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Effect of Risedronate on Hip Structural Geometry: A 1-Year, Double-Blind Trial in Chemotherapy-Induced Postmenopausal Women

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Abstract

Introduction—Chemotherapy induced menopause is associated with bone loss. The effect on structural geometry is unknown. Our objective was to determine if oral bisphosphonate therapy could maintain or improve femoral geometry in breast cancer patients with chemotherapy-induced menopause.

Methods—This preplanned one year interim, secondary analysis of the Risedronate's Effect on Bone loss in Breast CAncer Study (REBBeca Study) examined hip structure analysis (HSA), i.e. changes in the bone cross sectional area (bone CSA), section modulus (SM: measure of bending strength), cortical thickness (CT) and buckling ratio (BR: index of cortical bone stability), in a double-blind trial of 87 newly postmenopausal, nonmetastatic breast cancer patients, randomized to risedronate, 35 mg once weekly (RIS) versus placebo (PBO).

Results—After 12 months, intertrochanteric parameters demonstrated percentage improvement (RIS vs. PBO) from baseline in bone CSA (mean±SD: 4.25±6.29 vs. 0.60±5.99%), SM (3.97±6.40

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Trial registration:

- Unique trial number: NCT00118508.
- Trial registration date: June 30th 2005.

Conflict of Interest:

Dr Bhattacharya has received an investigator initiated grant from 'Procter & Gamble'.

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vs. $0.80 \pm 7.08\%$), and CT [5.20 ± 6.98 vs. $1.13 \pm 6.87\%$ (all p -values < 0.05 except SM $p=0.0643$)]. Similar improvements were observed at the femoral shaft [bone CSA: 2.24 ± 5.74 vs. $-0.78 \pm 5.73\%$; SM: 1.62 ± 6.23 vs. $-1.39 \pm 7.06\%$; CT: 3.79 ± 7.84 vs. $-0.17 \pm 7.90\%$ (all p -values < 0.05 , RIS vs. PBO, except SM $p=0.0568$)]. At both sites, the BR had significant decreases consistent with improved strength.

Conclusion—We conclude that RIS improves measures of hip structural geometry in women with breast cancer following chemotherapy.

Keywords

Breast cancer; chemotherapy; osteoporosis; risedronate; hip structural analysis

Introduction

Over the last 25 years breast cancer mortality has decreased due to earlier detection and treatment resulting in prolonged time to relapse and overall survival [1–3]. However, these adjuvant chemotherapy regimens often induce premature menopause due to ovarian failure, especially in women over age 40 years [4–7]. Female breast cancer patients who acquire a hypo-estrogenic state resulting from chemotherapy-induced early menopause can have an increased rate of bone loss and fractures [8–12].

Fracture risk reduction is only partially explained by increased bone mineral density (BMD) and bone mineral content (BMC) [13–15]. Bone strength and the ability to withstand a fracture is also a function of structure, composition, and bone turnover [16–19]. Therefore, it is important to examine underlying changes in bone structural geometry as well as the conventional bone mineral density or bone mass. Ultimately, it would be useful to determine if the increased rate of fractures following chemotherapy-induced bone loss is associated with a structural change in bone microarchitecture.

The Risedronate's Effect on Bone loss in Breast CAncer Study (REBBeca Study) [20] found that once weekly risedronate prevented bone loss and reduced bone turnover at one-year follow-up in women with breast cancer treated with chemotherapy. The objective of this secondary analysis was to 1) examine changes in hip structural geometry in women following chemotherapy-induced bone loss and determine if a once weekly bisphosphonate, risedronate, would protect against these alterations in hip architecture, using the hip structural analysis (HSA) program of Beck [21–23], and to 2) correlate the bone mineral density assessed via standard DXA-scan and HSA-analysis.

Materials and Methods

Study Design

The REBBeca Study was a 12 month, double-blind, randomized, placebo-controlled clinical trial with a 12-month extension (as previously described) [20]. This report presents the preplanned analyses focused on hip structural geometry at 1 year.

One hundred and six women age 18 years and older from the greater Pittsburgh area, who became newly postmenopausal (up to 8 years) after treatment with polyadjuvant chemotherapy for nonmetastatic breast cancer, were screened between May 2003 to July 2005. Eighty-seven women were randomly assigned to either active treatment with risedronate (35 mg po once weekly) or a matched placebo. We used permuted block randomization within strata based on the participant's self-reported age (less than or greater than age 52 years) at baseline.

Participants were not included if they suffered from a second primary cancer or from abnormal bone and mineral metabolism (due to medications or underlying disorders such as hyperthyroidism, malabsorption, renal failure, hepatic failure). Oncologists or primary care physicians were allowed to prescribe tamoxifen or aromatase inhibitors for their patients. Women with a current fracture or osteoporosis by bone mineral density (initial BMD T-score of -2.5 or below at the hip or spine) were counseled about therapy and given the option to participate in the study. Participants were advised of the nature of the study and provided written informed consent prior to participation. The University of Pittsburgh Institutional Review Board provided approval of the protocol.

If participants were found to have a daily calcium intake < 1200 mg using a validated questionnaire [24], they received supplementary calcium with vitamin D (Oscal Plus D, calcium carbonate 500mg with 200 IU of vitamin D, supplied by Glaxo SmithKline, Pittsburgh, PA).

Outcome Variables

Conventional BMD—Using a QDR-4500A bone densitometer (Hologic, Inc., Bedford, MA), bone mineral density (BMD) was measured at the hip (total hip, femoral neck, trochanter, and intertrochanter) and PA-spine by dual-energy X-ray absorptiometry (DXA) at six month intervals (baseline, month 6, and month 12). The coefficients of variation of BMD in adults using our densitometer are 1.4% for the total hip and 1.3% for the PA spine [25].

Hip Structural Analysis—The hip structural analysis (HSA) program uses mineral mass and dimensional data from conventional DXA images of the hip to measure the structural dimensions of bone cross-sections corresponding to three thin regions traversing the proximal femur. These include the narrow neck (across the neck at its narrowest point), the intertrochanteric region (along the bisector of the angle between neck and shaft axes), and the femoral shaft (at a distance equal to 1.5 times minimum neck width, distal to the intersection of the neck and shaft axes). The HSA-parameters assessed at these three sites include BMD as well as five geometric parameters, i.e. bone cross sectional area (bone CSA), section modulus (SM: measure of bending strength), cortical thickness (CT), outer diameter (OD), and buckling ratio (BR: index of cortical bone stability) as previously described [21–23]. The CV for each calculated parameter ranges from 0.8% to 4.7% calculated on paired scans with repositioning of 24 elderly volunteers with repositioning between scans. The error, expressed as the CV, ranged from 1.6% to 6.0% at the intertrochanter [23].

Statistical Analysis

Descriptive statistics were used to summarize characteristics and baseline measures separately for subjects who stayed in the study and dropped out after one year. Fisher's exact, or Wilcoxon rank sum tests, as appropriate, were used to identify any significant differences between those who did and did not drop out. Only those subjects remaining in the study after one year were considered in the main analysis. Descriptive statistics were used to summarize subject characteristics and baseline measures separately for participants in the two randomized treatment groups. Fisher's exact or Wilcoxon rank sum tests, as appropriate, were used to identify any significant baseline differences between the two treatment groups. For each treatment group, the significance of the percent change in hip structural geometry and BMD measures between baseline and one-year assessments was obtained using a Wilcoxon signed rank test for the change scores. The percent change in structural geometry and BMD outcomes between treatment groups were compared using Wilcoxon rank sum tests. Finally, the sensitivity of all results to the use of alternative definitions of outcomes such as the raw one-year measurement and baseline to one-year absolute (as opposed to percent) change (data not shown); and to the use of last-value-carried-forward approach as opposed to analyzing only

the 81 subjects who stayed in the study were examined (data not shown). Spearman correlation coefficients were used to examine the associations between baseline conventional DXA BMD measures and those estimated using hip structural geometry. SAS® version 9.1.3 (SAS Institute, Inc., Cary, North Carolina) was used for all statistical analyses.

Results

Subject Retention and Compliance

Of the 87 participants randomized (43 in the risedronate group and 44 in the placebo group), 83 remained in the study after one year. Hip structural analysis could not be performed on 2 individuals and therefore we present the results on 81 participants (39 in the risedronate group and 42 in the placebo group). The medication compliance based on pill counts (defined as missing less than 20% of the medication) was 82% and retention was 93% after one year. We compared the baseline characteristics between the 81 subjects with complete data who stayed in the study and 6 who had dropped out or had no follow-up HSA data and found that they were not significantly different except that the 6 participants who dropped out or had no follow-up HSA data were younger (mean age 44.1 years vs. 50.0; $p=0.0112$).

Clinical characteristics at baseline

The baseline clinical and skeletal-related characteristics of two treatment groups were not significantly different as displayed in Table 1. The mean age was 50. According to the World Health Organization femoral neck BMD classification system [26,27] only 2.3% had osteoporosis, 48.3% had low bone mass and 49.4% were normal.

Changes from baseline over 12 months in HSA obtained structural parameters

- *Intertrochanter:* In the risedronate group, after one year, the bone CSA (mean $\pm$ standard deviation), section modulus (SM), and cortical thickness (CT) increased by $4.25 \pm 6.29\%$, $3.97 \pm 6.40\%$, and $5.20 \pm 6.98\%$, respectively, while the buckling ratio (BR) decreased by $4.18 \pm 6.07\%$ (all $p < 0.002$ for change from baseline). The outer diameter (OD) did not show a significant change (Figure 1; $p=0.1160$). In the placebo group, none of the above parameters showed a significant change. The between group differences in percentage change at one year were statistically significant for all parameters at this site (all $p < 0.05$) except for SM ($p=0.0643$).
- *Femoral shaft:* The changes from baseline after 12 months in the risedronate and placebo groups respectively were $2.24 \pm 5.74\%$ and $-0.78 \pm 5.73\%$ for CSA, $3.79 \pm 7.84\%$ and $-0.17 \pm 7.90\%$ for CT, $1.62 \pm 6.23\%$ and $-1.39 \pm 7.06\%$ for SM, $-2.69 \pm 4.93\%$ and $-0.40 \pm 5.35\%$ for OD, and $-3.74 \pm 6.97\%$ and $0.43 \pm 8.54\%$ for BR. All risedronate group improvements except SM and OD were significantly greater than placebo group ($p < 0.05$) while the between-group differences in SM and OD were only marginally significant ($p=0.0568$ and $p=0.0755$ respectively). Except for SM ($p=0.2293$), all HSA-parameters in the risedronate-group significantly changed from baseline ($p < 0.05$; figure 1). Placebo group changes were not significant in any of these parameters.
- *Narrow neck:* Similar trends were observed in the narrow neck, although none of the changes after 12 months were significantly different between the groups. However, compared to baseline, the outer diameter in both the risedronate and placebo groups significantly increased by $1.01 \pm 2.45\%$ ($p=0.0121$) and $1.27 \pm 2.67\%$ ($p=0.0073$).

HSA-obtained BMD

After one year, the HSA-obtained BMD (mean $\pm$ SD) at the intertrochanteric site and femoral shaft significantly changed by $4.10\pm 6.31\%$ ($p=0.0002$) and $2.77\pm 5.77\%$ ($p=0.0073$), respectively, in the risedronate group, while in the placebo group these changes were non-significant at $-0.05\pm 5.36\%$ ($p=0.7917$) and $-0.34\pm 6.18\%$ ($p=0.7634$). At the intertrochanteric site and femoral shaft the between-group difference in change after one year were significant (both $p<0.05$). In contrast, none of the within-group changes or between-group differences in HSA-obtained BMD were found to be significant at the narrow neck.

Associations of standard hip and HSA-obtained Bone Mineral Density

The HSA-obtained BMD at the narrow neck correlated highly with the standard DXA-obtained BMD at the femoral neck (Spearman correlation coefficient $r=0.850$, Table 2, $p<0.0001$). In addition, the HSA-obtained BMD at the intertrochanteric site correlated highly with the DXA-obtained BMD measured at the trochanteric ($r=0.831$), intertrochanteric ($r=0.830$), and total hip sites ($r=0.843$; all $p<0.0001$). The HSA-obtained BMD at the shaft was also highly correlated with the DXA-obtained BMD measured at the intertrochanteric ($r=0.704$) and trochanter ($r=0.601$) and total hip sites ($r=0.658$, all $p<0.0001$).

All results were robust against use of absolute change instead of percent change, and against using the last-value-carried-forward approach to account for the 6 subjects not used in the main analyses.

Adverse events

Risedronate was well tolerated. There were no significant differences of adverse events between the women in the two groups [20].

Discussion

This secondary analysis of the Risedronate's Effect on Bone loss in Breast Cancer Study (REBBeca Study) demonstrated that therapy with an oral, once weekly bisphosphonate (risedronate) improved structural geometry (as well as the areal density of the bone) in a population of women with chemotherapy-induced menopause. We found that for early stage breast cancer patients, these DXA derived measures of femoral strength revealed improvements at the intertrochanteric and femoral shaft with similar trends at the narrow neck.

There is an emerging awareness that bone structure, in addition to bone mass, determines bone strength [16–19]. Only a few investigators have examined the protective effects of female hormones on bone structure. Beck and colleagues analyzed hip DXA-scan data for bone density and structural geometry in elderly women participating in the Study of Osteoporotic Fractures (SOF) [22]. This prospective, observational study suggested that current, but not prior use of estrogen therapy improved geometric properties at the hip, while it affected bone density to a much lesser degree. Another study also suggested that sex steroids in young women were able to continue to improve femoral neck bone bending strength despite stable BMD [28]. We have previously shown in a randomized double blinded, clinical trial that hip structure analysis indices of postmenopausal women, age 65 and over, were significantly improved with alendronate or hormone replacement therapy (HRT) alone [23]. But combination therapy led to a larger improvement which was significant at the intertrochanteric site (compared to only HRT) and at the narrow neck (compared to alendronate). Finally, two studies performed by Uusi-Rasi et al., utilizing the HSA-program, found that the use of HRT in perimenopausal women [29] and long term postmenopausal women [30] helped maintain bone mass as well as femoral neck structure as compared to the placebo arm. In contrast to these studies investigating the effect of hormonal supplementation on bone, our study examined the structural bone

parameters of breast cancer patients who have undergone chemotherapy-induced ovarian failure, and determined if those parameters were preserved with a once weekly bisphosphonate.

The preventive role of a selective estrogen receptor modulator on HSA has been examined in postmenopausal women. Investigators reported that raloxifene resulted in improved conventional hip BMD and was associated with improvement of bone CSA, section moduli, and buckling ratios over 3 years as assessed by Beck's HSA analysis[31]. Raloxifene did not affect periosteal apposition, but produced minimal significant increases in cross sectional areas and section moduli. The impact of teriparatide on bone structural geometry was analyzed with Beck's HSA-program and found to be associated with positive structural changes in the proximal regions of the femur in a large sample of postmenopausal women[32]. Women randomized to teriparatide were noted to have significantly improved structural parameters as compared to placebo at the narrow neck and intertrochanteric site.

Although we observed structural changes at all three sites (femoral shaft, intertrochanteric site and narrow neck), the changes at the narrow neck were not as significant as at the other two proximal femur areas. Other studies investigating the effect of HRT [22], raloxifene [31], or the combination of HRT and alendronate [23] on HSA have not reported this discrepancy, which might be explained by the fact that these studies included women age 65 and older. We recruited a younger, newly postmenopausal population, mean age 50, whose skeleton might be more resilient to negative impact. However, a few other studies did observe a differential effect of some agents at specific sites. For example, teriparatide was found to have an apparent lack of treatment effect at the femoral shaft which was attributed to the greater efficacy of teriparatide at bone sites with a higher rate of remodeling [32]. Also steroid hormones were observed to have a site-specific preference of action (i.e. estradiol at the femoral shaft and testosterone at the narrow neck) [28].

We observed different outcomes for the outer-diameter parameter after one year of treatment with risendronate vs. placebo when compared to existing literature. In our study, the outer diameter had statistically significantly decreased compared with placebo at all sites except for the narrow neck, even though the narrow neck is the only site where the outer diameter had changed significantly from baseline in the placebo group. The inability to detect treatment effects at the narrow-neck might be influenced by the fact that HSA measurement precision is worst at that location [33]. We had found previously [23] that women who were randomized to hormone replacement, alendronate, or a combination of these two, had increased outer diameter measurements at all sites compared with baseline. In contrast, a study in which participants were randomized to therapy with raloxifene or placebo for 3 years [31] did not detect any significant changes in the outer diameter compared with placebo. These observed differences in the response of the outer diameter among the published studies may be due to differences in the duration of study, age of patient, rate of bone turnover, or action of therapy.

Similar to other studies [31,34], we found that the HSA-obtained BMD was highly correlated to standard hip BMD. The HSA-obtained BMD at the narrow neck correlated best with the conventional DXA-assessment of BMD at the femoral neck. The HSA-obtained BMD however correlated with the BMD obtained at several sites via conventional DXA assessment (trochanteric, intertrochanteric, and total hip). On the other hand, the associations of HSA-obtained BMD at the femoral shaft and conventional femoral neck BMD were weak.

Although some studies suggest that HSA provides significant additional information to BMD in predicting the occurrence of hip fracture [35–37], especially at the femoral neck [38], not all studies agree [39,34,40]. The latter studies suggest that HSA indices provide prediction of fracture risk, but might not contribute additional information beyond BMD. BMD assessed by DXA measures areal density which is not a true volumetric density. Ongoing improvements

in this technology are underway and may provide additional information on bone structure independent of areal bone density.

HSA methodology is associated with some methodological limitations as outlined previously [23,41]. The structural indices were assessed by DXA scanners which were not designed for this purpose. The section modulus, a measurement of bending strength, might be different when bent in alternate directions than the scanned plane, since most bones are not axially symmetric. Another important limitation is related to the basics of DXA-methodology which only assesses inorganic, not the organic matrix, consequently not allowing the evaluation of the density. HSA calculations assume that the tissue mineralization is a constant factor. Since bisphosphonates are known to cause as well an increase of bone quantity as well as mineralization, this might cause a potential overestimation of geometric parameters. There is evidence that bisphosphonates make bones stronger and reduce incidence of fractures. Strength can be improved by either improving the geometry which reduces load stress or by improving the tissue so that it can tolerate higher stresses. Tissue properties are determined by the collagen matrix, which is not measured in DXA.

There are several general limitations to this study. Menopausal status varied up to 8 years, although the average time since menopause was 3.3 years prior to participation. This however allows the results to be more generalizable to a larger spectrum of breast cancer patients. The second potential limitation concerns the use of bone active agents during the trial. Oncologists were allowed to start study participants at any point during the study on aromatase inhibitors or tamoxifen if deemed medically necessary. While tamoxifen may have a beneficial effect, the aromatase inhibitors may have a negative impact on bone [42–44]. Fortunately, there were no significant prescribing differences for either of these agents between the 2 groups. The follow-up time of 12 months might be too short to observe any significant changes. Finally, comparison of the baseline characteristics between the participants who stayed in the study versus those who had dropped out revealed that the participants who dropped out were more likely to be younger, have a lower buckling ratio, and a lower outer diameter at the femoral shaft. It is not clear how these differences, seen in six patients, would impact the results.

There are also several strengths to this study. This study is the first study to examine the effect of risedronate on geometric-, and strength-derived parameters in chemotherapy-induced postmenopausal women. The control group received calcium and vitamin D, and therefore the risedronate effect was compared to a more challenging standard than a passive placebo. Another positive aspect of our study is that it was conducted in a single center by a limited number of technologists using a single bone densitometer to obtain a more accurate estimate of the true treatment effect void of between-equipment and between-site variability.

We conclude that over 12 months, therapy with a once weekly antiresorptive agent risedronate, in women who become hypo-estrogenic following adjuvant chemotherapy-induced menopause, improves hip structural geometry in addition to the observed beneficial effects on HSA-obtained BMD. This study provides additional information on the potential mechanism for fracture reduction with antiresorptive agents. These results have important clinical ramifications for breast cancer survivors who go into remission after early, aggressive therapy, and are at risk for bone loss and osteoporosis.

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Figure 1.

Percent change in the (A) intertrochanteric region, (B) femoral shaft, and (C) narrow neck cross-sectional parameters measured by HSA after one year of therapy with risedronate versus placebo of newly postmenopausal women due to adjuvant chemotherapy for breast cancer. Results are mean $\pm$ SE (* p -value < 0.05 risedronate vs. placebo, ♦ p -value < 0.05 difference from baseline).

Abbreviations: Bone CSA – Bone Cross Sectional Area, SM – Section Modulus, CT – Cortical Thickness, OD – Outer Diameter, BR – Buckling Ratio.

Table 1

Baseline clinical characteristics, bone mineral density and hip structural parameters by treatment group [mean±standard deviation or N(%)].

	Placebo (N=42)	Risedronate (N=39)	p-Value
Age	49.6 ± 5.8	50.5 ± 5.1	0.4398
Postmenopausal years	2.9 ± 1.5	3.5 ± 2.0	0.4076
Breast cancer treatment			0.9056
SERM	26 (61.9)	22 (56.4)	
AI	6 (14.3)	6 (15.4)	
None	10 (23.8)	11 (28.2)	
HSA-obtained BMD (g/cm ³)			
Intertrochanter	0.79 ± 0.12	0.81 ± 0.11	0.4602
Femoral shaft	1.25 ± 0.15	1.25 ± 0.16	0.9437
Narrow neck	0.80 ± 0.11	0.83 ± 0.10	0.1729
Hologic BMD (g/cm ³)			
Posteroanterior spine	1.00 ± 0.13	0.99 ± 0.11	0.8515
Total hip	0.90 ± 0.10	0.91 ± 0.09	0.4268
HSA measures			
Intertrochanter			
Cross-sectional area (cm ²)	3.74 ± 0.52	3.86 ± 0.56	0.2951
Outer diameter (cm)	4.31 ± 0.32	4.37 ± 0.30	0.5532
Section modulus (cm)	3.06 ± 0.46	3.20 ± 0.58	0.2263
Cortical thickness (cm)	0.32 ± 0.05	0.32 ± 0.05	0.8505
Buckling ratio	8.95 ± 1.73	8.98 ± 1.53	0.7739
Femoral shaft			
Cross-sectional area (cm ²)	3.30 ± 0.41	3.40 ± 0.51	0.4834
Outer diameter (cm)	1.87 ± 0.24	1.95 ± 0.26	0.2158
Section modulus (cm)	1.67 ± 0.24	1.76 ± 0.31	0.2040
Cortical thickness (cm)	0.46 ± 0.07	0.45 ± 0.07	0.8248
Buckling ratio	3.18 ± 0.62	3.29 ± 0.63	0.4574
Narrow Neck			
Cross-sectional area (cm ²)	2.23 ± 0.34	2.33 ± 0.29	0.0636
Outer diameter (cm)	2.64 ± 0.19	2.65 ± 0.21	0.7956
Section modulus (cm)	0.97 ± 0.18	1.03 ± 0.17	0.1494
Cortical thickness (cm)	0.15 ± 0.02	0.16 ± 0.02	0.1742
Buckling ratio	10.5 ± 1.74	10.28 ± 1.79	0.4937

BMD=bone mineral density; HSA=hip structural analysis; SERM=selective estrogen receptor modulator.

Table 2
Spearman correlations between baseline conventional hologic and hip structural analysis derived bone mineral density.
Conventional Hologic BMD

	Femoral Neck	Trochanter	Intertrochanter	Total Hip
HSA-Derived BMD				
Narrow neck	0.850*	0.660*	0.644*	0.728*
Intertrochanter	0.701*	0.831*	0.830*	0.843*
Femoral shaft	0.370*	0.601*	0.704*	0.658*

BMD=bone mineral density; HSA=hip structural analysis.

* *p*-value < 0.001.