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Heel Ultrasound Can Assess Maintenance of Bone Mass in Women with Breast Cancer

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Abstract

Postmenopausal women with early-stage breast cancer are at increased risk for bone loss and fractures. Bisphosphonates can prevent bone loss, but little data are available on changes in bone mass assessed by heel quantitative ultrasound (QUS). Our objectives were to determine if (1) heel QUS would provide a reliable and accessible method for evaluation of changes in bone mass in women with breast cancer as compared to the current standard of bone mass measurement, dual-energy x-ray absorptiometry (DXA), and (2) oral risedronate could affect these changes. Eighty-six newly postmenopausal (up to 8 years) women with nonmetastatic breast cancer were randomized to risedronate, 35 mg once weekly or placebo. Outcomes were changes in heel QUS bone mass measurements and conventional dual-energy x-ray absorptiometry (DXA) derived bone mineral density (BMD). Over 2 years, bone mass assessed by heel QUS remained stable in women on risedronate, while women on placebo had a 5.2% decrease ($p = 0.05$) in heel QUS bone mass. Both total hip BMD and femoral neck BMD assessed by DXA decreased by 1.6% ($p = 0.05$) in the placebo group and remained stable with risedronate. Spine BMD remained stable in both groups. Heel QUS was moderately associated with BMD measured by DXA at the total hip ($r = 0.50$), femoral neck ($r = 0.40$), and spine ($r = 0.46$) at baseline (all $p = 0.001$). In conclusion, risedronate helps to maintain skeletal integrity as assessed by heel QUS for women with early-stage breast cancer. Heel QUS is associated with DXA-derived BMD at other major axial sites and may be used to follow skeletal health and bone mass changes in these women.

Keywords

Aromatase inhibitors; breast cancer; heel ultrasound; dual-energy x-ray absorptiometry; bone mineral density

Introduction

As a growing number of women with hormone receptor-positive, early-stage breast cancer are being treated with adjuvant hormonal therapy, the importance of monitoring their bone health has substantially increased (1,2). Recent studies suggest that AIs are superior to the antiestrogen tamoxifen for both progression-free survival and overall survival in women

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with breast cancer (3–6). However, because AIs significantly lower circulating estrogen levels, women with breast cancer on AIs are at increased risk for bone loss and fracture (7–10).

Though the current conventional method for the classification of osteopenia (low bone mass) and osteoporosis is dual-energy x-ray absorptiometry (DXA) (11), little data are available on changes in bone mass assessed by quantitative ultrasound (QUS) of the calcaneus for women with breast cancer. Assessment of bone mass by heel QUS has many potential benefits: it is highly portable, cost-effective, does not involve radiation exposure, and may even provide information on bone structure and elasticity that is not available via DXA assessment (12). Furthermore, it could potentially be performed at a routine oncology office visit to monitor changes in bone mass in women undergoing cancer therapy.

The REBBeca (risedronate's effect on bone in women with breast cancer) study demonstrated that over 2 years, the administration of once weekly risedronate in postmenopausal women with early-stage breast cancer positively affected spine and hip bone mineral density (BMD) and bone turnover, independent of the concurrent use of an aromatase inhibitor (13–14). In the present study, we have evaluated a highly portable, gel-coupled scanning calcaneal ultrasonometer, the QUS-2, to assess changes in bone mass in these women. The aims of this investigation were (1) to determine if a peripheral technique, heel QUS, would provide a reliable and accessible method for evaluation of bone mass maintenance as compared to the current standard of bone mass measurement, DXA; and (2) to examine whether risedronate will help maintain skeletal integrity in women with breast cancer as assessed by heel QUS and DXA.

Materials and Methods

Study design

This analysis of secondary outcomes reports the changes in bone mass assessed by heel QUS and DXA of 86 women in a double-blind, placebo-controlled, randomized clinical trial conducted over 12 months with a 12-month extension (as previously reported in detail (14)). Briefly, participants were randomly assigned with equal distribution to either active treatment with risedronate 35 mg orally, once weekly, or matching placebo.

All participants completed an assessment of their dietary calcium and vitamin D intake using a validated questionnaire (15). Participants with a daily calcium intake of less than 1200 mg received supplementary calcium with vitamin D in the form of calcium carbonate, 500 mg, with 200 IU vitamin D (Os-Cal Plus D; Procter and Gamble, Inc.).

Participants

Women from the greater Pittsburgh area with stage I–III breast cancer who were newly postmenopausal (i.e., ≥8 years postmenopausal as verified by gonadotropin levels) were screened for this study as previously reported (13). These women were treated with chemotherapy with or without tamoxifen, an antiestrogen, or an aromatase inhibitor. Women with stage IV breast cancer or any disease known to affect bone mineral metabolism (such as renal failure, hyperparathyroidism, and malabsorption), as well as those on medications

known to affect bone mineral metabolism, were excluded. Patients who had an initial BMDT-score in the osteoporotic range were advised about options for therapy versus participation in the study. Eighty-seven women were eligible and randomized. The protocol was approved by the University of Pittsburgh Institutional Review Board, and participants provided written informed consent before participation in the study.

Outcome variables

The main outcome variable of interest for this secondary report was the percent change in heel quantitative ultrasound (QUS-2 ultrasonometer, Quidel Corp, Mountainview, CA) by broadband ultrasound attenuation (BUA, dB/MHz). The QUS of the calcaneus was measured as previously described (16–17). Briefly, the right calcaneus was scanned unless there was clinical justification for scanning the left (e.g. previous orthopedic surgeries, open wounds, and/or edema). An aqueous-based gel (Aquasonic 100, Parker Laboratories, Fairfield, NJ) was used as the coupling agent. The transducers of the QUS-2 ultrasonometer are mounted on motorized arms. At the beginning of the scan, the QUS-2 anatomically locates the region of interest (ROI) by repositioning the transducers to detect the acoustic edges at the posterior and plantar surfaces of the calcaneus. The ROI is a parallelogram beginning 4 mm above the bottom and 8 mm forward from the back acoustic edges. The BUA value for a given scan is the average of values determined at a total of 88 points on a 1 mm grid within this parallelogram. The QUS-2 uses a two-step signal processing method: (1) the dominant early period, the average period of a selected portion of the first substantial received sound wave cycle, is quantified, then (2) a mathematical model is used to convert this dominant early period to the corresponding value of BUA. When the low-pass filtering action of the bone is stronger, the dominant early period is longer and the value of BUA is higher. The same operator performed all of the examinations.

Conventional BMD(g/cm^2) was assessed by dual energy x-ray absorptiometry (DXA) of the posterior anterior lumbar spine, total hip and femoral neck (Hologic Discovery, Hologic Inc, Bedford, MA). T-scores, the number of standard deviations by which a patient's BMD differs from that of a healthy 30-year-old sex-and race-matched control, were determined. World Health Organization (WHO) definitions (18) for normal bone density, low bone mass (osteopenia), and osteoporosis based on T-score were used for DXA BMD measurements. The coefficients of variation of BMD in adults using our densitometer are 1.3% for the PA spine and 1.4% for the total hip (19).

Statistical analysis

Statistical analysis was performed using SAS[®] version 9.1 (SAS Institute, Cary, NC). We compared the baseline characteristics of the two treatment arms (risedronate/placebo) using independent samples *t*-tests and Fisher's exact tests, as appropriate. Association between actual BUA measurements (dB/MHz) and DXA-derived BMD (g/cm^2) at baseline was assessed with Pearson correlation coefficients (*r*). Paired samples *t*-tests were used to assess significance of baseline to 12-month and 24-month change over time within each treatment arm. To examine risidronate's effect on QUS-obtained and DXA-derived bone mass outcomes, linear mixed models implemented in SAS[®] MIXED procedure were used. In our linear mixed models, we used change from baseline in each outcome as the dependent

variable; treatment arm (risedronate/placebo), follow-up time point, and their interaction as fixed effects of interest; and a subject random effect to account for multiple follow-up assessments from the same subjects. Both raw change and percent change were considered in all analyses. A p -value of 0.05 or less was considered statistically significant.

Results

Clinical characteristics at baseline

Screening, randomization, and follow-up procedures for this study are described in detail elsewhere (13–14). In brief, 106 women were screened and 87 were eligible for randomization. Of the 87 participants who were randomized (43 for risidronate and 44 for placebo), 72 remained in the study after 2 years (34 risidronate and 38 placebo). One participant did not receive heel ultrasound due to size limitations of our ultrasonometer and thus was not included in our current analysis.

Baseline clinical characteristics of both treatment arms have previously been published in detail (13–14). At baseline, groups had similar clinical characteristics (Table 1). The mean age was 50 years. There were no significant differences in the number of women who had lumpectomy, mastectomy, radiation therapy, or adjuvant hormonal therapy. According to WHO criteria (18), 49.4% were classified as having normal BMD, 48.3% had low bone mass (osteopenia) and 2.3% had osteoporosis as previously reported (14).

Changes from baseline over 24 months in QUS-obtained bone mass and DXA-derived BMD

Over 24 months, heel QUS bone mass remained stable in women on risidronate ($p = 0.05$) (Figure 1). In comparison, women on placebo had a significant decrease of $5.2 \pm 1.3\%$ ($p = 0.05$) in QUS-obtained bone mass. At 24 months, there was a significant difference ($p = 0.05$) between groups in heel QUS BUA measurements (Figure 2).

Total hip BMD and femoral neck BMD assessed by DXA decreased by $1.6 \pm 0.4\%$ and $1.6 \pm 0.7\%$ respectively in the placebo group ($p = 0.05$) and remained stable with risidronate. BMD at the spine remained stable in both groups (14).

Comparison between bone mass methods

Each of the methods for the assessment of bone mass maintenance (i.e. DXA and heel QUS) evaluated in this study demonstrated that women who were on placebo had significant bone loss over 2 years, though bone mass at the spine remained stable in both groups. Pearson product-moment correlation coefficients between BUA heel QUS measurements and DXA-derived BMD showed moderate correlations with r ranging from 0.50 for the total hip, 0.40 for the femoral neck, and 0.46 for the spine (all $p = 0.001$).

Discussion

This secondary analysis of the REBBeca study showed that bone mass assessed by heel QUS remained stable in women on risidronate over 2 years, while women on placebo had a significant decrease in heel QUS bone mass. Total hip and femoral neck BMD assessed by DXA decreased in the placebo group and remained stable with risidronate. Spine BMD

remained stable in both groups. Heel QUS measurements were moderately associated with DXA-derived BMD measurements at the total hip, femoral neck, and spine.

Although many studies have reported the negative effects of adjuvant chemotherapy and hormonal therapy with AIs on bone mass in women with breast cancer (1,2,7–10), few data are available on bone mass outcomes assessed by heel QUS in this patient population. In a study of premenopausal women with breast cancer on adjuvant chemotherapy, Hadji et al. found changes in bone mass assessed by DXA correlated with changes identified using QUS of the phalanges and calcaneus (20). Our study is unique in that we examined the effect of risedronate on bone mass assessed by both conventional DXA as well as heel QUS in postmenopausal women with breast cancer. We also found that heel QUS bone mass measurements correlated with those obtained via DXA at major axial sites.

In addition, several studies have addressed the larger issue of whether QUS measurements can be used to monitor response to antiresorptive therapy. Frost et al. found that though heel QUS measurements show a highly significant response to antiresorptive therapy, the precision of these measurements was not sufficient to allow QUS to be used for monitoring response to treatment (21). Paggiosi et al. showed that QUS of the calcaneus and phalanges may be useful for monitoring response to raloxifene therapy in conjunction with central DXA, as individual response to this therapy may be difficult to detect by DXA alone. However, this group acknowledged that a high degree of variability in QUS measurements was observed and that QUS measurements should only be used in conjunction with DXA-derived BMD until further studies have been completed (22). The 2007 ISCD official positions on QUS in the management of osteoporosis also recognize that the possible added value of combining DXA and heel QUS measurements warrants additional research (23). The benefits of heel QUS, including its portability, low cost, lack of radiation, and its ability to provide information on material properties of bone (12), make it an appealing tool for the management of bone loss, especially for women with breast cancer undergoing adjuvant therapy. Though we did observe a moderate correlation of QUS-obtained BMD with BMD measured by DXA in this study, heel QUS may better serve as a tool for diagnosis as opposed to one for monitoring response to therapy, at least until further research is completed.

There are some general limitations to this study. The primary outcome variable for the original analysis was DXA-derived BMD, whereas heel QUS results were a secondary endpoint. However, we did observe bone mass changes using heel QUS that correlated with BMD at major axial sites. Additionally, heel QUS results may be variable due to difficulty in positioning the foot and locating heel landmarks during the scan due to edema or other pathologies of the foot and ankle (11). Another limitation is that menopausal status varied up to 8 years, though participants were on average 3.3 years postmenopausal at baseline. The third potential limitation involves the fact that the FDA approved AIs for adjuvant hormone replacement therapy of breast cancer patients during the course of our study, and some patients began AI therapy during the trial. We have previously reported this change (14). As such, our ability to detect a sustained treatment effect of AIs versus no AIs on bone mass throughout the 2-year duration of the study without a change may have decreased.

Despite these limitations, there are several important strengths to this study. This study was a double-blind, placebo-controlled, randomized clinical trial that resulted in heel QUS data that correlate with DXA-derived BMD. Additionally, this was a single center study in which a single bone densitometer and a single QUS-2 ultrasonometer were operated by one technologist, allowing for a reduction in equipment-related and between-site variability. Although this can be viewed as a limitation from the perspective of generalization, it is in fact a strength in these initial investigations involving heel ultrasound where identifying a signal unhampered by noise is important. Third, as the placebo group did receive a standard of care therapy for early postmenopausal women (i.e. calcium and vitamin D supplementation), it was more challenging to detect a treatment effect difference between groups. If we had used a placebo control group rather than an active control, our estimates of between treatment differences likely would have been greater.

In conclusion, similar to DXA at major axial sites, heel QUS demonstrates therapeutic maintenance of bone mass in women with breast cancer on risedronate for 2 years. A portable, low-cost, and radiation-free method of bone mass evaluation such as heel QUS may be useful and feasible for women with breast cancer undergoing adjuvant therapy.

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Fig. 1. Percent changes (mean $\pm$ SD) over 24 mo of heel QUS BUA measurements (dB/MHz) and DXA-derived BMD (g/cm²) at the total hip, femoral neck, and posterior anterior lumbar spine of women randomized to risedronate vs placebo. *Difference from baseline, p-value $\leq$ 0.05. †Difference between groups, p-value $\leq$ 0.05. QUS, quantitative ultrasound; BUA, broadband ultrasound attenuation; DXA, dual-energy X-ray absorptiometry; BMD, bone mineral density; SD, standard deviation.

Fig. 2.

Absolute changes (mean $\pm$ SD) over 24 mo of heel QUS BUA measurements (dB/MHz) of women randomized to risedronate vs placebo. *Difference between groups, p -value ≤ 0.05 . QUS, quantitative ultrasound; BUA, broadband ultrasound attenuation; SD, standard deviation.

Table 1

Baseline Clinical Characteristics, BMD and Calcaneal BUA Measurements (13)

Variable	Placebo (mean ± SE)	Risedronate (mean ± SE)	p-Value
	n = 44	n = 43	
Age (yr)	49 ± 5.9	50.1 ± 5.1	0.52
Years postmenopausal	3.2 ± 2.0	3.4 ± 2.0	0.61
Breast cancer treatment [N (%)]			
Chemotherapy	44 (100)	43 (100)	N/A
Lumpectomy	21 (61.4)	28 (65.1)	0.83
Mastectomy	20 (45.5)	21 (48.8)	0.83
Radiation therapy	32 (72.7)	31 (72.1)	1.00
Breast cancer therapy [N (%)]			
Tamoxifen, toremifene, or fulvestrant	30 (68.2)	32 (74.4)	0.64
Aromatase inhibitor	6 (13.6)	8 (18.6)	0.57
BMD, g/cm ²			
Posteroanterior lumbar spine	0.995 ± 0.127	0.985 ± 0.119	0.70
Total hip	0.901 ± 0.103	0.910 ± 0.094	0.66
Femoral neck	0.768 ± 0.099	0.785 ± 0.105	0.43
Calcaneal BUA, dB/MHz	83.255 ± 2.169	82.148 ± 2.325	0.73
Breast cancer treatment, %			
Chemotherapy	100	100	N/A
Lumpectomy	61.4	65.1	0.83
Mastectomy	45.5	48.8	0.83
Radiation therapy	72.7	72.1	1.00
Tamoxifen, toremifene citrate, or fulvestrant	68.2	74.4	0.64
Aromatase inhibitor	13.6	18.6	0.57

Abbr: BMD, bone mineral density; BUA, broadband ultrasound attenuation; SE, standard error; N/A, not applicable.