Methods

Sample

The sample for this pilot exploratory study was a subgroup (n = 29) of postmenopausal BCS currently taking AIs who had completed a larger NIH funded (R01 NR07743-05A1) 24 month randomized clinical trial testing the effectiveness of progressive strength/weight training (n = 110) vs. no strength/weight training (n = 113) for prevention and treatment of osteoporosis in BCS. The recruitment process and baseline characteristics are described elsewhere.[41, 42] As part of the 24 month study, all the BCS had taken 1200 mg calcium carbonate or calcium citrate with 400 IU of vitamin D_3 (cholecalciferol) supplements daily. Mean adherence to supplements over 24 months was 92.5%.

The major relevant inclusion criteria for the larger parent intervention study were: a) bone mineral density T-score of −1.0 SD or lower at one or more skeletal sites (spine, hip, or forearm), and; b) treatment completion (except tamoxifen or aromatase inhibitors) for stage 0, I, or II breast cancer at least 6 months prior to admission to the parent study. The major relevant exclusion criteria were: a) recurrence of breast cancer; b) currently taking corticosteroids, hormone replacement therapy, or medications for bone loss; c) serum calcium, creatinine, or thyroid stimulating hormone (TSH) outside the normal limits, and d) concomitant conditions that would prohibit calcium or vitamin D intake.

The larger parent study with 223 BCS included 57 BCS who were taking AIs for at least 2 months by the end of the study. Some of these women had anecdotally reported musculoskeletal symptoms to the exercise trainers and research nurses. This pilot exploratory study was developed to gain a greater understanding of musculoskeletal symptoms in BCS on AI therapy and to determine whether these women had insufficient levels of vitamin D. Approval for the study was obtained from the University Institutional Review Board. Twenty-nine of the 57 subjects who had been on AI therapy for at least 2 months signed consent forms agreeing to complete an investigator-developed questionnaire on aromatase inhibitors and vitamin D intake and to have serum drawn for a one time for measurement of 25(OH) D levels. These 29 BCS completed this exploratory study from 1 to 24 months (M = 12.97 ±7.46) after completion of the 24 month multicomponent intervention.

Instruments—The *Aromatase Inhibitor Questionnaire* was a 48 item investigator-developed questionnaire querying the type and dose of current AI medication, supplemental vitamin D intake, minutes outdoors in daylight hours without sun block lotion, and any current musculoskeletal symptoms. Twenty items related to intensity of five types of musculoskeletal

symptoms (muscle pain, muscle weakness, bone pain, joint pain and joint stiffness) for each of three to four areas of the body, e.g. muscle pain in back/neck, muscle pain in arms, and muscle pain in legs. Symptoms were rated on an 11 point scale anchored by 0 = none to 10 = worst discomfort. Data were examined for each of the individual 20 items. In addition, a mean rating for each the five types of musculoskeletal symptoms was calculated for the combined areas of the body, e.g. combined bone pain (of back/neck, arms, and legs). One item queried the overall effect of the musculoskeletal symptoms on activity using NCI toxicity categories of 0 = no interference with activity, 1 = interference with athletic activity, 2 = interference with function but not ADLs; 3 = interference with ADLs, and 4 = disabling. Ten items queried the frequency of the musculoskeletal symptoms in the past week and other items related to timing of onset or increase of the symptoms in relation to initiation of AI therapy (i.e., before initiating or number of weeks after initiating).

Blood samples were drawn for measurement of 25(OH) D levels from the 29 BCS at three regional laboratory sites in the state with shipping for batch analysis to a single laboratory at the clinical research laboratory at the medical center. The kit used for analysis was 25(OH) D I-radioimmunoassay (RIA) from DiaSorin with an assay sensitivity of 1.5 ng/mL (Stillwater, MN, USA). All blood samples were drawn in November and results were not adjusted for a seasonal effect with the neutral value for April and October because this usually accounts for only about 3% of the total variance.[27]

Three-Day Diet Records were completed by the subjects at the end of the 24 month intervention. The food records were analyzed for intake of IU of vitamin D using Nutritionist Five™ (First DataBank) software. Validity and reliability for dietary records have been documented in the literature.[43] Supplemental daily intake of vitamin D and calcium were also recorded on the Three-Day Diet Record.

All data were entered into and analyzed with SPSS (version 15.0). Descriptive analysis (e.g., mean, standard deviation, standard error of means and/or frequency distributions and percentages) were calculated for all the variables. The data were examined for normative distribution. Pearson r correlations were calculated to determine the relationships of serum 25 (OH) vitamin D levels to other variables. Student t-tests were calculated for continuous/interval data to examine for differences between types of musculoskeletal symptom intensity levels and between BCS in the strength/weight training group and those in the non-strength/weight training group.

Results

The subgroup of 29 BCS on AI therapy in this pilot exploratory study were all Caucasian women, and 62% lived in rural, non metropolitan settings (see Table 1). All women resided at latitudes of 41–43°N. At entry into the larger study, reports from Dual Energy X-ray Absorptiometry (DXA) testing indicated that 5 BCS (17%) had osteoporosis (T-scores of 2.5 or lower) and 24 BCS had osteopenia, i.e. T-scores −1.0 to −2.4.[44] Mean age for the 29 BCS was 60.1 ± 8.3 years and time since menopause and/or time since hormone replacement therapy (HT) was 62.72 months (range 12 to 300). Characteristics of the 29 BCS on AI therapy were similar to the characteristics of the larger group of 223 women.[41, 42]

The majority of women (see Table 2) had a history of Stage 0 or I breast cancer. Upon entry into the larger parent intervention study, the 29 BCS were a mean of 38.8 ± 32.6 months past completion of cancer treatment (except for tamoxifen and AIs). Twenty five (86%) of the 29 BCS had a history of taking tamoxifen. These BCS had taken AIs for a mean lifetime duration of 25.4 months and had taken tamoxifen a mean duration of 48.4 months. The large majority were taking non-steroidal AIs (letrozole or anastrazole); only 5 BCS (17%) were taking the

steroidal AI, exemestane. Results of this study will be organized to respond to purposes of the study:

#1. Determine whether serum levels of 25-hydroxyvitamin D concentration (25[OH] D) were below normal (<30 ng/ml) in a sample of 29 breast cancer survivors (BCS) on aromatase inhibitor therapy (AIs) for at least 2 months

Only 4 (14%) of the 29 BCS had serum vitamin D levels at or above 30 ng/mL. The other 25 BCS (86%) had insufficient levels of serum 25(OH) D; 23 BCS had moderate vitamin D insufficiency (20–29 ng/mL). None of the BCS had serum levels below 10 ng/ml (see Table 3), but 2 BCS had severe vitamin D insufficiency and both were taking the nonsteroidal, letrozole (see Table 4). However, 2 of the 4 BCS with normal serum 25(OH) D levels were also taking letrozole. The mean serum 25(OH) D level for the 29 women was 25.62 ± 9.23 ng/mL. There was not a significant correlation between serum 25(OH) D levels and lifetime months on AI therapy.

At the time of the 25(OH) D serum draws, these 29 BCS reported a mean supplemental intake of vitamin D of 665 ± 424 IU; range 0 – 1829 IU. Twenty six (90%) of the BCS reported vitamin D intake either from a calcium supplement and/or from a multivitamin. There was not a significant correlation of 25(OH) D serum levels with IU of vitamin D intake via supplements. Mean dietary intake of vitamin D for these 29 BCS during the 24 month study was approximately only 95 IU per day.

Data from the 29 BCS indicated that in the previous week (in November), women spent a mean time of about 39 minutes in the sun. Current recommendations are that women spend a minimum of 15 minutes in the sun without sun block lotion. Four women (14%) received no sunshine during that week (see Table 5).

#2 Describe musculoskeletal symptoms experienced by BCS on AI therapy

Descriptive analysis of musculoskeletal symptoms indicated that 21 (72%) BCS reported AI-related musculoskeletal symptoms. Thirteen BCS (45%) reported that the symptoms started after AIs were initiated with 10 of the 13 reporting onset of the symptoms within 16 weeks. Eight (27%) reported that prior musculoskeletal symptoms increased after initiation of AIs. Fourteen (48%) had sought help from their healthcare provider for relief of the musculoskeletal symptoms. The providers' advise for treatment varied and included acetaminophen, celecoxib, exercise, glucosamine chondroitin, or changing to a different AI. Only 3 women indicated that they had taken pain medication for the symptoms.

The 29 BCS reported mean intensity levels of less than 3.0 (on scales of 0 –10) for musculoskeletal symptoms (joint pain or stiffness, muscle pain or weakness, and bone pain) (see Table 6). When a mean symptom rating was calculated for each type of musculoskeletal symptom with all the body sites combined, significant differences were found. The intensity of muscle pain was significantly worse than bone pain ($t [28] = 3.55$; $p = .001$), worse than muscle weakness ($t [28] = 3.26$; $p = .003$), and worse than joint stiffness ($t [28] = 2.25$; $p = .0032$). There were no significant differences between subjects in the strength/weight training group ($n = 11$) and those in the non strength/weight training group ($n = 18$) for any symptoms related to muscles, bones, or joints.

In regard to the frequency of the musculoskeletal symptoms, 6 BCS (21%) reported daily muscle pain, whereas only three reported daily muscle weakness or daily bone pain. Nine BCS (31%) reported daily joint pain and 8 BCS (28%) reported daily joint stiffness. In response to the overall effect of musculoskeletal symptoms on activity (using NCI toxicity rating levels), 15 BCS (52%) reported no interference, 2 (7%) reported interference only with athletic activity,

9 (31%) reported interference with function but not ADLs, 3 (10%) reported interference with ADLs, and no BCS reported the symptoms to be disabling.

#3. Determine if any musculoskeletal symptoms (joint pain and stiffness, bone and muscle pain, and muscle weakness) experienced by these women on AI therapy were related to their vitamin D levels

Five BCS (17%) reported no musculoskeletal symptoms for any part of the body. In the other 24 women, the highest mean rating was for muscle pain in the back and neck, and there was a significant inverse relationship between this muscle pain and serum levels of 25(OH) D ($r = -0.422$, $p < .05$).

Discussion

The 86% prevalence of vitamin D insufficiency (levels below 30 ng/mL) in this sample of 29 BCS was higher than in samples of postmenopausal women from the general population at the same latitude, i.e. 52%[24] to 68%.[27] Prevalence in the current study sample was also higher than in the 67% of BCS at similar latitude who were taking AIs and experiencing musculoskeletal symptoms.[2] The prevalence of vitamin D insufficiency in this sample was high despite the fact that their mean daily intake of vitamin D supplements was 665 IU and mean time in the sun in past week was reported as 39 minutes. Low levels of vitamin D in this sample of 29 BCS may be due to aromatase inhibitor medications utilizing the CYP34A system for metabolism. Any metabolic utilization of the CYP34A system increases the body's requirements for vitamin D.[38, 39] The vitamin D insufficiency could also be partially attributed to seasonal variations because the serum was drawn at only one time (in November) rather than multiple times inclusive of the optimal times of April through October.

Seventy-two percent of this sample of BCS on AI therapy reported new onset or worsening of musculoskeletal symptoms. This percentage was much higher than what was reported in large trials on the efficacy of AIs. These trials reported that 19 to 36% of the women had musculoskeletal symptoms [8–12] The 72% reported was also higher than prevalences of 44–47% with joint stiffness and pain, and 61% with arthralgia and/or bone pain documented in two recent smaller clinical cross sectional studies of BCS on AI therapy.[16,17] While musculoskeletal symptoms were frequent in the current study, the mean intensity of the symptoms was low. However, nearly half the subjects reported that the symptoms interfered with activity or function. The lack of significant differences in musculoskeletal symptoms between the strength/weight training group and the non-strength/weight training group in these BCS suggests that the symptoms were not exercise-induced; thus other sources of the symptoms must be sought and treated. The finding that these 29 BCS had a significantly higher intensity of muscle pain than bone pain, muscle weakness or joint stiffness, suggests the need to evaluate musculoskeletal symptoms specifically rather than globally and to develop validated measures to assess musculoskeletal symptoms.

The higher incidence of musculoskeletal symptoms in this pilot study compared to previous studies with BCS on AIs may be explained by the corresponding high incidence of vitamin D insufficiency. This is the first study of BCS to find a significant inverse correlation between the level of muscle pain (in back/neck) and the serum level of vitamin D.

One limitation of this study is the possibility that the consent process may have biased subjects' reports of musculoskeletal symptoms. When completing the questionnaire, subjects may have felt obligated to report the presence of musculoskeletal symptoms, even though they had no symptoms to report. Because of the small sample size, convenience sample, and lack of a comparison group, results of this pilot study cannot be generalized beyond the sample studied. However, results do suggest hypotheses for future studies with larger sample sizes and with

comparison groups of women. Future studies could examine relationships between vitamin D levels and musculoskeletal symptoms in BCS on AI therapy with larger samples of women of different ages, races, lifestyles, and geographic areas. Comparison groups should be included to examine whether BCS prescribed AI therapy have greater frequency and intensity of musculoskeletal symptoms than BCS not on AI therapy. In future studies, serum phosphate levels could be measured along with vitamin 25(OH)D levels, and relationships could be examined between muscle pain and weakness and hypophosphatemia,

Vieth[45] and others have suggested that optimal serum vitamin D levels for postmenopausal women should be higher than 30 ng/mL. Suggested optimal levels would be in the 40 –50 ng/mL range for prevention of increases in parathyroid hormone (PTH) production and for promotion of optimal bone health. Future studies measuring serum levels of vitamin D could also include measures of PTH, and relationships between serum levels of vitamin D and PTH production could be examined.

The National Osteoporosis Foundation currently recommends that adults 50 years of age and older obtain 1,000 IU of vitamin D3 per day.[46] However, the daily dose of vitamin D that will provide optimal benefits for women and pose no risk for adverse effects has yet to be determined. Researchers have suggested that daily doses of vitamin D of 2000 IU per day or greater may be necessary for postmenopausal women to maintain optimal bone health, and that these doses can be safely administered.[47–48]

Vitamin D supplements are easy for patients to self-administer, well tolerated, and very economical. However, patients should be warned against purchasing larger-dose supplements of vitamin D unless they are directed to do so. Findings from this study can not be directly applied to clinical practice. Rather, findings can be used to inform future studies examining musculoskeletal symptoms in BCS on AI therapy and relationships with serum levels of vitamin D. If musculoskeletal symptoms in BCS on AI therapy are related to low levels of vitamin D, randomized controlled trials should be conducted to determine the optimal dosing of vitamin D necessary to minimize these symptoms. Based on results of these controlled trials, strategies could be developed to maintain bone and muscle health while optimizing adherence to AI therapy.

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Table 1

Demographic and Osteoporosis Profile Characteristics (n = 29)

Variable	Value	Percentage
Age in years	*M* = 60.10	
	SD = 8.37	
Months since menopause or HT	*M* = 62.72	
	SD = 68.88	
Race/Ethnicity		
Caucasian	*f* = 29	100%
Other	*f* = 0	
Employment		
Employed	*f* = 19	31.0%
Not employed (retired or unemployed)	*f* = 8	27.5%
Missing	*f* = 2	
Residence		
Urban	*f* = 11	37.9%
Rural	*f* = 18	62.1%
Family history of osteoporosis		
Yes	*f* = 6	20.7%
No	*f* = 23	79.3%
Bone Loss		
Osteoporosis (T-score ≤ − 2.5)	*f* = 5	17.2%
Osteopenia (T-score −1.0 to −2.4)	*f* = 24	82.7%
Fracture in past 6 months	*f* = 0	0%

Table 2

Breast Cancer Treatment Profile of Subgroup (n = 29)

Variable	Value	Percentage
Stage of breast cancer		
Stage 0 (in situ)	*f* = 1	3.4%
Stage I	*f* = 15	51.7%
Stage II	*f* = 13	44.9%
Treatment for breast cancer		
Surgery	*f* = 28	96.6%
Intravenous chemotherapy	*f* = 24	82.7%
Radiation	*f* = 20	69.0%
Months since treatment completed	*M* = 38.79	
	SD = 32.6	
Mean months on aromatase inhibitors	*M* = 25.41	
	SD = 13.22	
Months on aromatase inhibitors		
2 – 12 months	*f* = 6	20.7%
13 – 24 months	*f* = 8	27.6%
25 – 36 months	*f* = 10	34.5%
37 – 48 months	*f* = 3	10.3%
49 – 53 months	*f* = 2	6.9%
Type of aromatase inhibitors		
letrozole	*f* = 19	65.50%
exemestane	*f* = 5	17.25%
anastrazole	*f* = 5	17.25%
History of tamoxifen use		
Yes	*f* = 25	86.2%
No	*f* = 4	13.8%
Mean life-time months on tamoxifen	*M = 48.44*	
	SD = *18.65*	

Table 3

Level of serum 25(OH) D (n = 29)

Levels (ng/ml)	Frequencies	Percentage
< 10*	*f* = 0	0%
10 to 19†	*f* = 2	6.9%
20 to 29‡	*f* = 23	79.3%
> 30§	*f* = 4	13.8%

*Vitamin D deficiency.

†Severe vitamin D insufficiency.

‡Moderate vitamin D insufficiency.

§Optimal vitamin D level.

Table 4

Hydroxyvitamin D Levels by Lifetime Months on Aromatase Inhibitors (n= 29)

Type & Months on AI	10–19 ng/mL *f* =	20–29 ng/mL *f* =	≥30 ng/mL *f* =
Anastrozole			
2–12			
13–24		1	
> 24		4	
Letrozole			
2–12	1	4	
13–24		4	
> 24	1	7	2
Exemastane			
2–12		1	
13–24		2	1
> 24			1

Table 5

Vitamin D Serum and Intake Variables (n = 29)

Variable	Mean	SD	Range
-Serum 25(OH) D levels	25.62	9.23	17– 41
-Supplement intake over past 24 month intervention	370.11	43.83	225–400
-Dietary intake at end of 24 month intervention	95.12	78.96	6 –365
-Combined supplement and dietary intake over past 24 month intervention	465.32	103.74	294–764
-Current daily IU reported intake of supplements	665.02	424.87	0–1829
-Minutes of average daily sunshine over one year	64.64	52.58	0 – 174
-Minutes of daily sunshine in past week - November	38.79	45.61	0 – 171

Table 6

Relationships of intensity of musculoskeletal distress with serum 25(OH) D (n = 29)

Site	M	SD	Range	Pearson *r* with 25(0H) D
Muscle pain all sites	2.44	2.07	0–6.33	NS
Back/neck	2.93	2.60	0 – 9	r = − 0.422; p <.05
Arms	1.79	2.18	0 – 8	NS
Legs	2.59	3.08	0– 10	NS
Muscle weakness all sites	1.44	1.59	0 – 5	NS
Joint pain all sites	2.09	2.28	0 – 7	NS
Bone pain all sites	1.30	1.91	0–6.67	NS
Joint stiffness all sites	1.89	2.01	0–6.25	NS
Sensory alteration/tingling	2.55	3.07	0 – 10	NS