



Differential effects of abaloparatide and teriparatide on hip cortical volumetric BMD by DXA-based 3D modeling

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Abstract

Summary In postmenopausal osteoporotic women in ACTIVE, abaloparatide reduced fracture risk and increased areal bone mineral density (BMD) more than teriparatide at the hip and wrist. DXA-based 3D modeling showed significantly greater increases in hip cortical volumetric BMD with abaloparatide versus teriparatide. This may explain differences reported in aBMD by DXA.

Introduction In ACTIVE, abaloparatide (ABL) increased bone mineral density (BMD) shown by dual-energy X-ray absorptiometry (DXA) while reducing fracture incidence in postmenopausal osteoporotic women. Changes in DXA BMD with ABL, 80 µg, were significantly greater than with open-label teriparatide (TPTD), 20 µg, at cortical sites including total hip, femoral neck, and 1/3 distal radius. The purpose of this study was to better understand the relative effects of ABL and TPTD on cortical and cancellous compartments in the proximal femur.

Methods Hip DXA images from a subset of randomly selected patients in the ACTIVE trial ($n = 250/\text{arm}$) were retrospectively analyzed using three-dimensional modeling methods (3D-SHAPER software) to evaluate changes from baseline at months 6 and 18.

Results Similar significant increases in trabecular volumetric BMD (vBMD, + 9%) and cortical thickness (+ 1.5%) were observed with ABL and TPTD by 3D-DXA at 18 months. In contrast, only ABL significantly increased cortical vBMD versus baseline (+ 1.3%), and changes in both cortical vBMD and cortical surface BMD were significantly greater with ABL versus TPTD. In the TPTD group, changes in cortical vBMD were inversely correlated with changes in serum CTX (carboxy-terminal telopeptide of type I collagen) and PINP (procollagen type I N-terminal propeptide), suggesting that higher bone turnover may have attenuated cortical gains.

Conclusion These results suggest previously reported differences in areal BMD increases between ABL and TPTD may be due to differential effects on cortical vBMD. Further studies are warranted to investigate how these differences affect therapeutic impact on hip strength in postmenopausal women with osteoporosis.

Keywords Abaloparatide · Cortical volumetric BMD · Dual-energy X-ray absorptiometry · Osteoporosis · Teriparatide · 3D modeling

Introduction

Abaloparatide (ABL) is a human parathyroid hormone-related peptide (PTHrP)(1-34) analog that stimulates bone formation, resulting in significant increases in areal bone

mineral density (aBMD) and reductions in fracture incidence after 18 months of daily subcutaneous administration in postmenopausal women with osteoporosis [1–3]. Teriparatide (TPTD), or PTH(1-34) which binds the same PTH type 1 receptor (PTH1R), also stimulates bone formation, but results in significantly smaller increases in BMD at the total hip, femur neck, and distal radius than ABL at the US Food and Drug Administration (FDA)-approved clinical doses [1, 2, 4, 5]. These differences may be related to their relative affinities to the RG and R0 conformations of the PTH1R [1], resulting in differential activation of pathways that regulate bone formation and bone resorption [6]. Lesser stimulation of serum

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carboxy-terminal cross-linking telopeptide of type I collagen (s-CTX) with ABL relative to TPTD in the ACTIVE trial suggested that bone resorption may mediate these BMD differences, which were greater at sites with more cortical bone, such as the femoral neck and radius [2, 4].

PTH is an important regulator of calcium homeostasis, and pathologic elevations in PTH due to renal disease result in bone loss and hypercalcemia, associated with increased bone resorption [7]. Although daily TPTD provides a positive balance between bone formation and resorption and increases BMD at most skeletal sites, BMD has been shown to decrease at purely cortical sites [8]. Unlike its effects on trabecular or endocortical surfaces, where TPTD-stimulated “over-filling” of each bone multicellular unit is part of its anabolic effect, the increased rate of remodeling within the cortex has been associated with increased cortical porosity and decreased cortical volumetric BMD (vBMD) in both monkeys [9, 10] and humans [11]. The intracortical effects of ABL have not been thoroughly examined in humans; however, cortical vBMD and cortical porosity did not change with ABL treatment for up to 16 months in ovariectomized primates [12]. In addition, unlike TPTD, ABL did not lead to significant decreases in aBMD versus placebo at the purely cortical 1/3 distal radius in humans [4], suggesting a fundamental difference in the cortical effects of ABL.

Further clinical examination of the specific effects of ABL on cortical versus trabecular bone have been limited, as quantitative computed tomography (QCT) was not performed at the hip in the ACTIVE trial. Recently, three-dimensional (3D) modeling methods were developed to estimate cortical and trabecular measurements from two-dimensional (2D) dual-energy X-ray absorptiometry (DXA) scans. At the proximal femur, these 3D-DXA measurements were shown to correlate well with QCT results [13], and provided insights into the compartmental effects of various osteoporosis therapeutics including TPTD [14]. Therefore, to better understand and compare the effects of ABL and TPTD on the cortical and trabecular compartments of the proximal femur over 18 months, hip DXA images were subjected to 3D modeling in a subset of randomly selected patients from the ACTIVE trial.

Methods

Study design

The ACTIVE trial (conducted from March 2011 to October 2014) was a phase 3, double-blind, placebo-controlled trial with an open-label active comparator arm that enrolled 2463 postmenopausal women from 10 countries [2]. Patients were randomized 1:1:1 to receive daily subcutaneous injections of placebo, 80 µg ABL, or 20 µg TPTD (open-label) for 18 months. Inclusion criteria required that patients from 49 to

86 years of age have BMD T-scores ≤ -2.5 and > -5.0 at the femoral neck or lumbar spine and either ≥ 2 mild or 1 moderate vertebral fracture or a history of low-energy nonvertebral fracture within the past 5 years. Patients older than 65 years were included if they met the fracture criteria and had a T-score ≤ -2.0 and > -5.0 or did not meet fracture criteria and had a T-score ≤ -3.0 and > -5.0 . Additional entry criteria can be found in the primary publication [2].

As part of the ACTIVE trial, DXA scans were collected at the spine and hip at baseline and 6, 12, and 18 months after treatment initiation. A subset of 750 patients from the ACTIVE trial, 250 from each treatment group (placebo [PBO], ABL, TPTD), were randomly selected for inclusion in the 3D-DXA analysis performed on the hip scans collected at baseline, month 6, and month 18. Blood samples were collected from a smaller subset (within each subset of 250 patients) to measure biomarkers of bone turnover (procollagen type I N-terminal propeptide [s-PINP] and carboxy-terminal cross-linking telopeptide of type I collagen [s-CTX]) at months 1, 3, 6, 12, and 18 (Nordic Biosciences). Randomized patients were stratified by study site, and patient race/ethnicity and uniformity were ensured across groups.

3D-DXA analysis

Blinded image files of the subset of hip DXA scans at baseline and months 6 and 18 were transferred for DXA-based 3D modeling (3D-SHAPER v2.10.1, Galgo Medical, Spain), the details of which are described elsewhere [13]. Briefly, the software built a QCT-like 3D proximal femur model for each DXA image, based on a database of QCT scans from Caucasian men and women (Fig. 1). The total proximal femur model included a surface mesh and a vBMD image, from which integral vBMD was extracted. The cortex was then segmented by fitting a function of the cortical thickness and density, location of the cortex, density of surrounding tissues, and imaging blur to the density profile computed along the normal vector at each node of the proximal femur surface mesh [15]. Cortical 3D-DXA measurements included cortical vBMD (in mg/cm^3), cortical thickness (in mm), and their product cortical surface BMD (sBMD, in mg/cm^2). Cortical sBMD provides an evaluation of the overall behavior of the cortical compartment, a complete description of which is available elsewhere [14]. The remainder of the image was considered trabecular, and trabecular vBMD (in mg/cm^3) was computed. Temporal changes in cortical parameters were illustrated in 3D by registration of group average models at follow-up timepoints to those at baseline; percent changes were computed and displayed on the timepoint image. Group average changes from baseline in vBMD were also plotted in 2D and shown in the coronal plane.

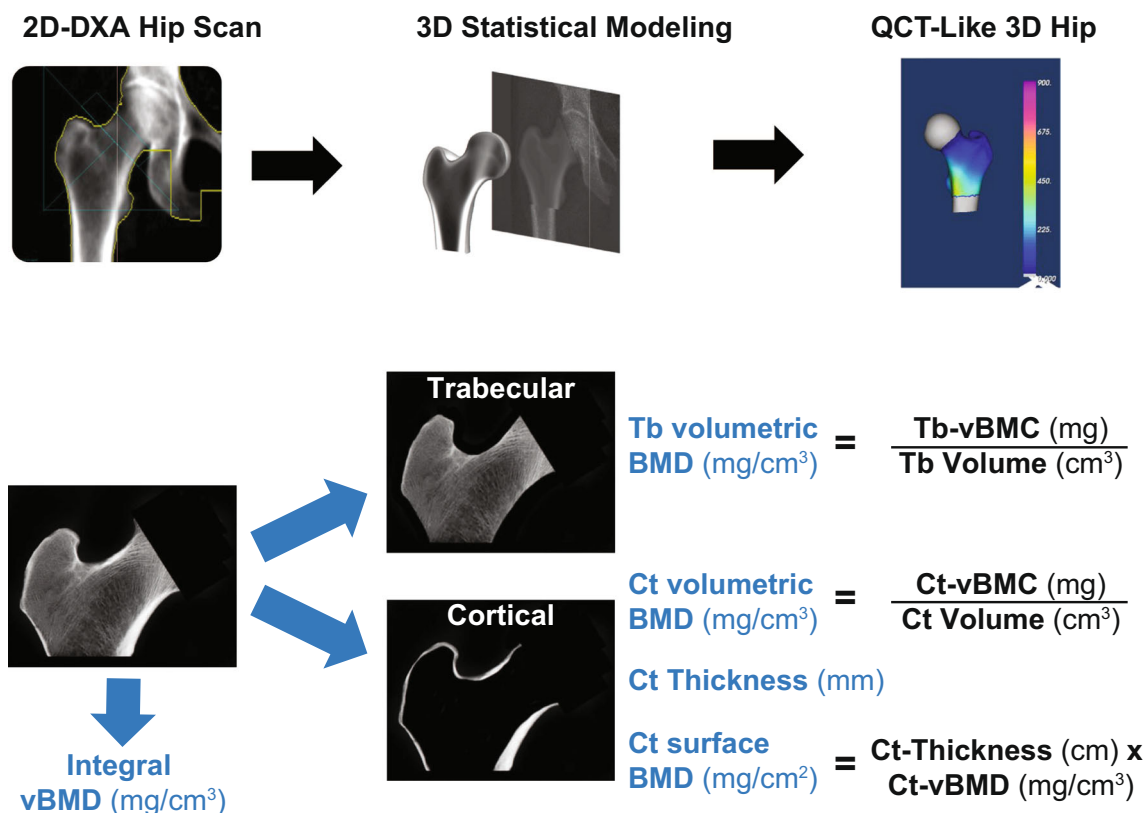


Fig. 1 Derivation of 3D-DXA endpoints. Two-dimensional hip DXA acquisitions performed at baseline and at months 6 and 18 were subjected to 3D modeling using 3D-DXA® software (v2.10.1, Galgo Medical, Spain) to generate a QCT-like proximal femur model. Volumetric BMD (vBMD) in the trabecular compartment and vBMD for cortical

thickness and cortical surface BMD in the cortical compartment were generated. 3D-DXA, three-dimensional dual-energy X-ray absorptiometry; Ct, cortical; QCT, quantitative computed tomography, Tb, trabecular; vBMC, volumetric bone mineral content

Statistics

All statistical analyses were performed within SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) unless otherwise indicated. Pairwise group comparisons were made for percentage change from baseline data using *P* values derived from contrast tests based on a mixed-effect repeated-measure model adjusting for body mass index (BMI), age, value at baseline, and DXA scanner. Significance versus baseline was calculated using two-tailed *t* tests in R version 3.4.3 (R Core Team, 2017, Vienna, Austria). Pearson correlation coefficients were generated between 3D-DXA measurements (% change from baseline) and DXA aBMD (% change from baseline), as well as between 3D-DXA measurements and biomarkers of bone turnover (log ratio of postbaseline divided by baseline) for the smaller subset of patients who had serum biomarker measurements.

Visualizations include both 3D distribution of the group mean percentage changes from baseline in cortical parameters and 2D coronal cross sections of group mean percentage changes from baseline in vBMD across both cortical and trabecular compartments.

Results

The 3D-DXA cohort was well balanced across groups for age, DXA BMD, and prior fracture history (Table 1). The baseline demographics in the cohort were consistent with the intent-to-treat (ITT) population reported in the overall ACTIVE study [2].

2D-DXA

Changes in total hip aBMD were generally consistent between the ACTIVE ITT population [2] and the subset of patients in 3D-DXA cohort, with significant increases in both the ABL and TPTD groups at months 6 and 18 (Fig. 2a; all *P* < 0.001 vs PBO). In the 3D-DXA cohort at 18 months, increases in total hip aBMD with ABL (+ 4.2%) were significantly greater than with TPTD (+ 3.3%; *P* < 0.05).

3D-DXA

The increases in areal BMD corresponded to progressive significant increases in all 3D-DXA indices with ABL and TPTD at months 6 and 18, with the exception of cortical vBMD at

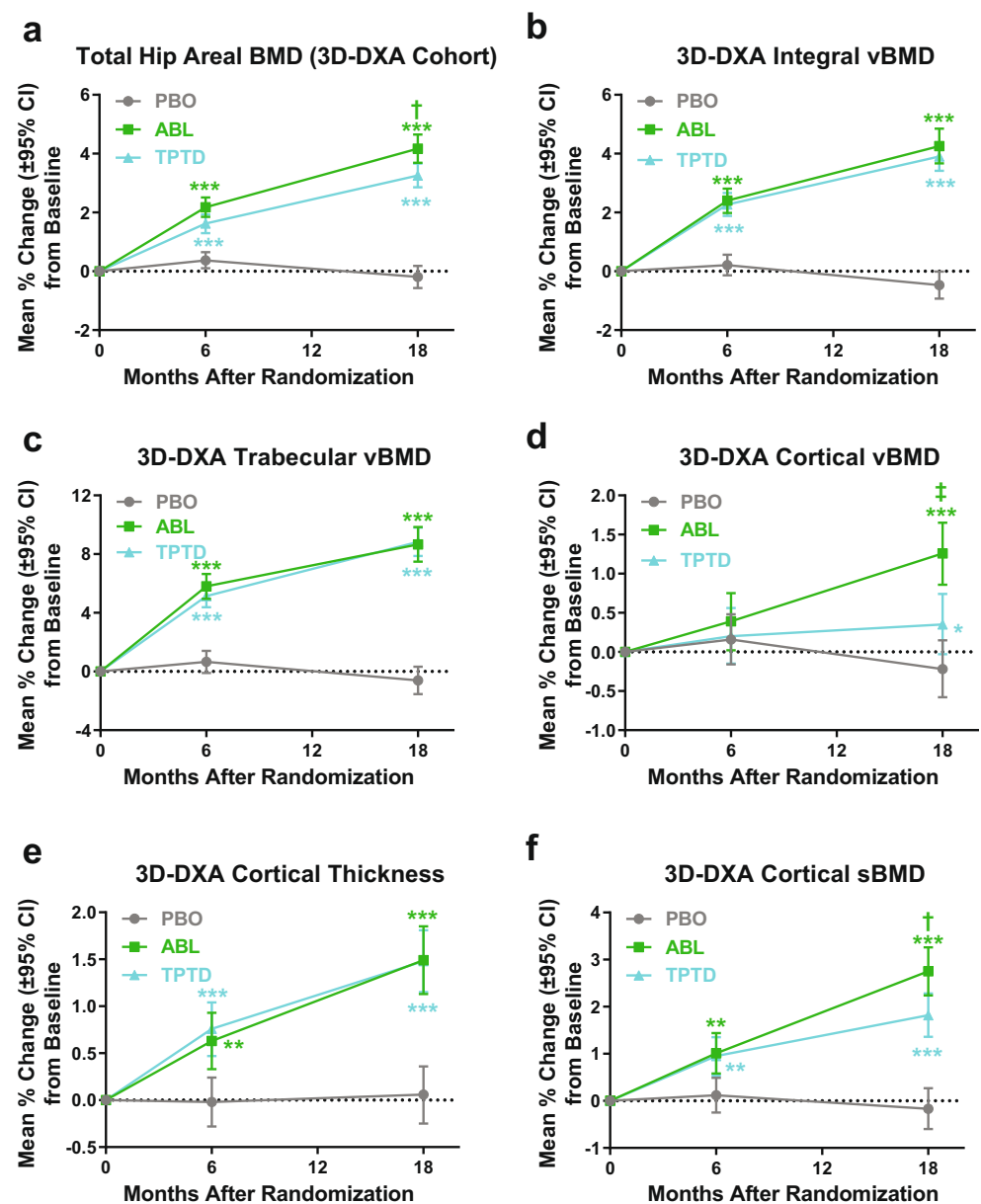
Table 1 Baseline characteristics and clinical characteristics for 3D-DXA cohort

Characteristic	PBO (<i>n</i> = 250)	ABL (<i>n</i> = 250)	TPTD (<i>n</i> = 250)
Age (years)			
Mean (SD)	69 (6.1)	69 (6.7)	68 (6.0)
Median (min, max)	69 (52, 86)	69 (50, 85)	68 (51, 84)
BMD T-score, mean (SD)			
Lumbar spine	-2.9 (0.8)	-2.8 (1.0)	-2.9 (1.0)
Total hip	-1.9 (0.8)	-1.9 (0.8)	-1.8 (0.7)
Femoral neck	-2.2 (0.7)	-2.2 (0.7)	-2.1 (0.6)
Baseline prevalent vertebral fracture, <i>n</i> (%)	60 (24.1) ^a	55 (22.0)	79 (31.6)
≥ 1 prior nonvertebral fracture within past 5 years, <i>n</i> (%)	71 (28.4)	74 (29.6)	73 (29.2)
No prior fracture, <i>n</i> (%)	98 (39.2)	86 (34.4)	90 (36.0)

^a*N* = 249

3D-DXA, three-dimensional dual-energy X-ray absorptiometry; ABL, abaloparatide; BMD, bone mineral density; PBO, placebo; SD, standard deviation; TPTD, teriparatide

Fig. 2 Longitudinal changes in hip aBMD and 3D-DXA endpoints. 2D- and 3D-DXA endpoints collected from scans at 0, 6, and 18 months after randomization. **a** 2D areal BMD from the cohort subjected to 3D-DXA modeling (*n* = 250/group). **b–f** 3D-DXA endpoints from the proximal femur (excluding femur head). Data shown as mean ± 95% CI for % change from baseline. Significant group differences shown as *P* < *0.05, **0.01, and ***0.001 versus PBO and *P* < †0.05 and ‡0.01 versus TPTD. 2D, two-dimensional; 3D-DXA, three-dimensional dual-energy X-ray absorptiometry; ABL, abaloparatide; BMD, bone mineral density; CI, confidence interval; PBO, placebo; TPTD, teriparatide



month 6 (Fig. 2). At month 18, integral vBMD was increased to a similar extent as total hip aBMD in the ABL (+ 4.3%) and TPTD (+ 3.9%) groups (Fig. 2b). Trabecular vBMD was significantly increased by approximately 9% in the ABL and TPTD groups at 18 months (Fig. 2c). Although cortical thickness was significantly improved by approximately 1.5% in both groups at month 18, cortical vBMD was increased to a greater extent in the ABL group (1.3%) versus the TPTD group (0.4%) (Fig. 2d, e). These increases in cortical vBMD were significantly greater than placebo for both agents; however, only ABL significantly increased cortical vBMD versus baseline (Fig. 3). The product of cortical thickness and cortical vBMD, cortical sBMD, was increased significantly in both

groups, to a greater extent in the ABL group (2.8%) than in the TPTD group (1.8%) at month 18 (Fig. 2f).

Visualization of the average spatial changes of the 3D-DXA parameters in the cortical portion of the proximal femur at month 18 is shown in Fig. 3. Uniform percent increases from baseline in these cortical parameters were observed with ABL, with more modest changes in the TPTD group, and no significant changes with placebo. Coronal cross sections in Fig. 3 further illustrate the mean spatial changes in vBMD from baseline to month 18, highlighting the positive changes in the cortical and trabecular regions with ABL and TPTD.

Correlation analyses were performed to determine how the changes in 3D-DXA parameters compared with the changes

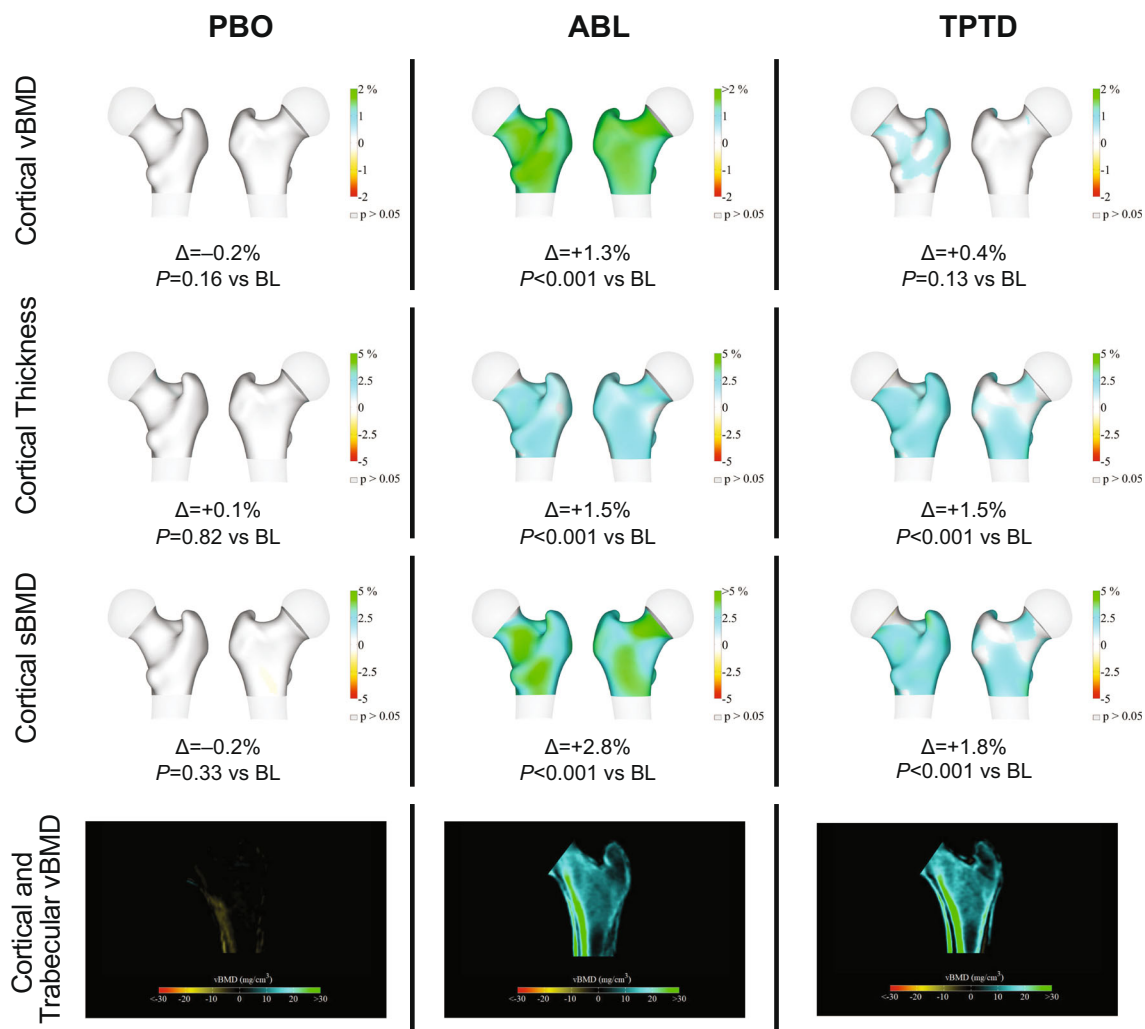


Fig. 3 Spatial changes in 3D-DXA cortical endpoints and cross-sectional representations of spatial changes in vBMD at month 18. Average spatial changes at month 18 in cortical 3D-DXA endpoints are shown for PBO, ABL, and TPTD. Anterior (left) and posterior (right) views are shown of a standardized proximal femur model for each endpoint and group. Increases in cortical sBMD, cortical vBMD, and cortical thickness are presented in blue-green colors while decreases are presented in yellow-red colors. Data are expressed as mean % change from baseline (Δ), with

P values highlighting changes from baseline value. Representative coronal views of the average vBMD changes (mg/cm^3) at month 18 in each group highlight the treatment effects in both the cortical and trabecular compartments. 3D, three-dimensional; ABL, abaloparatide; BL, baseline; DXA, dual-energy X-ray absorptiometry; PBO, placebo; sBMD, surface bone mineral density; TPTD, teriparatide; vBMD, volumetric bone mineral density

Table 2 Correlation coefficients for month 18 3D-DXA parameters versus total hip aBMD

Parameter	PBO	ABL	TPTD	Overall
Integral vBMD	0.84	0.90	0.82	0.89
Trabecular vBMD	0.76	0.84	0.76	0.84
Cortical vBMD	0.47	0.48	0.43	0.48
Cortical thickness	0.37	0.48	0.33	0.46
Cortical sBMD	0.65	0.73	0.60	0.70

$P < 0.0001$ for all correlations

Pearson correlations were performed using % change from baseline data 3D-DXA, three-dimensional dual-energy X-ray absorptiometry; aBMD, areal bone mineral density; ABL, abaloparatide; PBO, placebo; sBMD, surface bone mineral density; TPTD, teriparatide; vBMD, volumetric bone mineral density

in total hip DXA aBMD at 18 months (Table 2). Changes in areal BMD across all groups were best reflected by changes in integral vBMD with an r value of 0.89. The next best surrogates were trabecular vBMD ($r = 0.84$) and cortical sBMD ($r = 0.70$), with lesser though still-significant correlations for cortical vBMD ($r = 0.48$) and cortical thickness ($r = 0.46$) ($P < 0.0001$ for all correlations). These relationships were generally consistent across treatments and numerically highest with ABL.

Further correlations were performed to explore potential relationships between the treatment-related changes in serum biomarkers and the observed changes in 3D-DXA parameters at 18 months (Table 3). Serum biomarker data was available for 76 patients in the ABL group and 81 patients in the TPTD group. At month 3, both serum PINP and CTX were significantly and positively correlated with integral vBMD, trabecular vBMD, and cortical thickness in the ABL group ($r = 0.24$ to 0.45 ; $P < 0.05$), but not in the TPTD group ($r = -0.03$ to 0.11). At month 18, only trabecular vBMD remained significantly and positively

correlated with serum PINP and CTX in the ABL group. In the TPTD group, significant inverse correlations were found between cortical vBMD and serum CTX ($r = -0.22$ at month 3 and -0.24 at month 18), and between cortical vBMD and serum PINP ($r = -0.37$ at month 18), with cortical sBMD significantly and inversely correlated with both biomarkers at month 18.

Discussion

3D modeling methods using DXA images provide a unique opportunity to revisit the 2D-DXA data collected in osteoporosis therapeutic studies, to predict whether DXA aBMD changes were driven by effects in the trabecular or cortical compartments. Although both ABL and TPTD stimulate bone formation through the same receptor, in the ACTIVE trial, ABL increased aBMD at the total hip, femur neck, and distal radius to a significantly greater extent at 18 months [2, 4]. The current results indicate that this difference corresponded to significant increases in 3D-DXA-based cortical vBMD and sBMD with ABL relative to TPTD, while trabecular vBMD and cortical thickness were both increased to a similar extent. Furthermore, the differential effect of TPTD on cortical vBMD may be related to its inverse relationship with serum biomarkers of bone turnover, a relationship that was not present with ABL.

The current data are consistent with a previous 3D-DXA study that examined the effects of alendronate, denosumab, and TPTD over a 24-month period [14]. In that study, the antiresorptive agents consistently increased cortical bone indices in the proximal femur, while TPTD simultaneously increased cortical thickness and decreased cortical vBMD. Decreased cortical vBMD with TPTD has been reported in both animal [9] and human [16] studies, an effect attributed

Table 3 Correlation coefficients for month 18 3D-DXA parameters versus month 3 or 18 serum biomarkers

Parameter	Month 3				Month 18			
	Serum CTX		Serum PINP		Serum CTX		Serum PINP	
	ABL	TPTD	ABL	TPTD	ABL	TPTD	ABL	TPTD
Integral vBMD	0.31*	-0.03	0.39*	0.01	0.13	-0.13	0.24*	-0.13
Trabecular vBMD	0.37*	0.06	0.45*	0.07	0.40*	0.00	0.44*	0.06
Cortical vBMD	-0.11	-0.22*	0.08	-0.15	-0.18	-0.24*	-0.09	-0.37*
Cortical thickness	0.33*	0.11	0.24*	0.09	0.04	0.01	0.12	0.05
Cortical sBMD	0.12	-0.14	0.22	-0.08	-0.11	-0.22*	0.01	-0.32*

* $P < 0.05$

Pearson correlations were performed using % change from baseline DXA data and log ratio change from baseline for serum biomarkers

3D-DXA, three-dimensional dual-energy X-ray absorptiometry; ABL, abaloparatide; sBMD, surface bone mineral density; TPTD, teriparatide; vBMD, volumetric bone mineral density

to increased intracortical remodeling. In humans, the decrease in cortical vBMD with TPTD has been associated with both increased porosity [11] and decreased cortical tissue mineralization observed in iliac biopsies [17, 18]. Cortical porosity increases with TPTD have been hypothesized to be transient and this parameter is often not significantly increased in iliac crest biopsies after up to 2 years of treatment [19], despite continued elevations in the intracortical remodeling rate [20]. However, cortical porosity has been shown to expand with TPTD over time at clinically relevant cortical sites by HRpQCT (high-resolution peripheral QCT), with increases at the radius of 19% and 32% at 6 and 18 months, respectively, corresponding to declines in cortical vBMD of -2.0% and -2.4% [11]. Similar observations were found after 12 and 24 months of TPTD [21]. Decreases in cortical vBMD with TPTD have also been reported at the femur neck by QCT both in treatment-naïve patients [22] and, to a greater extent, in alendronate-pretreated patients [23, 24].

In the current study in treatment-naïve patients, TPTD had a neutral effect on cortical vBMD, while ABL resulted in a significant increase from baseline. The positive effect of ABL on cortical vBMD may reflect a reversal of age-related [25] and menopause-related [26] trabecularization of the cortex through bone apposition. As both ABL and TPTD resulted in similar increases in cortical thickness reflecting appositional growth, much of the difference in cortical vBMD may be due to increased cortical porosity rather than to lower tissue mineralization of newly formed bone. Nevertheless, conclusions cannot be made regarding the relative impact of ABL and TPTD on cortical porosity from the results in this study, and it is likely that the differences in serum CTX levels at the end of the study between ABL and TPTD may reflect some differential effects on tissue mineralization.

Cortical porosity (as estimated from hip QCT scans) has been identified as a risk factor for nonvertebral fragility fractures in postmenopausal women, independent of both FRAX (Fracture Risk Assessment Tool) score and hip BMD [27]. Thus, changes in porosity and vBMD should be considered in the context of their impact on bone strength. Previous studies using finite element modeling have demonstrated that TPTD-mediated reductions in femur neck cortical vBMD prevented significant improvements in proximal femur strength in patients treated for up to 18 months [23, 28]. No data on estimated strength indices have been generated in ABL clinical studies to date. Further analysis to estimate changes in strength in the current study may provide additional insights into the mechanisms by which ABL and TPTD affect bone fragility.

3D-DXA demonstrated the degree to which cortical and trabecular regions may be affected by anabolic therapy and how these changes are reflected in DXA BMD. Both ABL and TPTD increased vBMD in the trabecular compartment to a similar degree, with increases that were twice those for total hip aBMD over an 18-month period. These results are

consistent with the greater trabecular vBMD increases reported previously for TPTD by QCT of the proximal femur [22, 29], and reflect the robust anabolism that can occur in trabecular bone with PTH1R agonism. Cortical thickness was increased to a similar though lesser degree in both the ABL and TPTD groups, and only ABL significantly increased cortical vBMD from baseline.

Correlation analyses demonstrated that trabecular vBMD was a better surrogate for DXA total hip aBMD than cortical endpoints suggesting that, despite the importance of cortical bone to proximal femur strength [30], DXA BMD may underestimate the changes that occur in this compartment with anabolic therapy.

Differences in the degree to which ABL and TPTD stimulate bone resorption, and thus bone remodeling, are fundamental to the initial selection of ABL as a PTHrP analog with lower calcium-mobilizing potential [31]. These differences were reflected in lesser peaks and greater temporal declines in serum CTX with ABL versus TPTD, with similar gradual declines in serum PINP with continued ABL reflecting the decreasing remodeling rate. In the current study, the changes in serum biomarkers with TPTD were inversely correlated with cortical vBMD and cortical sBMD, further supporting that higher levels of bone resulted in lower cortical bone density and thus lower bone mass. These results suggest that persistent elevations in bone turnover may be a limiting factor in cortical bone mass accrual with TPTD. That no such relationship existed for ABL suggests that intracortical remodeling was less of a factor in determining cortical vBMD, particularly at month 18 when serum CTX was not elevated above baseline compared to a 40% increase above baseline for TPTD (by geometric means) [2]. In contrast, changes in serum biomarkers at month 3 were positively correlated with month 18 trabecular vBMD and cortical thickness in the ABL group, but not in the TPTD group. Similar observations were reported for lumbar aBMD changes in ACTIVE [32], suggesting that early serum biomarker responses are a better predictor of the later bone mass increases with ABL compared to TPTD.

Limitations in this study include the use of a subset of patients instead of the entire cohort from ACTIVE. However, at 250 patients per group, this subset represents the largest treatment study reported to date for 3D-DXA, and the baseline characteristics and hip BMD response in this subset were consistent with the overall patient population in ACTIVE. The 3D modeling approach itself is a relatively new technique and has several limitations as described elsewhere [14]. The software was originally developed to mimic QCT endpoints from DXA images in a treatment-naïve population and measurements correlate well between the two methods. However, the effects of therapeutics on this relationship are unknown. QCT-based delineation of cortical thickness and cortical vBMD can vary by imaging technique, making these endpoints less consistent across studies. However, their

product, cortical sBMD, may be more precise and continues to reflect the differences in cortical effects between ABL and TPTD. A final limitation of the study is that data are provided across the entire proximal femur, which contains subregions that are both predominantly trabecular (intertrochanteric) and cortical (femur shaft). Region-specific analysis of treatment-related changes in the trabecular and cortical parameters remain to be determined.

In summary, 18 months of ABL administration was associated with significant improvements in 3D-DXA-based vBMD in both cortical and cancellous compartments of the proximal femur. Although TPTD increased cortical thickness and trabecular vBMD to a similar extent as ABL, cortical vBMD remained at baseline levels. These results suggest that the greater increase in hip areal BMD and lesser serum CTX response with ABL may reflect a lower stimulation of intracortical remodeling than TPTD.

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Data availability Data that underlie the results reported in a published article may be requested for further research 6 months after completion of FDA or EMA regulatory review of a marketing application (if applicable) or 18 months after trial completion (whichever is latest). Radius will review requests individually to determine whether (i) the requests are legitimate and relevant and meet sound scientific research principles, and (ii) are within the scope of the participants' informed consent. Prior to making data available, requestors will be required to agree in writing to certain obligations, including without limitation, compliance with applicable privacy and other laws and regulations. *Proposals should be directed to* info@radiuspharm.com.

Compliance with ethical standards

Conflicts of interest RW and LH are employees of Galgo Medical and paid consultants of Radius. LH is a shareholder of Galgo Medical. MSO, YW, and RJW are employees and shareholders of Radius.

Ethics approval The ACTIVE study on which this post hoc analysis was based was conducted in accordance with the ethical principles in the Declaration of Helsinki in its revised edition (Tokyo, 2004), the guidelines for current Good Clinical Practice (GCP), and the ACTIVE trial was approved by the appropriate ethics and institutional review boards.

Consent to participate Written informed consent was obtained from each patient participating in the ACTIVE study on which this post hoc analysis is based.

Consent for publication For this post hoc analysis study, formal consent is not required.

Code availability 3D-DXA software (v2.10.1, Galgo Medical, Spain)

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