Bisphosphonate protects cortical bone at key locations of the femur in aromatase-inhibitor associated bone loss: a 3D cortical bone mapping study

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Abstract

Aromatase inhibitor treatment in breast cancer is associated with accelerated bone loss and increased risk of fracture. Bisphosphonates (BP) are the mainstay treatment of aromatase inhibitor associated bone loss (AIBL), which might improve femoral bone at key locations prone to fracture. To test this hypothesis, we performed 3D cortical bone mapping based on QCT scans in postmenopausal women with early breast cancer receiving aromatase inhibitors. Data of subjects who had both baseline and at least one time of follow-up QCT at Severance Hospital, South Korea, between 2005 and 2015 were analyzed (BP user, n=93; non-user, n= 203). After excluding BP users with low medication persistence (proportion of days covered < 50%), BP users and non-users were 1:1 matched (n=54 for each group) by age, lumbar spine vBMD (LSvBMD), femoral neck areal BMD (FNaBMD), and total hip areal BMD (THaBMD). During median follow-up of 2.1 years, BP use attenuated bone loss in LSvBMD (+7.2% vs. -3.8%, p<0.001), FNaBMD (+1.3% vs. -2.7%, p<0.001), and THaBMD (-0.3% vs. -2.5%, p=0.024). BP had a protective effect on cortical parameters of femoral bone: estimated cortical thickness (CTh), +3.3% vs. +0.1%, p=0.007; and cortical mass surface density (CMSD, cortical mass per unit surface area calculated by multiplying cortical BMD × CTh), +3.4% vs. -0.3%, p<0.001. CMSD increased by up to 15% at key locations including the superior part of femoral neck and lateral femoral trochanter. BP prevented the thinning of average CTh of femoral neck (-1.4% vs. -6.1%, p<0.001), particularly at superior anterior quadrant of femoral neck (absolute difference +12.8% point vs. non-users). Compared to non-users, BP users had improved the cross-sectional moment of inertia (+4.4% vs. -0.7%, p=0.001), withless increase in buckling ratio (+1.3% vs. +7.5%, p<0.001). In summary, BP use prevented cortical bone loss in AIBL at key locations of the proximal femur.

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Introduction

Aromatase inhibitors are used as the standard adjuvant therapy for hormone-sensitive breast cancer after mastectomy. [1, 2] Aromatase inhibitor induced bone loss (AIBL) in post-menopausal women with early breast cancer is known to be associated with rapid loss of bone density, decrease of trabecular bone score, impaired femoral geometry, and increased incidence of both hip and vertebral fractures. [3-5] In our prior study on patients with AIBL using quantitative computed tomography scans (QCT), we found that aromatase inhibitor use in postmenopausal women was associated with cortical bone thinning, particularly at superior femoral neck lesion. [4]

The cortical bone compartment plays an important role in determining femoral bone strength. [6, 7] Cortical thinning at the femoral neck is prevalent in the aged population, and this focal, structural weakness could increase risk of hip fracture. [8, 9] Advanced imaging techniques such as cortical bone mapping (CBM) based on quantitative QCT scans allow measures of cortical bone parameters with the investigation of spatial heterogeneity between study groups. [10-12] CBM was also reported to have potential to improve fracture risk prediction when added to aBMD parameters. [13-15] Given that bisphosphonates (BP) are the mainstay treatment of AIBL, it is important to investigate whether BP use can attenuate cortical bone deficits observed in AIBL at key locations of the proximal femur. [16, 17]

In this study, we hypothesized that BP use in AIBL would have a beneficial effect on cortical parameters at key locations of the proximal femur. To test this hypothesis, site-specific longitudinal changes of QCT-derived bone parameters between BP users and non-users, among AI-treated patients, were analyzed using the CBM technique.

Methods

Study subjects

The study flow is presented in Figure 1. Clinical data of patients with early breast cancer, who received adjuvant endocrine therapy after breast cancer surgery and had a baseline QCT scan between January 2006 to December 2015 at Severance Hospital, were retrieved from Severance Clinical Data Repository System. This study was approved by the Institutional Review Board of Severance Hospital, Seoul, Korea, with a waiver for written permission for retrospective data review (IRB no. 4-2018-0635). After excluding individuals with tamoxifen use or without any follow-up QCT data, 354 early breast cancer patients, who received aromatase inhibitor treatment during the observation period (between baseline and follow-up QCT scans), were grouped into bisphosphonate users (n=148) and non-users (n=206). Among bisphosphonate users, the proportion of days covered by bisphosphonate less than 50% were further excluded to ensure drug persistency. Given the older age, lower bone density and higher serum c-telopeptide level in BP users compared to non-users in the unmatched cohort (supplementary table 1), we performed 1:1 propensity score matching based on age at baseline, QCT-derived bone density parameters (including lumbar spine volumetric BMD, femoral neck areal BMD and total hip areal BMD) and serum c-telopeptide level at baseline to adequately compare BMD changes between baseline and follow-up QCT in BP users and non-users (supplementary figure 1). A total of 108 subjects (54 BP users and 54 non-users) remained in the final analysis.

QCT protocol

Baseline and follow-up QCT scans were performed using a LightSpeed VCT (GE Healthcare, USA; n=87, 81%) or Somatom Definition AS+ (Siemens Healthcare,

Forchheim, Germany; n=21, 19%), with a scan protocol 120 kVp and 150 mA, using a 50-cm scan field of view. All paired images were taken using the same CT scanners. A liquid dipotassium phosphate (K_2HPO_4) intrascan phantom (Model 3; Mindways Software, Austin, TX, USA) was included in each scan. CT images were reconstructed at slice thickness 3-mm for lumbar spine and 1-mm for lumbar spine and proximal femur, using standard body reconstruction kernel, with in-plane pixel size 512 X 512 and display field-of-view 250 mm. QCTPro software (Mindways Software Inc, Austin, TX, USA) was used to analyze the QCT scans. Lumbar volumetric BMD (LSvBMD) was calculated as the average vBMD of L1 and L2. Along with volumetric BMD, DXA-equivalent areal BMD and T-score for the proximal femur was calculated using a computed tomography x-ray absorptiometry program (CTXA; Mindways Software). [18]

Cortical bone mapping

Cortical bone mapping (CBM) of the proximal femur was performed according to the previously proposed CBM pipeline, a surface-based technique to reveal the localized skeletal changes and significance from clinically available low resolution QCT data [19]. Briefly, bone properties including cortical thickness (CTh, mm), cortical bone mineral density (CBMD, mg/cm^3), endocortical trabecular density (ECTD, mg/cm^3), and cortical mass surface density (CMSD, mg/cm^2; cortical mass per unit surface area, calculated by multiplying CBMD X CTh) were calculated at each of roughly 8000 to 12000 locations, covering the surface of the bone , which was represented as a triangle mesh. To compare the obtained bone properties among multiple subjects and time points, each surface was registered to a template (canonical) hip surface, with individual cortical data transferred to the canonical surface. The mapped individual

cortical data were then used to build generalized linear regression models, along with potential regressors including time points and the intervention group. Statistical parametric mapping was used to visualize localized regions of the surface with significant difference by time points and intervention. The coefficient of variation (CV) for repeat scanning for individual measurements (interval 3 months) has been shown to be 6%, 3%, 5%, and 9% for CTh, CBMD, CMSD, and ECTD, respectively, in a prior study. [15]

Femoral neck geometry analysis

The Bone Investigational Toolkit (Mindways Software Inc, Austin, TX, USA) was used to calculate three-dimensional femoral neck geometry parameters from QCT scans. Femoral neck geometry parameters including cross-sectional area (CSA), cortical thickness (CTh), cross-sectional moment of inertia (CSMI), section modulus (Z), and buckling ratio (BR) were obtained at femoral neck area, with further analysis for CTh by quadrants (superior anterior, SA; superior posterior, SP; inferior anterior, IA; inferior posterior: IP). [20]

Statistical analysis

Clinical characteristics of study subjects (BP users versus non-users) were compared using independent two-sample t-tests, Wilcoxon rank sum tests, or chi-square tests as appropriate. A paired t-test was used to compare the changes of bone density between baseline and follow-up QCT scans in BP users and non-users. Propensity score matching was performed using the Stata ‘psmatch2’ command, with the nearest-neighbor algorithm on a 1:1 basis without replacement. A caliper of 0.2 X standard deviation of log-transformed propensity score was used. [21] Covariate balance was

checked by standardized mean difference with a threshold >0.2 (20 %) as an indicator for substantial imbalance. [22] After propensity score matching, the standardized differences decreased to <0.2 in all matched variables (supplementary figure 1). Percent changes (%) in bone parameters between BP users and non-users were compared using an independent two sample t-test. A linear regression model was built to assess the independent effect of BP use on changes in femoral neck estimated CTh on average and in each quadrant, with adjustment for covariates. In statistical parametric mapping, random field theory was used to correct multiple comparisons to control the overall image-wise chance of false positives. Statistical parametric mapping was performed using MATLAB (Release R2019a, The MathWorks Inc, MA, USA). All statistical analyses were performed using Stata 14.1 (College station, TX, USA). The statistical significance level was set at a two-sided p value <0.05.

Results

Characteristics of study subjects

A total of 108 subjects (54 BP users and 54 BP non-users) were analyzed in a propensity score-matched cohort (mean age 62.4 year). In this matched cohort, BP users and non-users did not differ significantly in age (62.6 vs. 61.6 years), LSvBMD (77.2 vs. 80.7 mg/cm^3), FNaBMD (0.564 vs. 0.576 g/cm^2) or THaBMD (0.676 vs. 0.677 g/cm^2; $p>0.05$ for all; Table 1). For BP users, the proportion of observation period covered by BP prescription was median 80% with interquartile range 68 to 93%. For bisphosphonate groups, oral risedronate (35 mg weekly or 150 mg monthly) were the most common (n=41, 76%), followed by oral alendronate 70 mg weekly (n=9, 17%) and oral monthly ibandronate 150 mg (n=4, 7%).

Changes in QCT-derived bone density parameters

In the matched cohort, the follow-up duration between QCT scans was median 2 years (760 vs. 757 days in BP users and non-users, p=0.327). Volumetric bone densities at lumbar spine (-4.2%), femoral neck (-3.3%), and total hip (-4.7%) all decreased significantly in BP non-users during aromatase inhibitor treatment, whereas BP use showed a protective effect against the deterioration of bone density by aromatase inhibitor use (LS: +5.5%; FN -0.5%; TH -1.2%; Table 2). Similar findings were observed for changes in FNaBMD and THaBMD.

Localized bone changes in cortical bone mapping

Results of cortical bone mapping analysis are presented in Figure 2. Compared to BP non-users, BP use had a favorable effect on preserving average CMSD (+3.4% vs. -0.3%, $p<0.001$), CTh (+3.3% vs. +0.1%, p=0.007), and ECTD (+1.8% vs. -4.3%,

p=0.004) of the proximal femur. Three-dimensional cortical mapping revealed that BP treatment in aromatase inhibitor users had protective effects on specific key locations of the proximal femur including superior femoral neck and lateral trochanter lesions, with a prominent effect on CTh at superior femoral neck. The protective effect of BP on ECTD was significant at lesser trochanteric lesion (supplementary figure 2).

Changes in femoral neck geometry

In femoral neck geometry quadrant analysis, BP use protected against the deterioration in average femoral neck CTh (-1.4% vs. -6.1%) in all quadrants (SA: -7.9% vs. -20.7%; IA: -1.7% vs. -5.9%; IP: +2.6% vs. -0.6%; $p<0.05$ for all) except SP lesion (-10.4% vs. -18.4%, p=0.188; Figure 3). BP use showed favorable effects in changes in CSMI (+4.4% vs. -0.7%, p=0.001), section modulus (+1.1% vs. -1.7%, p=0.013) and buckling ratio (+1.3% vs. +7.5%, $p<0.001$) of the femoral neck during aromatase inhibitor use. The effect of BP use on CTh at average femoral neck (+4.7% point difference between BP users and non-users, 95% CI +2.2 to 7.1, $p<0.001$) and at quadrants remained independent after adjustment for age, baseline femoral neck vBMD, and c-telopeptide level (Table 3).

Discussion

Our study demonstrates that BP use in postmenopausal women with early breast cancer receiving aromatase inhibitor treatment could prevent cortical bone loss at key locations of the proximal femur. BP users had beneficial effects in preserving LSvBMD, THaBMD and CBM parameters, including CMSD, CTh and ECTD at the proximal femur compared to age- and baseline BMD-matched non-users. The protective effect of BP against cortical bone deficit by AIBL was most prominent at the superior part of femoral neck and lateral trochanteric region, showing substantial heterogeneity. The protective effect of BP use on CTh at the femoral neck remained robust after adjustment for age, baseline femoral neck BMD and c-telopeptide level.

Several studies have shown favorable effects of BP use on post-menopausal women with early breast cancer receiving aromatase inhibitor therapy. Postmenopausal women with AIBL treated with oral risedronate showed BMD changes of +2.3% at lumbar spine (LS) and +0.6% at total hip (TH), whereas the placebo group showed -1.7% and -2.7% decreases at 24 months after active treatment [23]. Another study with oral risedronate use on postmenopausal women with anastrozole treatment showed a +1.1% gain at LS and -0.7% loss in BMD at TH after 36 month follow up, while those given placebo lost -2.6% and -3.5% at LS and TH, respectively [24]. In this study, BMD at lumbar spine, femoral neck and total hip all decreased significantly (-4.2%, -3.3%, -4.7%, respectively) in BP non-user group during median 2 years, whereas BMD at lumbar spine or hip in BP users remained spared or relatively increased. Our results are in line with previous findings regarding the protective role of BP for AIBL. Furthermore, we investigated spatial heterogeneity of BP effects on longitudinal changes in cortical parameter at the proximal femur. To our knowledge, our study is the first to use QCT and 3D CBM techniques to assess

the positive impact of BP in patients with AIBL. Our results could support the recent guidelines on BP treatment in post-menopausal women with AIBL, suggesting a potential role of BP as an effective treatment against cortical bone deficit by aromatase inhibitors at key locations of the proximal femur [25].

By using the CBM technique, we were able to visualize substantial local differences in the cortical bone changes by BP treatment in patients with AIBL. CBM had been used in prior studies for assessing treatment response in cortical bone. Denosumab increased CMSD and CTh compared to placebo at key locations of the femoral cortex, such as lateral trochanter, compared to placebo in postmenopausal women with osteoporosis [26]. The key locations with most benefit were similar with sites observed in our study. Patterns of focal cortical defect were linked to different fracture types [13]. Local bone parameters derived from CBM improved prediction of fracture risk and type when added to DXA-derived parameters [14, 15]. Focal thinning of the lateral trochanter has also been associated with trochanteric fracture [27]. Thinner estimated cortical thickness at the superior region of femoral neck was associated with higher incidence and pathogenesis of femoral neck fracture [28]. In this study, BP treatment on aromatase inhibitor users with early breast cancer showed favorable effects on cortical parameters at superior femoral neck and lateral trochanter, with prominent improvement in CTh at superior anterior region of the femoral neck. In the light of previous findings, our study may suggest that BP treatment would have a beneficial effect on fracture risk reduction by preventing cortical bone loss at key locations of the proximal femur, which needs to be investigated further [29, 30].

In a study conducted by Cheung and colleagues, AIBL was associated with more dramatic changes in the cortical compartment than the trabecular compartment in peripheral QCT scans of distal tibia and radius [31]. While the group treated with

exemestane showed up to 8-fold rapid decline in both cortical thickness and area compared to the placebo group, there was little difference in trabecular thickness or number between the two groups [31]. The authors argued that effects of aromatase inhibitor on bone strength could have not been fully captured by central bone DXA testing [32]. Our study evaluated the effect of aromatase inhibitor on the proximal femur, which is a site with high clinical importance, in a longitudinal setting. In line with previous findings from studies using peripheral QCT, we observed that aromatase inhibitor was associated with progression of cortical bone deficit at the proximal femur. These findings also align with the prior notion that estrogen deficiency in postmenopausal women is associated more strongly with cortical bone loss compared to trabecular bone loss. [33] These findings may suggest that a negative impact of aromatase inhibitor use on the cortical compartment of the proximal femur would lead to additional fracture risk, at least in certain subgroups: this needs to be validated further.

Our study has several limitations. Because it is a non-randomized observational study based on retrospective medical record review, BP users and non-users could have systemic differences, although we tried to match key baseline characteristics of two groups as much as was possible, with additional statistical adjustment in multivariable models. Median 2-year follow up duration might not be long enough to evaluate meaningful changes in bone structure. However, our studies showed similar change of BMD compared to previous key randomized clinical trials with 24-month follow up on BP treatment in postmenopausal women with early breast cancer [23, 34]. Subgroup analyses based on types of bisphosphonates were not possible due to limited sample size. Further studies on effects of other antiresorptives, such as intravenous BP or denosumab, on cortical deficit in AIBL would be needed.

Although we used QCT scans reconstructed to 1-mm slice thickness to evaluate cortical parameters of proximal femur, the resolution of clinical QCT data may not be sufficient to analyze intracortical remodeling and cortical porosity or to avoid the partial volume effect enitrely [35]. However, the 3D CBM pipeline allowed us to perform reliable, reproducible analysis on spatial heterogeneity in cortical parameters using clinical QCT [10-12].

In conclusion, BP use prevented cortical bone loss at key locations of the proximal femur in AIBL. BP use increased CMSD by up to 15% at key locations of the hip including the superior part of femoral neck and lateral femoral trochanter. BP prevented the thinning of average estimated CTh of the femoral neck (-1.4% vs. -6.1%, $p<0.001$), particularly at the superior anterior quadrant. Improvements in key locations of cortical femoral bone could support the effect of BP treatment in lowering hip fracture risk, which merits further investigation.

Declarations

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Data availability

The data analyzed in this study are available upon reasonable request to corresponding author (YR).

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Conflict of interest

Namki Hong, Seung Won Burm, Graham Treece, Keenan Brown, Kyungjin Kim, Seunghyun Lee, Sungjae Shin, Heajeong Park, and Yumie Rhee declare no conflicts of interest with regard to the completion and reporting of this study.

Ethical approval

This study was approved by the institutional review board of Severance Hospital, Seoul, Korea (IRB no. 4-2018-0635) with the requirement for informed consent waived due to the fact that medical records were reviewed. All procedures performed in the studies involving human participants were in accordance with ethical

standards of the institutional research committee and the 1964 Helsinki declaration and its later amendments.

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Table 1. Characteristics of study subjects

	Bisphosphonate users (N = 54)	Bisphosphonate non-users (N = 54)	P value
Age, year	62.6 ± 6.9	61.6 ± 8.1	0.516
Body mass index, kg/m^2	24.6 ± 3.0	24.9 ± 3.3	0.526
Systolic blood pressure, mmHg	124 ± 16	124 ± 16	0.411
Diabetes mellitus	12 (22)	12 (22)	0.999
Hypertension	11 (20)	17 (31)	0.188
Adjuvant chemotherapy	31 (57)	30 (55)	0.846
Adjuvant radiotherapy	35 (65)	35 (65)	0.999
Pathologic stage 2-3	22 (41)	22 (41)	0.999
Estimated glomerular filtration rate (ml/min/1.73m^2)	89 ± 15	88 ± 18	0.783
Serum calcium, mg/dL	9.1 ± 0.5	9.1 ± 0.5	0.999
Inorganic phosphorus, mg/dL	3.9 ± 0.6	3.9 ± 0.7	0.708
25-hydroxyvitamin D, ng/mL	19 ± 9	16 ± 9	0.059
Serum C-telopeptide, ng/mL	0.694 [0.333 to 0.941]	0.686 [0.401 to 0.927]	0.954
LSvBMD, mg/cm^3	77.2±18.4	80.7±24.5	0.390
FNaBMD, g/cm^2	0.564±0.070	0.576±0.075	0.401
THaBMD, g/cm^2	0.676±0.091	0.677±0.091	0.934
QCT follow-up duration, days	760 [732-1115]	757 [720-1095]	0.327
Proportion of days covered, %	80 [68-93]	N/A	N/A

Abbreviations: N/A, not applicable; QCT, quantitative computed tomography. Proportion of days covered: covered percentage of duration between baseline and follow-up QCT by bisphosphonate prescription records (drug persistence)

Table 2. Changes in QCT-derived bone density during aromatase inhibitor use

	Bisphosphonate users (N = 54)			Bisphosphonate non-users (N=54)		
	Baseline	Follow-up	P value	Baseline	Follow-up	P value
LS vBMD	77.2±18.4	81.5±17.8	0.006	80.7±24.5	77.4±24.9	0.015
FN aBMD	0.564±0.070	0.570±0.070	0.157	0.576±0.075	0.557±0.071	<0.001
FN T-score	-2.4±0.6	-2.4±0.6	0.180	-2.4±0.6	-2.5±0.6	<0.001
FN vBMD	261±34	259±35	0.145	265±33	256±32	<0.001
TH aBMD	0.676±0.091	0.673±0.091	0.510	0.677±0.091	0.659±0.086	<0.001
TH T-score	-2.2±0.7	-2.2±0.7	0.515	-2.2±0.7	-2.3±0.7	<0.001
TH vBMD	248±38	245±36	0.040	249±30	242±28	<0.001

Abbreviations: LS, lumbar spine; FN, femoral neck; TH, total hip; vBMD, volumetric bone mineral density; aBMD, areal bone mineral density.

Table 3. Effect of bisphosphonate use on femoral neck cortical thickness in aromatase inhibitor users

Sites	Adjusted beta coefficient (95% CI) (bisphosphonate user vs. non-user)*	P value
Femoral neck estimated cortical thickness (average), percent change (%)	+4.7 (+2.2 to +7.1)	< 0.001
Quadrants		
Superior anterior, %	+12.8 (+3.1 to +22.4)	0.010
Inferior anterior, %	+4.1 (+0.1 to +8.2)	0.047
Inferior posterior, %	+3.1 (+0.4 to +5.9)	0.025
Superior posterior, %	+8.0 (-4.1 to +20.1)	0.193

*Adjusted for age, baseline femoral neck volumetric bone mineral density, and c-telopeptide level. Median follow-up duration was 757 days (interquartile range 727 to 1109).

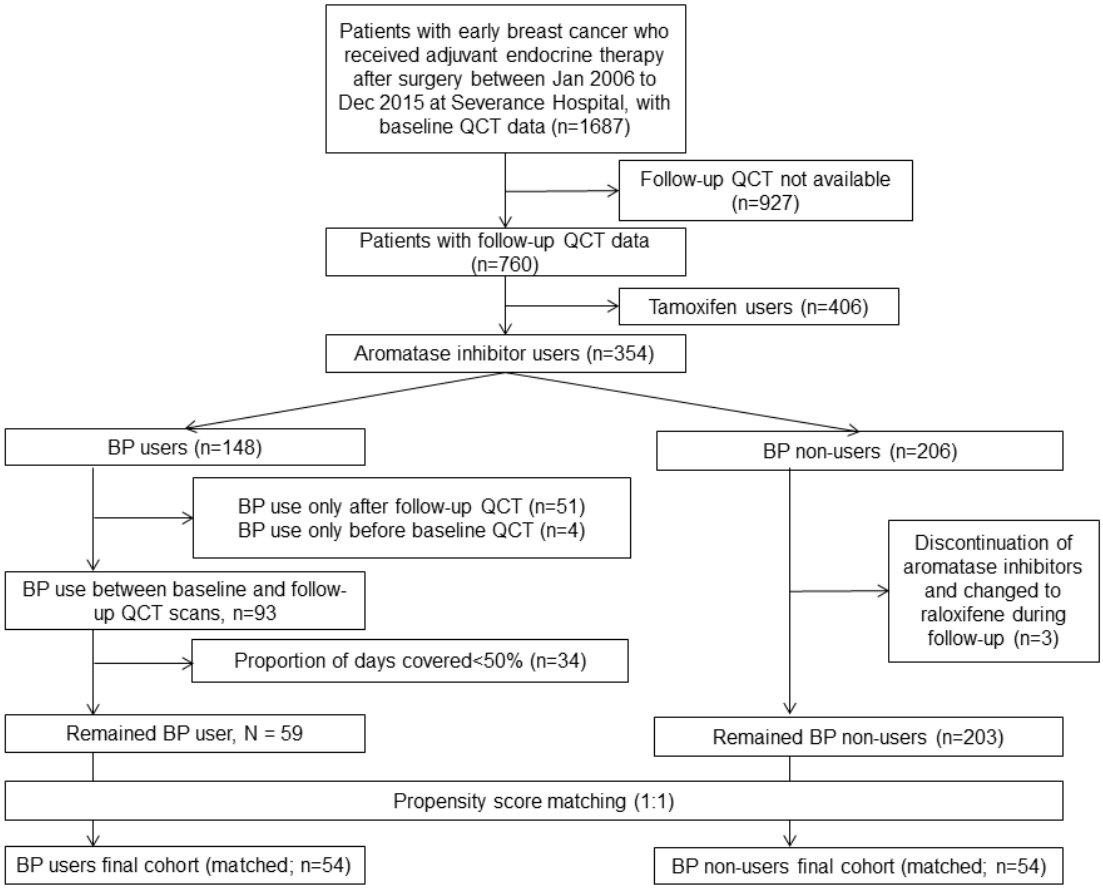


Figure 1. Study flow. Abbreviations: BP, bisphosphonate; QCT, quantitative computed tomography.

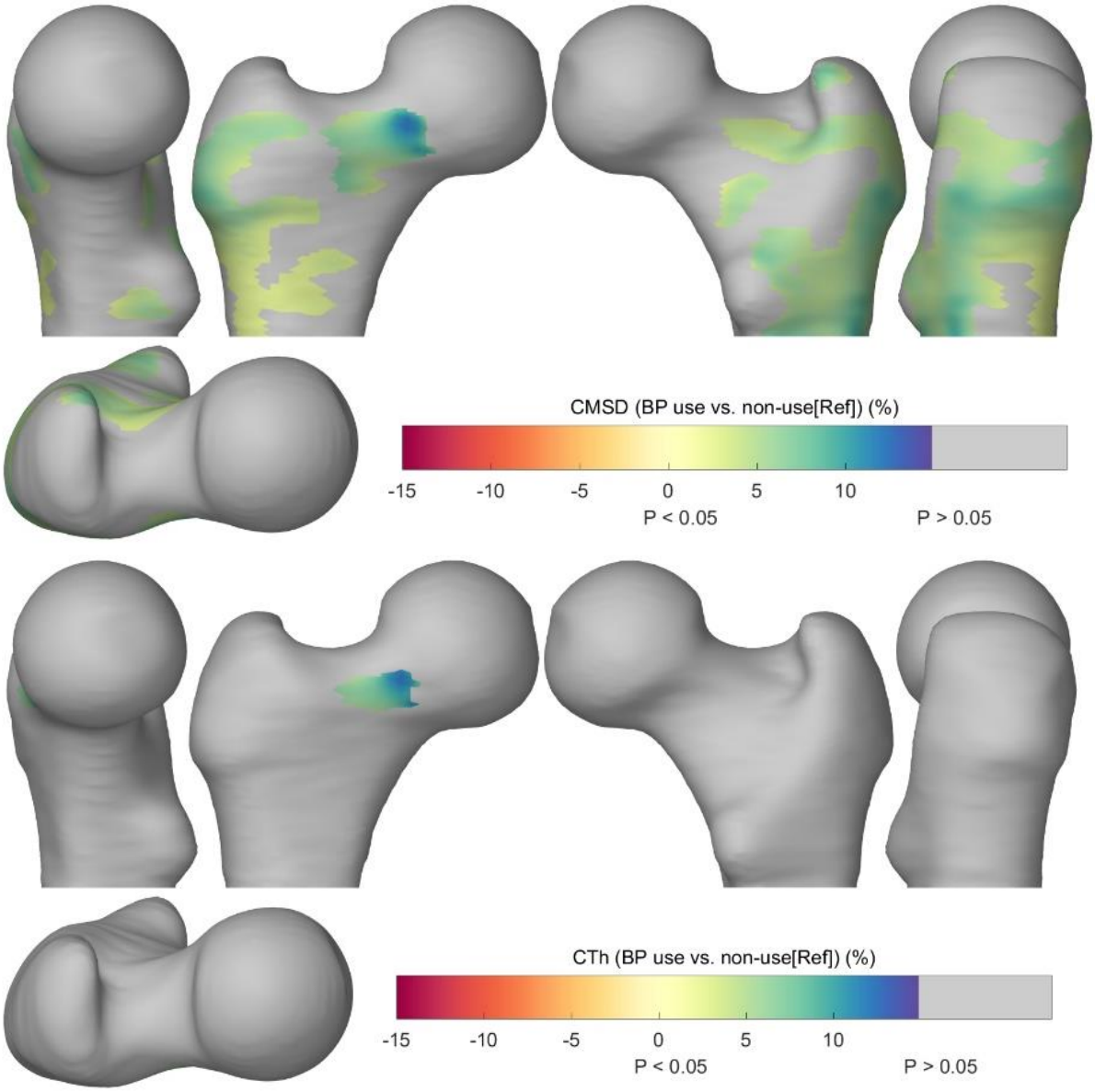


Figure 2. 3D Cortical mapping of absolute difference in changes of cortical mass surface density (CMSD) and cortical thickness (CTh) in BP users vs. non-users during median 2 years in patients with early breast cancer on aromatase inhibitor treatment. Colored areas indicate key locations with significant difference in CMSD and CTh changes between BP users and non-users. BP use had a favorable effect on CMSD at the superior femoral neck and lateral trochanter, with prominent changes in CTh at the superior femoral neck.

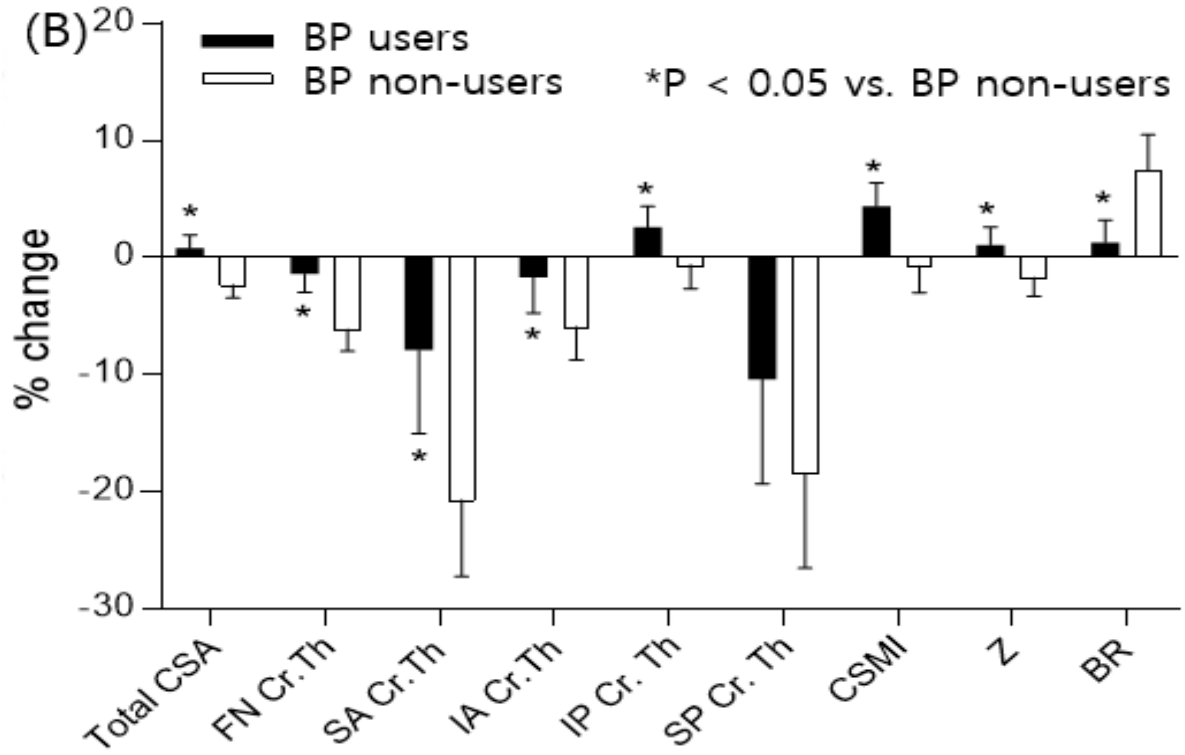
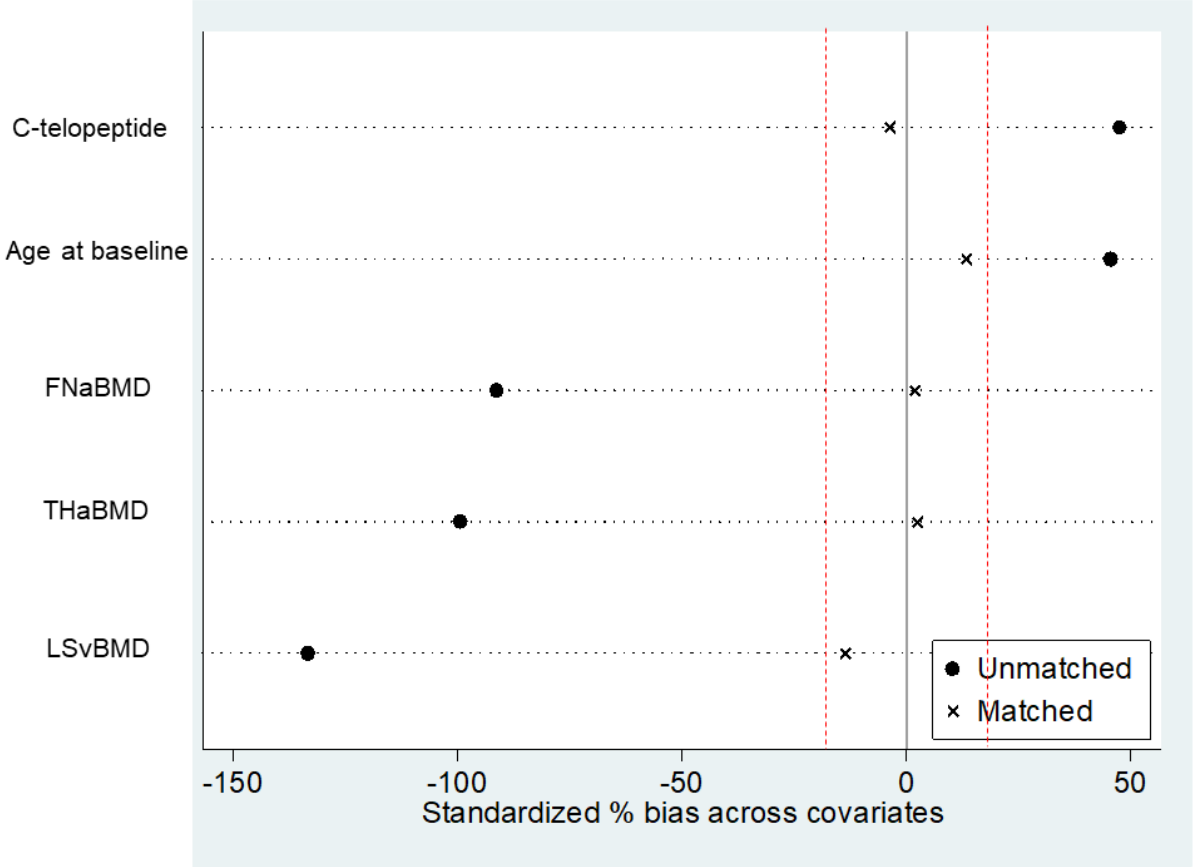


Figure 3. Quadrant analysis of femoral neck cortex. BP users had a favorable profile in changes of cortical thickness and bone geometry parameters at the femoral neck. Abbreviations: CSA, cross-sectional area; FN, femoral neck; Cr.Th, cortical thickness; SA, superior anterior; IA, inferior anterior; IP, inferior posterior; SP, superior posterior; CSMI, cross-sectional moment of inertia; Z, section modulus; BR, buckling ratio; BP, bisphosphonates.

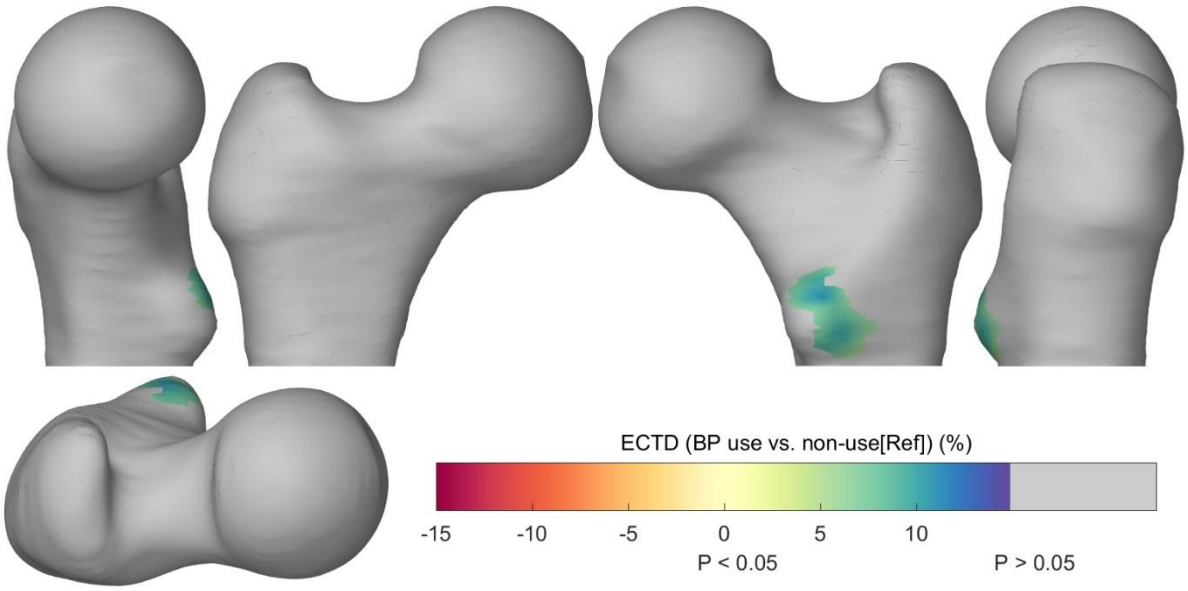
Supplementary table 1. Clinical characteristics of unmatched study subjects

	BP users (N = 59)	BP non-users (N = 203)	P value
Age	62.2 ± 6.7	59.1 ± 7.3	0.004
BMI	24.5 ± 2.9	24.7 ± 3.3	0.284
SBP	122.6 ± 16.9	120.2 ± 14.4	0.218
DBP	78.8 ± 10.4	79.2 ± 9.9	0.793
DM	19 (20.6)	46 (22.6)	0.700
HTN	24 (26.1)	44 (21.7)	0.405
Angiotensin blockers	12 (34.3)	13 (22.4)	0.211
Chemotherapy	52 (56.5)	132 (65.0)	0.163
Radiotherapy	62 (67.4)	138 (67.9)	0.920
Hemoglobin, g/dL	12.1 ± 1.4	11.9 ± 1.4	0.391
ALT	21.2 ± 14.0	24.0 ± 17.7	0.180
Albumin	4.2 ± 0.3	4.2 ± 0.4	0.916
Total cholesterol, mg/dL	194.1 ± 36.0	198.8 ± 39.7	0.330
Fasting plasma glucose, mg/dL	108.5 ± 32.9	107.6 ± 26.7	0.816
Pathologic stage 2-3	37 (40.2)	98 (48.2)	0.198
LSvBMD	74.7 ± 19.6	109.7 ± 32.3	<0.001
FNaBMD	0.560 ± 0.072	0.647 ± 0.090	<0.001
THaBMD	0.670 ± 0.095	0.769 ± 0.105	<0.001
GFR (CKD-EPI)	90.9 ± 13.7	90.5 ± 15.6	0.814
Serum calcium	9.1 ± 0.3	9.1 ± 0.5	0.898
Serum phosphate	3.8 ± 0.5	3.9 ± 0.6	0.367
25-hydroxyvitamin D	18.5 ± 9.1	16.0 ± 7.9	0.075
Serum C-telopeptide	0.720 [0.408 to 0.964]	0.483 [0.305 to 0.723]	0.002
QCT FU duration	754 [728-1113]	748 [658 to 1096]	0.327
Proportion of days covered	84.4% (68.4-94.4)	N/A	N/A

Abbreviations



Supplementary figure 1. Standardized difference after propensity matching. Standardized difference for all matched variables were reduced to less than 20% as the threshold for acceptable balance between two groups.



Supplementary figure 2. Difference in changes of endocortical trabecular density between BP users and non-users during median 2 years in patients with early breast cancer on aromatase inhibitor treatment