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Effect of vitamin D supplementation on serum 25-hydroxy vitamin D levels, joint pain, and fatigue in women starting adjuvant letrozole treatment for breast cancer

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Abstract

Vitamin D deficiency and insufficiency may contribute to musculoskeletal symptoms and bone loss observed in women taking aromatase inhibitors (AIs). This study was conducted to determine the prevalence of suboptimal vitamin D levels in women initiating adjuvant letrozole for breast cancer and to determine whether supplementation with 50,000 IU of vitamin D3 weekly could reduce musculoskeletal symptoms and fatigue in women who have suboptimal vitamin D levels. Sixty women about to begin an adjuvant AI were enrolled. Baseline 25OHD levels were obtained, and women completed symptom questionnaires. They were then started on letrozole, along with standard dose calcium and vitamin D. Four weeks later, women with baseline 25OHD levels < 40 ng/ml started additional vitamin D3 supplementation at 50,000 IU per week for 12 weeks. 25OHD levels were re-assessed at 4, 10, and 16 weeks; the questionnaires were repeated at weeks 4 and 16. At baseline, 63% of women exhibited vitamin D deficiency (<20 ng/ml) or insufficiency (20–

31 ng/ml). 25OHD levels >40 ng/ml were achieved in all 42 subjects who received 12 weeks of supplementation with 50,000 IU vitamin D3 weekly, with no adverse effects. After 16 weeks of letrozole, more women with 25OHD levels >66 ng/ml (median level) reported no disability from joint pain than did women with levels <66 ng/ml (52 vs. 19%; $P = 0.026$). Vitamin D deficiency and insufficiency are prevalent in post-menopausal women initiating adjuvant AI. Vitamin D3 supplementation with 50,000 IU per week is safe, significantly increases 25OHD levels, and may reduce disability from AI-induced arthralgias.

Keywords

Breast cancer; Vitamin D; Letrozole; Vitamin D deficiency; Aromatase inhibitors; Endocrine therapy; Joint pain; Arthralgias

Introduction

Musculoskeletal complaints and fatigue are well known side effects of treatment with aromatase inhibitors (AIs) [1–5]. Up to 50% of women treated with AIs have new or increased joint pain or stiffness [6], and 30% complain of fatigue [1–5]. Musculoskeletal symptoms impact adherence to these drugs [7] and, in one study, 22% of women discontinued an AI because of these side effects [8].

Subjective musculoskeletal symptoms from AIs are associated with physiologic joint changes and functional impairment. Women taking AIs are more likely than those on tamoxifen to have tenosynovial changes seen on magnetic resonance imaging, and a decrease in hand grip strength [9]. Vitamin D (VitD) deficiency results in a similar syndrome of musculoskeletal symptoms with generalized non-specific musculoskeletal pain and stiffness, and impaired muscle strength and function [10–14].

Experts define VitD deficiency as 25-hydroxyvitaminD (25OHD) level of <20 ng/ml [14–16], 21–31 ng/ml considered as a relative insufficiency [17]. Proximal muscle strength seems to improve when 25OHD levels increase from 4 to 16 ng/ml and continues to improve as the levels increase to >40 ng/ml [12]. This suggests that 25OHD of 40 ng/ml may be required for optimum musculoskeletal performance.

A possible biologic explanation of AI-induced musculoskeletal symptoms is that reduction in joint estrogen levels may unmask subclinical VitD deficiency as estrogen increases activity of 1- α hydroxylase responsible for conversion of 25OHD to the biologically active 1,25-di-hydroxyvitaminD and in addition increases activation of the VitD receptor [18].

We conducted a prospective study to determine the prevalence of VitD insufficiency in post-menopausal women about to start adjuvant letrozole. On the assumption that there would be sufficient women with 25OHD levels below a value of 40 ng/ml, the trial was designed to supplement those women with 50,000 IU VitD3 per week so as to determine the effect on 25OHD levels and to verify the safety of this approach. Those women with levels above 40 ng/ml were maintained on standard supplementation doses which, while not as robust as a

randomized, placebo-controlled trial design, would allow some estimate of differences between standard and high dose supplementation. Lastly, a number of exploratory, hypothesis-generating analyses were planned on the effect of high dose supplementation on musculoskeletal symptoms associated with adjuvant use of letrozole; and the correlation between letrozole levels, 25OHD levels, and musculoskeletal symptoms. The long-range objective, should favorable results be obtained, was to inform the design of a randomized, placebo-controlled trial of vitD3 supplementation in breast cancer patients starting treatment with adjuvant letrozole.

Methods

Cohort

The study was conducted at the University of Kansas Medical Center, under an IRB-approved protocol. Post-menopausal women with early-stage, receptor-positive invasive breast cancer, who were candidates for an adjuvant AI, were eligible. Pre-menopausal women were eligible if they received ovarian suppression with a GnRH analog. Calcium and VitD as a daily supplement were allowed, as was adjuvant chemotherapy, prior to enrollment. Women with a history of renal stones or hypercalcemia were excluded.

Study schedule

Baseline—Demographic and medical data were collected prospectively. Blood was tested for calcium, phosphorus, electrolytes, renal, hepatic function, and 25OHD levels; women were asked to complete questionnaires prior to initiation of letrozole.

Women were asked to stop any multivitamin and calcium supplements and start standard supplementation with 1,200 mg/day of calcium and 600 IU/day via Viactiv® chews, the same day as letrozole was started. All study medications were provided to the subjects.

Week four—Women completed questionnaires. Blood was drawn for 25OHD and letrozole levels. Women with 25OHD levels ≤ 40 ng/ml at baseline began 50,000 IU of oral VitD3 every week (Maximum D3, BTR Group, Inc.; Pittsfield, IL) for 12 weeks (designated as VitD-HD). Women with a 25OHD level >40 ng/ml at baseline did not receive the higher dose VitD3 but continued on standard supplementation VitD and calcium only (designated as VitD-ss).

Follow-up assessments—At weeks 10 and 16, blood was drawn for measurements similar to baseline. Because 25OHD levels were used for safety monitoring, assays were performed in real time by a clinical laboratory rather than being run in batches at the end of study. Plasma collected at week 16 was stored frozen for later measurement of letrozole levels. At week 16 (end of study), questionnaires were completed similar to baseline.

Serum 25OHD and plasma letrozole levels

25OHD assays were performed at Quest Diagnostics, using LC/MS/MS [http://www.questdiagnostics.com/hcp/topics/endo/vitamin_d.html]. Plasma letrozole levels were

assayed by Clinical Reference Laboratory (Lenexa, KS) using GC/MS [<http://www.crlcorp.com>].

Symptom questionnaires

A validated musculoskeletal symptom-directed questionnaire, the HAQII, was administered to assess disability from musculoskeletal symptoms (Table 1) [19]. Patients were also asked to report any joint pain in the last 24 h, and if present whether the severity was mild, moderate, severe, or disabling. BFI, a tool for rapid assessment of fatigue severity in cancer patients was administered [20]. Menopausal symptoms were assessed using the MENQOL [21].

Statistical analysis

The planned accrual of 60 subjects was intended to allow us to estimate the proportion of women with low VitD levels, with a margin of error of no greater than 13% with 95% confidence interval. Because of the small sample sizes and the fact that most variables were not normally distributed, non-parametric tests were used throughout. For categorical variables, Fisher's exact test was used. For continuous variables, the Mann-Whitney test or Kruskal-Wallis test was used for comparison between groups; the Wilcoxon's signed rank test was used for within-subject changes over time. Given the exploratory nature of the tertiary analyses dealing with musculoskeletal symptoms, no corrections were made for multiple comparisons.

Results

Characteristics of subjects

Sixty women about to start an adjuvant AI were enrolled over a 12-month period (Table 2). Fifty-four women were Caucasian (four Hispanic), five African American and one Asian. Median age was 56 and median BMI, 27 kg/m². Thirty women (50%) had received adjuvant chemotherapy. Only four women were on a bisphosphonate therapy (all oral) at study entry; no additional women started bisphosphonate therapy while on the study.

Prevalence of VitD deficiency and insufficiency

At baseline, median 25OHD level was 27 ng/ml (9–61 ng/ml). Eighteen women (30%) had vitD deficiency (< 20 ng/ml); an additional 20 (33%) had VitD insufficiency (21–31 ng/ml). Only 37% had levels considered sufficient for bone health (Fig. 1). Only 22% of the women had levels >40 ng/ml. Women exhibiting 25OHD levels < 40 ng/ml at baseline were slightly older and had higher BMIs compared to women with levels >40 ng/ml. At entry, 31 women (52%) were taking daily multivitamins, and 17(28%) were on VitD supplementation (Table 2).

There was a decided seasonal effect, with women having baseline blood drawn in months with lower sun exposure (December through April) exhibiting lower levels than did women with blood drawn during the months with higher sun exposure (May through November); medians of 21 vs. 35 ng/ml, respectively ($P < 0.001$). Thus, although there were an equal number of subjects accrued in the two time intervals, 29 (97%) of 30 subjects screened in

winter exhibited 25OHD <40 ng/ml, compared to only 18 (60%) of 30 subjects screened in summer (Table 2; $P = 0.001$).

Study completion and evaluability

Nine women, who began the study were considered non-evaluable for the analysis of effects of VitD-HD. Five women were not able to complete the study: three women withdrew within a few weeks because of personal reasons, one woman receiving VitD-HD discontinued adjuvant letrozole due to severe arthralgia at 11 weeks, and one woman did not return for the 16 week visit. In addition, one woman declined to have blood drawn at 16 weeks (thus, letrozole and 25OHD levels were not available), and two women exhibited letrozole levels of 0 at 16 weeks, indicating non-compliance with treatment. Finally, one woman assigned to VitD-HD on the basis of low baseline 25OHD level did not take it due to her concern about potential toxicities. The remaining analyses therefore included 51 evaluable subjects who completed the 16 week study, nine on VitD-ss, and 42 on VitD-HD.

Effect of VitD-ss and VitD-HD supplementation on serum 25OHD levels

Nine women with baseline 25OHD levels >40 ng/ml received VitD-ss throughout the study. For these women, 25OHD levels dropped by a median of 6 ng/ml at week 10 and 5 ng/ml at week 16. Three of these nine women had levels <40 ng/ml at 16 weeks, the lowest at 32 ng/ml, despite receiving VitD-ss.

After only 6 weeks of VitD-HD, 25OHD levels had increased from a median of 23 ng/ml at baseline and 29 ng/ml at 4 weeks (when VitD-HD was initiated) to a median of 59 ng/ml (range 40–97 ng/ml). After 12 weeks of VitD-HD, levels increased to a median of 66 ng/ml (range 35–116 ng/ml). All women receiving VitD-HD exhibited an increase in 25OHD levels, with a median change of 47 ng/ml (7–87 ng/ml) between baseline and 16 weeks (Fig. 2). All women achieved levels of 40 ng/ml by week 10 on study (6 weeks of VitD-HD).

Relationship of 25OHD levels with disability from joint pain, severity of joint pain, fatigue, and menopausal symptoms

Relationship between baseline 25OHD levels and baseline symptoms—At baseline, 11 of 51 (21%) women reported joint pain that was moderate to disabling in severity. There was no association between 25OHD levels and reported severity of joint pain, with 2/9 (22%) of women with 25OHD levels >40 ng/ml and 9/42 (21%) of women with 25OHD levels ≤ 40 ng/ml reporting joint pain. However, by the more sensitive HAQII assessment, women with lower 25OHD levels reported higher scores (greater disability) ($P = 0.045$). Baseline 25OHD levels did not exhibit any correlation with the BFI score or the summary score of the MENQOL.

Relationship between VitD levels and musculoskeletal symptoms (HAQII) at 16 weeks—Sixteen weeks after starting letrozole, HAQ scores were better (median 0.1 vs. 0.6) in individuals whose 25OHD levels were above versus below the median of 63 ng/ml for all 51 subjects ($P = 0.035$, Mann–Whitney test). The separation was even better when considering only the 42 subjects who received VitD-HD: median of 0.61 for women with

25OHD levels below the median of 66 ng/ml vs. 0.0 for women with 25OHD levels above the median ($P = 0.008$; Mann–Whitney test). Viewed another way, more women (52%) with 25OHD levels above the median value reported absolutely no disability from joint pain (HAQ scores of 0), compared to women with 25OHD levels below the median (19%) ($P = 0.026$, 1-sided Fisher's Exact test). Similarly, twice as many women (58%) with 25OHD levels above the median exhibited no clinically significant disability from joint pain (defined as having a HAQII value >0.25) compared to women with levels below the median (29%). Alternatively, the 25OHD levels were higher (median 78 ng/ml) for women with no clinically significant joint disability than for women with disability (median 63 ng/ml) ($P = 0.039$; Mann–Whitney test). However it is analyzed, it appears that higher 25OHD levels are associated with less disability related to joint pain (Table 3).

Relationship between VitD levels, fatigue, (BFI) and menopausal symptoms (MEN-QOL) at 16 weeks—As was observed for HAQII scores, women who had received VitD-HD and exhibited 25OHD levels above the median (66 ng/ml) reported lower BFI scores (median = 1.4) than did women with 25OHD levels below the median (BFI median = 2.9), although this was not statistically significant difference (Table 3).

Women, who had received VitD-HD and exhibited 25OHD levels above the median reported lower (less severe symptoms) MENQOL summary scores (median = 2.2) than those with 25OHD levels below the median (median = 3.2) ($P = 0.035$; Mann–Whitney test). The lower summary scores were the result of lower scores in the Vasomotor and Physical sub-sections (Table 3).

Relationship between VitD levels and joint pain at 16 weeks—Although twice as many women (48 vs. 24%) reported a lack of any subjective joint pain if they had serum 25OHD levels above versus below the median value, the difference was not statistically significant (Table 3).

Change in musculoskeletal symptoms (HAQII) over time—There was no significant change in HAQ scores from baseline to 4 weeks. More than twice as many women on VitD-HD (45%) as on VitD-ss (22%) exhibited improvement in disability from joint symptoms, between week 4 and week 16. Thirty-three percent of women receiving letrozole and VitD-ss exhibited a worsening (increased score) in joint symptoms from baseline to week 16, and 33% had an improvement. For women receiving letrozole and VitD-HD, 19% had worsening in joint symptoms, and 50% exhibited an improvement (Fig. 3). Despite the excess number of improved scores (21) relative to worse scores (8), and the change in median HAQII score from 0.6 to 0.4 in the VitD-HD group, this did not reach statistical significance ($P = 0.059$, Wilcoxon signed rank test).

Change in fatigue (BFI) and menopausal symptoms (MEN-QOL) over time—There were no differences in fatigue or menopausal symptoms between baseline to 4 weeks or 4–16 weeks, nor was there a difference in fatigue and menopausal symptoms at 16 weeks between women on VitD-ss and women who received VitD-HD ($P = 0.15$ for BFI, $P = 0.93$ for MENQOL; Mann–Whitney test).

Change in joint pain severity over time—From baseline to week 4, on letrozole and VitD-ss, 35% of women had worsening, and 7% had improvement in joint pain. From week 0 to week 16, on letrozole and VitD-HD, 33% had worsening, and 19% had improvement in joint pain. Although more women had improvement during the phase of VitD-HD, these changes were not significant. Furthermore, there was no difference in joint pain severity between the VitD-ss and VitD-HD groups.

Plasma letrozole levels

Median letrozole level was 70 ng/ml at 4 weeks and did not change at week 16 (76 ng/ml). Median letrozole level was similar in women who did or did not receive VitD-HD (76.5 vs. 71 ng/ml). At week 4, women with severe pain had the lowest plasma letrozole levels (median of 28.5 ng/ml) versus women with less than severe pain (median of 73.5 ng/ml) ($P = 0.006$, Mann–Whitney). Similarly, at 16 weeks, women reporting no pain had significantly higher letrozole levels (median 93 ng/ml) versus those with any reported pain (median 68.5 ng/ml) ($P = 0.002$, Mann–Whitney).

Adverse effects from VitD-HD

None of the 42 women developed VitD toxicity, hypercalcemia, or renal stones. CBCs and extended chemistry panels remained unremarkable at week 10 and at week 16.

Discussion

Aromatase inhibitors reduce estrogen production via inhibition of the enzyme aromatase [22]. Estrogen deprivation is believed to be the cause of most of their adverse effects such as accelerated bone loss and musculoskeletal pain [2, 3, 23]. Musculoskeletal side effects from AIs impact adherence to these drugs. Non-adherence rates of 22–38% have been reported among women receiving adjuvant AIs [7, 8].

In adults, vitD deficiency aggravates osteoporosis and causes osteomalacia, which results in musculoskeletal pain [11, 24, 25]. VitD deficiency has traditionally been defined as a 25OHD level <20 ng/ml [16]. However, higher 25OHD levels are probably necessary for optimum musculoskeletal function. Increased parathyroid hormone (PTH) is an indicator of adaptation to low systemic VitD. PTH levels are inversely proportional to 25OHD levels below 32 ng/ml and begin to level off above this level [15]. A 25OHD level <32 ng/ml was therefore defined as VitD insufficiency. In a cross-sectional study of 4,000 ambulatory women >60 years of age, serum 25OHD concentrations >40 ng/ml were the minimum values needed for optimal musculoskeletal function of the lower extremities [12].

AIs increase fracture risk [2, 26], and VitD deficiency may increase bone loss in women on AIs. In a randomized trial of exemestane versus placebo, exemestane modestly increased bone loss from the femoral neck. VitD level at baseline in women about to start exemestane was significantly correlated with bone loss at 24 months in the exemestane group [23, 27].

Our study shows that low 25OHD levels are prevalent in post-menopausal women with early-stage breast cancer about to start an AI, with 30 and 33% of subjects being VitD deficient or insufficient, respectively. Only 20% of women had levels >40 ng/ml, considered

necessary for optimal musculoskeletal function. These figures are similar to those reported by Crew et al. for pre-menopausal women and the Norwegian Breast Cancer Group for postmenopausal women [27, 28]. Accrual was distributed equally over 12 months minimizing the impact of seasonal variation wherein the median VitD level of subjects accrued in summer was more than twice that of subjects accrued in winter (Fig. 1). The Norwegian breast cancer group reported VitD insufficiency rates of 88–90%, perhaps reflecting differences between sunlight exposures in Europe and Midwest United States [23, 27].

Our results show that VitD-HD for 12 weeks is extremely effective in optimizing VitD levels and results in a predictable increase in 25OHD levels. With 6 weeks of VitD-HD, all women achieved a level of >40 ng/ml. In contrast, of nine women who did not receive VitD-HD because of adequate 25OHD levels at baseline, three had levels <40 ng/ml at 16 weeks, with the lowest value of 32 ng/ml, despite receiving VitD-ss. Comparing women who received VitD-HD versus VitD-ss, the former displayed statistically significant higher values ($P = 0.001$, Mann–Whitney test). Moreover, VitD-HD was safe in this population, with no cases of hypercalcemia or renal stones. Our results are consistent with an earlier report by Heaney et al. [29], which showed that VitD3 supplementation with doses of 35,000 IU, 70,000 IU per week for up to 20 weeks was safe and effective in increasing steady state 25OHD levels in healthy men. Our safety results are also consistent with previous studies by Holick et al. [10, 16], in which 50,000 IU of VitD2 given weekly for 8 weeks was shown to be safe. The safety and efficacy of VitD3 supplementation using 50,000 IU weekly has not been reported in post-menopausal women starting an AI, who are at high risk of bone loss and require adequate VitD stores for bone health.

Our results also suggest that 50,000 IU of VitD3, when given weekly to post-menopausal women starting adjuvant letrozole, results in clinically significant improvement in disability from joint symptoms. After 4 months of Letrozole and 3 months of VitD-HD, HAQ scores were better (median 0.0 vs. 0.6) in individuals whose 25OHD levels were above versus below the median of 66 ng/ml ($P = 0.008$, Mann–Whitney test). Regardless of which criterion is used for the HAQII score—either a value of zero (absolutely no reported disability) or a value of 0.25 (accepted as clinically significant increase in disability [30; Personal communication with Dr. F. Wolfe regarding HAQII])—fewer women with 25OHD levels above the median reported any disability related to joint pain. Although these findings are very suggestive of a VitD protective effect against AI-associated disability from joint pain, they need to be confirmed in the setting of a randomized trial. To that end, we have initiated a randomized study in breast cancer patients with low 25OHD levels who are starting letrozole treatment (clinicaltrials.gov NCT00867217).

In conclusion, VitD insufficiency is prevalent in post-menopausal women with newly diagnosed breast cancer about to start an AI. Such women are at increased risk of musculoskeletal symptoms; and VitD supplementation with 50,000 IU weekly may have a role in reducing the incidence of this side effect in addition to protecting women from accelerated bone loss observed with AIs.

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Fig. 1. Frequency distribution of subjects with serum 25OHD below specific levels. Levels of 25OHD were lower during the winter (*filled square*) than during the summer (*filled circle*)

Fig. 2. Increase in serum levels of 25OHD between baseline and 16 weeks for women who received 50,000 IU vitamin D3 weekly supplementation (*solid symbols*) versus no increase for women who received only standard dose vitamin D and calcium (*open symbols*). The *line* represents no change in 25OHD levels; thus points above the line reflect an increase

Fig. 3.

Decrease in disability from joint pain as assessed by HAQII scores between baseline and 16 weeks for women who received 50,000 IU vitamin D3 weekly supplementation (*solid symbols*) versus no change for women who received only standard dose vitamin D and calcium (*open symbols*). The *line* represents no change in HAQII scores; thus points below the line reflect a decrease, or a reduction in disability from joint pain

Table 1

Features of the Health Assessment Questionnaire II (HA-QII) for measuring functional status [19] (HAQII is a commonly used measure in rheumatology trials; a higher score indicates greater degree of disability)

Questions asked about effect of illness on ability in function in daily life during a period of 1 week
Get on and off the toilet?
Open car doors?
Stand up from a straight chair?
Walk outdoors on flat ground?
Wait in a line for 15 min?
Reach and get down a five-pound object (such as a bag of sugar) from just above your head?
Go up two or more flights of stairs?
Do outside work (such as yard work)?
Lift heavy objects?
Move heavy objects?
Descriptor and score
Without any difficulty (0)
With some difficulty (1)
With much difficulty (2)
Unable (3)

Table 2

Demographics and tumor characteristics of 60 subjects enrolled on study, categorized as having baseline serum 25OHD levels above or below 40 ng/ml

Feature	Serum 25OHD level at baseline		Comparison <i>P</i> -value*
	<40 ng/ml <i>N</i> = 47	40 ng/ml <i>N</i> = 13	
Median age at diagnosis (years)	56	52	0.049
Median weight (Kg)	79.5	62.7	0.014
Median height (m)	1.65	1.70	0.12
Median BMI (Kg/m ²)	28.9	21.3	0.001
Race			
Caucasian	41 (87%)	13 (100%)	0.21
Other than caucasian	6 (13%)	0 (0%)	
Educational level			
High school/GED	19 (40%)	1 (8%)	0.012
Vocational/technical	3 (6%)	3 (23%)	
Some college	12 (26%)	3 (23%)	
College degree	12 (26%)	3 (23%)	
Graduate/professional	1 (2%)	3 (23%)	
Taking multivitamin at baseline	22 (47%)	9 (69%)	0.21
Taking vitamin D at baseline	11 (23%)	6 (46%)	0.16
Entry on study during winter	29 (62%)	1 (8%)	0.001
<i>Tumor characteristics</i>			
Stage			
I	28 (60%)	9 (69%)	0.63
II	5 (11%)	0	
III	2 (4%)	0	
IV	1 (2%)	0	
No data	11 (23%)	4 (31%)	
SBR grade			
1	11 (23%)	4 (31%)	0.65
2	38 (60%)	8 (62%)	
3	5 (11%)	0	
Node positive			
No	24 (51%)	8 (62%)	0.46
Yes	11 (23%)	1 (8%)	
Not assessed	12 (26%)	4 (31%)	
Prior adjuvant chemotherapy	23 (49%)	7 (58%)	0.50
Prior adjuvant taxane	16 (34%)	1 (8%)	0.086

* For categorical variables, two-sided Fisher's exact test was used; for continuous variables, a non-parametric test (Mann-Whitney or Kruskal-Wallis) was employed

Table 3

Associations between serum 25OHD levels and symptoms at 16 weeks for 42 subjects who received 50,000 IU vitamin D3 weekly supplementation

Assessment	Serum 25OHD level at 16 weeks		Comparison <i>P</i> -value [*]
	<66 ng/ml <i>N</i> = 21	>66 ng/ml <i>N</i> = 21	
HAQII			
Score, median (range)	0.6 (0–2.3)	0.0 (0–1.2)	0.008
Number with scores = 0 (%)	4 (19%)	11 (52%)	0.026
Number with scores <0.25 (%)	6 (29%)	12 (57%)	0.059
BFI			
Score, median (range)	2.9 (0–8.0)	1.4 (0–7.2)	0.096
MEN-QOL			
Summary, median (range)	3.2 (0.2–5.4)	2.2 (0.5–3.8)	0.035
Vasomotor, median (range)	3.0 (0–5.0)	1.8 (0–5.0)	0.032
Psychosocial, median (range)	2.5 (0–6.0)	1.9 (0–4.1)	0.19
Physical, median (range)	3.5 (0.2–5.4)	2.2 (0–4.1)	0.028
Sexual, median (range)	0 (0–6.0)	0 (0–5.0)	0.75
Lack of subjective joint pain, number (%)	5 (24%)	10 (48%)	0.099
Lack of subjective muscle pain, number (%)	10 (50%)	11 (52%)	0.92

* For categorical variables, two-sided Fisher's exact test was used; for continuous variables, a non-parametric test (Mann–Whitney) was employed