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Assessment of DXA derived bone quality indexes and bone geometry parameters in early breast cancer patients: A single center cross-sectional study

Rebecca Pedersini [a,b,*,1], Deborah Cosentini [a,b,1], Luca Rinaudo [c], Manuel Zamparini [a], Fabio Massimo Ulivieri [d], Pierluigi di Mauro [a], Filippo Maffezzoni [b], Sara Monteverdi [e], Walter Vena [h], Lara Laini [a], Vito Amoroso [a], Edda Lucia Simoncini [b], Davide Farina [f], Gherardo Mazziotti [g,h,2], Alfredo Berruti [a,2]

[a] *Medical Oncology, ASST Spedali Civili, Brescia, Italy*
[b] *Breast Unit, ASST Spedali Civili, Brescia, Italy*
[c] *Tecnologie Avanzate Srl, Turin, Italy*
[d] *Casa di Cura la Madonnina, Milano, Italy*
[e] *Santa Chiara Hospital, Trento, Italy*
[f] *Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, Medical Oncology, University of Brescia, ASST Spedali Civili, Brescia, Italy*
[g] *Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, MI, Italy*
[h] *Endocrinology, Diabetology and Medical Andrology Unit, Metabolic Bone Diseases and Osteoporosis Section, IRCCS Humanitas Research Hospital, Rozzano, MI, Italy*

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ABSTRACT

Background: Bone mineral density (BMD) lacks sensitivity in individual fracture risk assessment in early breast cancer (EBC) patients treated with aromatase inhibitors (AIs). New dual-energy X-ray absorptiometry (DXA) based risk factors are needed.

Methods: Trabecular bone score (TBS), bone strain index (BSI) and DXA parameters of bone geometry were evaluated in postmenopausal women diagnosed with EBC. The aim was to explore their association with morphometric vertebral fractures (VFs). Subjects were categorized in 3 groups in order to evaluate the impact of AIs and denosumab on bone geometry: AI-naive, AI-treated minus (AIDen-) or plus (AIDen+) denosumab.

Results: A total of 610 EBC patients entered the study: 305 were AI-naive, 187 AIDen-, and 118 AIDen+. In the AI-naive group, the presence of VFs was associated with lower total hip BMD and T-score and higher femoral BSI. As regards as bone geometry parameters, AI-naive fractured patients reported a significant increase in femoral narrow neck (NN) endocortical width, femoral NN subperiosteal width, intertrochanteric buckling ratio (BR), intertrochanteric endocortical width, femoral shaft (FS) BR and endocortical width, as compared to non-fractured patients. Intertrochanteric BR and intertrochanteric cortical thickness significantly increased in the presence of VFs in AIDen- patients, not in AIDen+ ones. An increase in cross-sectional area and cross-sectional moment of inertia, both intertrochanteric and at FS, significantly correlated with VFs only in AIDen+. No association with VFs was found for either lumbar BSI or TBS in all groups.

Abbreviations: AI, aromatase inhibitor; AIDen+, aromatase inhibitor with denosumab; AIDen-, aromatase inhibitor without denosumab; BMD, bone mineral density; BMI, body-mass index; BR, buckling ratio; BSI, bone strain index; CSA, cross-sectional area; CSMI, cross-sectional moment of inertia; DXA, dual-energy X-ray absorptiometry; EBC, early breast cancer; FS, femoral shaft; HAL, hip axis length; HR, hormone receptor; HSA, Hip Structure Analysis; IT, intertrochanteric; NN, narrow neck; NSA, neck shaft angle; ROC, receiver operator characteristic; PS, propensity score; TBS, trabecular bone score; VF, vertebral fracture; Z, modulus.

* Corresponding author at: Oncologia Medica, ASST Spedali Civili di Brescia, Piazzale Spedali Civili 1, 20123, Brescia, Italy.
E-mail address: rebecca.pedersini@gmail.com (R. Pedersini).

[1] These authors equally contributed and are co-primary authors.
[2] These authors equally contributed and are co-senior authors.

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Conclusions: Bone geometry parameters are variably associated with VFs in EBC patients, either AI-naive or AI treated in combination with denosumab. These data suggest a tailored choice of fracture risk parameters in the 3 subgroups of EBC patients.

1. Introduction

Aromatase inhibitors (AIs) are widely used as adjuvant therapy in postmenopausal women with hormone receptor (HR)-positive early breast cancer (EBC) (Curigliano et al., 2017). These agents are known to induce a progressive deterioration of bone strength, leading to increased fracture risk (Rabaglio et al., 2009; Hirbe et al., 2006; Coleman et al., 2007).

Bone mineral density (BMD) is considered a valid surrogate of bone strength in postmenopausal women. In this setting, it has been shown that fracture risk doubles for each standard deviation reduction in BMD, due to the relationship between density and failure of a loaded material (Marshall et al., 1996; Ulivieri and Rinaudo, 2021).

However, BMD alone may lack sensitivity in individual fracture risk assessment, as many fractured patients present BMD values in the osteopenia or even in normal reference range (Siris et al., 2004). The susceptibility of incurring in fragility fractures cannot be reliably predicted by BMD measurement alone in patients treated with AIs (Pedersini et al., 2017; Pedersini et al., 2019; Monteverdi et al., 2021; Fonseca et al., 2014; NIH, 2001; Mazziotti et al., 2022). AI-therapy, in fact, causes not only a decrease in bone mass but also early alterations in trabecular and cortical bone microarchitecture, with a consequent deterioration in bone quality, which has been shown to occur independently of a decrease in BMD (Dalla Volta et al., 2020). Indeed, BMD does not reflect important determinants of bone strength, such as bone texture, bone geometry and other structural bone properties (Ulivieri and Rinaudo, 2021; Seeman and Delmas, 2006).

In this scenario, additional dual-energy X-ray absorptiometry (DXA) indexes have been developed to improve fracture risk prediction. Trabecular bone score (TBS) is a textural index automatically derived from DXA lumbar spine scan that evaluates local grey-level variations with an experimental variogram of two-dimension projections (Krohn et al., 2019), showing a good correlation with morphometric bone parameters (Hans et al., 2011a). TBS discriminates fractured patients and predicts fracture risk (Hans et al., 2011b; Pothuaud et al., 2009; Silva et al., 2015); however, it does not provide information about bone strength or fatigue, two factors that influence the resistance of a structure to loads over time (Mirzaali et al., 2018). A new DXA-based index has been recently proposed, namely the bone strain index (BSI), representing a deformation index automatically inferred from lumbar and femoral DXA scans (Ulivieri and Rinaudo, 2021; Colombo et al., 2019). Recent clinical studies demonstrated the usefulness of BSI in identifying patients at risk of fracture (Ulivieri et al., 2018a), in predicting the first fragility fracture (Ulivieri et al., 2021; Sornay-Rendu et al., 2022) and re-fracture (Ulivieri et al., 2021; Messina et al., 2021; Ulivieri et al., 2020a), and in characterizing young patients affected by secondary osteoporosis (Ulivieri et al., 2018b; Rodari et al., 2018; Ulivieri et al., 2020b). BSI has also been demonstrated to be a significant independent predictor of vertebral fractures (VFs) in primary hyperparathyroidism (Tabacco et al., 2021) and to be positively influenced by the anabolic treatments of fractured osteoporotic patients, defining an increase of bone strength not merely justified by BMD increase (Messina et al., 2020). Whether BSI could also be influenced also by anti-resorptive drugs has not been investigated so far.

Furthermore, it seems that geometry and size are parameters that govern the mechanical resistance of bone and might play an important role in predicting hip fracture independently of BMD (Brianza et al., 2007). Several studies have found a correlation between a longer hip axis length (HAL) and hip fracture (Broy et al., 2015), whereas it is not yet clear whether the neck shaft angle (NSA) can be used in clinical practice as an additional fracture risk parameter (Broy et al., 2015). In more recent years, the Hip Structure Analysis (HSA) algorithm has been proposed to further investigate the structure of the proximal femur, and improve fracture hip prediction (Beck, 2007; Ha et al., 2019). However, the use of HSA measures in the routine management of patients is still limited by the lack of sufficient clinical evidence (Broy et al., 2015).

The role of BSI and geometric parameters as a predictive fracture risk factor in EBC patients on adjuvant treatment with AIs has not been so far investigated. Indeed, although it is unclear whether AIs might functionally modify bone geometry and whether bone geometry parameters might have a role in predicting fractures in women exposed to long-standing AI-therapy, it is also unknown whether denosumab treatment might improve bone geometry and then modify the relationship between bone geometry parameters and fracture risk in this specific clinical setting. In order to verify the aforementioned working hypotheses, this study was undertaken to explore the association of the bone geometry parameters with the presence of VFs in 3 different subsets of EBC patients: AI-naive, AI treated without denosumab (AIden-), and AI treated in association with denosumab (AIden+).

2. Patients and methods

This cross-sectional study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline (von Elm et al., 2014). The study protocol and patient population characteristics were previously described in detail (Pedersini et al., 2017; Pedersini et al., 2019; Monteverdi et al., 2021). Briefly, eligible patients were postmenopausal women with HR-positive EBC who were candidates to adjuvant endocrine therapy with AIs, with normal renal function, without any bone metabolic disorders, and no previous or current treatment with anti-osteoporotic drugs or glucocorticoids.

The aim of this study was to explore the association between bone geometry and structural parameters and the presence of VFs in 3 different groups of postmenopausal EBC patients: 1) AI-naive, 2) AI-treated without concomitant denosumab therapy (AIDen-), 3) treated with both AI and denosumab (AIDen+), in order to provide information on which ones are worthy of prospective evaluation in these subgroups of patients. The ethics committee of Brescia, Italy, approved the study protocol and the patients provided written informed consent according to the tenets of the Declaration of Helsinki (World Medical Association, 2013). The study cohort was enlarged with respect to the last report (Monteverdi et al., 2021) and the updated database was locked on September 4, 2020. The dataset used for the present analyses included 610 cases: 305 patients assessed before initiating adjuvant endocrine therapy (AI-naive group) and 305 patients assessed while receiving adjuvant AI therapy for 2–5 years (AI-treated group). Among AI-treated patients, 118 were receiving denosumab as prophylaxis for fracture risk due to presented parameters indicative of greater bone fragility, such as the history of previous fractures, lower body-mass index (BMI), reduced BMD and/or T-score than naive-patients, whereas 187 did not receive any bone modifying agent owing to patient preferences, contraindications and/or clinical judgment.

As reported previously (Pedersini et al., 2017; Pedersini et al., 2019; Monteverdi et al., 2021), each patient underwent a DXA scan (Delphi Hologic), assessing BMD at the vertebral, hip, and femoral level, TBS and VF presence. VFs were assessed according to the validated Genant's semi-quantitative method (Genant et al., 1993). DXA analyses were performed by two experienced physicians who underwent a specific training course for this study. VFs were assessed by the two physicians, who were blinded to patient group assignment, using a quantitative

morphometric analysis of DXA images.

All DXA scans were sent to a separate computer data analysis for calculating the BSI on the lumbar spine and femur, using dedicated software Bone Strain Index Version 1.0 (Tecnologie Avanzate T.A. s.r.l., Torino, Italy). Geometric parameters were assessed through automatic analysis performed on DXA APEX Software Version 4.6.

2.1. BSI measurements

BSI calculation is based on a mathematical approach called the finite element method, relying on geometric and material information extrapolated from DXA images (Ulivieri and Rinaudo, 2021; Colombo et al., 2019).

In particular, bone geometry follows the segmentation analysis performed by DXA software on the greyscale image, and it is based on the same regions of interest defined by the DXA operator (i.e., L1-L4 area for lumbar scans; neck, trochanteric and intertrochanteric areas for hip scans). The material properties are assigned to each triangle of the generated mesh with a specific stiffness dependent on the BMD value, according to experimental relations and the specific anatomic site (Morgan and Keaveny, 2001). In the BSI model boundary conditions, the applied forces and constraints simulate a patient-specific stand-up condition for lumbar scans (Han et al., 2013) and a side-fall condition for femoral site (Terzini et al., 2019). BSI value represents the average equivalent strain in the skeletal site explored, assuming that a higher strain level (higher BSI) indicates higher fracture risk (Hart et al., 2017).

2.2. Geometry measurements

DXA images automatically obtain several geometric parameters (Table 1 of Supplementary Materials), two of which can synthetically describe the femur geometry: the neck shaft angle (NSA) and the hip axis length (HAL). NSA quantifies the femur neck angle with respect to the vertical axis, whereas HAL is defined as the distance from the inner pelvic brim to the greater trochanter. HSA automatically extracts geometrical and mechanical parameters in three regions of interest: the narrow neck (NN), intertrochanteric (IT), and femoral shaft (FS) regions (Table 1 of Supplementary Materials). The main HSA parameters are the cross-sectional area (CSA), which is proportional to the bone surface resistant to axial loads; the cross-sectional moment of inertia (CSMI), which describes how the bone mass is distributed around the femoral axis; the section modulus (Z), which represents the maximum bending stress. HSA analysis is based on the assumption that compression loads are uniformly distributed over the CSA, whereas, under bending conditions, the resistance of bone is proportional to the square of the distance from the neutral axis. As the main loads on the femoral site compression and bending, the higher the CSA and CSMI, the better bone resistance will be. Another important parameter is represented by the ratio of the outer radius to the cortical thickness (called buckling ratio, BR). If this ratio exceeds a factor of 10, long bone strength (and thus femur) decreases due to rising local instability (Beck, 2007).

3. Statistical analysis

The initial sample of 740 patients was adjusted by 1:1 propensity score (PS) matching between AI-treated (N = 309) and naive (N = 431) patients. The PS for the exposure has been calculated through a model of logistic regression based on age and presence of previous fractures as covariates at baseline, and the subjects of the two groups have been combined through the algorithm of nearest neighbor matching without substitution, matching each treated patient with the untreated patient who minimizes the absolute distance in terms of PS, with a maximum acceptable threshold of 0.01 (Austin, 2014). Six hundred ten patients remained after the application of the PS matching, as 305 were AI-treated and 305 AI-naive.

After verifying that most of the variables analyzed by Kolmogorov-Smirnov test violated the assumption of normality distribution, it was decided to use totally non-parametric tests.

AI-treated patients were divided according to whether they were denosumab naive (AIDen-) or receiving concomitant denosumab therapy (AIDen+). These two groups were individually compared with the AI-naive group. Differences in continuous variables were tested through the Mann-Whitney *U* test, while categorical variables were evaluated through chi-squared tests. Within each of the three subgroups we analyzed the distribution of parameters between fractured patients and non-fractured patients, to assess whether the different groups corresponded to different prognostic factors of fracture. We considered a significant threshold of $p < 0.05$, and to control for possible false positive results we applied the Bonferroni correction ($p' = \frac{p}{k}$, where k is the number of hypotheses tested). Given that Type I errors cannot decrease (the whole point of Bonferroni adjustments) without inflating type II errors, significant results in the raw test which did not maintain the statistical significance after correction were also mentioned (Perneger, 1998).

To summarize the large amount of results, we graphically represented the logistic regressions via receiver operator characteristic (ROC) curves, which report sensitivity (number correctly identified 1 s/total number Observed 1 s) and specificity (number correctly identified 0 s/total number Observed 0 s) for every possible cut-off. All the analyses were carried out via SPSS (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp) and R (R Core Team, 2022).

4. Results

Among the 610 selected EBC patients according to the propensity matched score, 305 were AI-naive and 305 AI-treated, among which 187 AIDen- and 118 AIDen+. The clinical characteristics of the study participants are reported in Table S2 of supplementary materials. These three groups were well-balanced with respect to age, tumour stage, nodal status, adjuvant chemotherapy, smoking habit, and alcohol consumption. The three groups differed in terms of BMI ($p = 0.005$), with the highest value (26.4) in AIDen- and the lowest (24.5) in AIDen+, the latter subgroup having a greater proportion of patients who performed regular physical activity. A greater numerical frequency of subjects with a history of previous fractures was found in AIDen+ subgroup, although not statistically significant (Table S2).

DXA-derived bone parameters are reported in Table 1. As expected, the AIDen+ patients presented densitometric parameters indicative of greater bone fragility as opposed to the others groups, such as reduced femoral neck BMD (0.67 ± 0.1) and T-score (−1.63 ± 0.9). Other bone parameters, such as TBS, femoral BSI, and HSA measures, were not statistically different among the three subgroups. Similarly, the bone geometry parameters failed to show a significant difference across the three patients' subgroups (Table 1).

Bone parameters stratified according to fracture events in the three patients' subgroups (AI-naive, AIDen-, and AIDen+) are reported in Table 2.

In the AI-naive group, fractured patients compared to non-fractured ones presented a lower total hip BMD (mean 0.77 vs 0.84, $p = 0.001$) and T-score (−1.38 vs −0.86, $p = 0.001$), but higher femoral BSI (femoral neck BSI 1.93 vs 1.70, $p < 0.001$). The HSA measures, conversely, increased in fractured patients as compared to non-fractured patients, i.e. NN endocortical (mean 3.10 vs 2.94 cm, $p = 0.037$) and subperiosteal width (3.43 vs 3.29 cm, $p = 0.045$), IT BR and endocortical width (4.99 vs 4.78 cm, $p = 0.042$), FS BR (3.44 vs 2.94, $p = 0.007$) and endocortical width (2.06 vs 1.87 cm, $p = 0.035$), and HAL (106.2 vs 102.8 cm, $p = 0.026$).

In AI-treated patients, none of the skeletal fragility parameters, such as BMD, T-score, BSI and TBS showed an association with the presence of VFs in both AIDen- and AIDen+ groups (Table 2). Correlations with

Table 1
Distribution of bone parameters in the patient subgroups of the study. Data are reported as mean (standard deviation).

Bone parameters	AI-naive (n = 305)	AI-treated without denosumab (n = 187)	AI-treated with denosumab (n = 118)	p[a]
Femoral neck BMD *(g/cm²)*	0.70 (0.11)	0.69 (0.09)	0.67 (0.10)	**0.044**
Femoral neck T-score	−1.37 (1.02)	−1.46 (0.78)	−1.63 (0.91)	**0.026**
Total hip BMD *(g/cm²)*	0.83 (0.12)	0.82 (0.10)	0.81 (0.11)	0.215
Total hip T-score	−0.93 (0.95)	−1.01 (0.83)	−1.10 (0.89)	0.190
TBS	1.22 (0.12)	1.22 (0.09)	1.25 (0.11)	0.365
Femoral neck BSI	1.73 (0.38)	1.78 (0.50)	1.81 (0.37)	0.150
Femoral total BSI	1.45 (0.27)	1.49 (0.37)	1.50 (0.27)	0.119
Total BMD *(g/cm²)*	0.93 (0.17)	0.90 (0.14)	0.89 (0.13)	0.066
Total T-score	−1.05 (1.56)	−1.28 (1.27)	−1.43 (1.19)	0.059
Total *Z*-score	0.68 (1.65)	0.54 (1.35)	0.21 (1.22)	0.050
Lumbar total BSI	2.10 (0.61)	2.24 (0.61)	2.10 (0.55)	**0.021**
HSA measures				
Narrow neck (NN) area				
NN BR	11.48 (2.62)	11.38 (2.94)	11.62 (2.95)	0.602
NN CSA *(cm²)*	2.76 (0.46)	2.70 (0.34)	2.65 (0.41)	0.077
NN CSMI *(cm⁴)*	2.54 (0.69)	2.44 (0.56)	2.37 (0.56)	0.147
NN cortical thickness *(cm)*	0.17 (0.03)	0.17 (0.02)	0.17 (0.03)	0.393
NN endocortical width *(cm)*	2.96 (0.30)	2.92 (0.32)	2.93 (0.31)	0.451
NN subperiosteal width *(cm)*	3.30 (0.28)	3.26 (0.29)	3.26 (0.28)	0.381
NN Z *(cm³)*	1.35 (0.29)	1.32 (0.23)	1.29 (0.25)	0.192
Inter-trochanteric (IT) area				
IT BR	8.70 (1.78)	8.86 (2.14)	8.80 (1.86)	0.836
IT CSA *(cm²)*	4.82 (0.83)	4.74 (0.77)	4.62 (0.68)	0.343
IT CSMI *(cm⁴)*	13.92 (3.52)	13.61 (3.84)	12.94 (3.03)	0.167
IT cortical thickness *(cm)*	0.39 (0.07)	0.39 (0.07)	0.38 (0.07)	0.619
IT endocortical width *(cm)*	4.81 (0.40)	4.84 (0.46)	4.77 (0.48)	0.572
IT subperiosteal width *(cm)*	5.59 (0.39)	5.61 (0.46)	5.54 (0.45)	0.390
IT Z *(cm³)*	4.19 (0.93)	4.09 (0.97)	3.96 (0.83)	0.237
Femoral shaft (FS) area				
FS BR	3.00 (0.75)	3.01 (0.85)	3.01 (0.78)	0.954
FS CSA *(cm²)*	3.99 (0.56)	3.97 (0.55)	3.84 (0.53)	0.057
FS CSMI *(cm⁴)*	3.50 (0.81)	3.45 (0.78)	3.25 (0.69)	0.053
FS cortical thickness *(cm)*	0.53 (0.10)	0.53 (0.11)	0.53 (0.10)	0.564
FS endocortical width *(cm)*	1.89 (0.36)	1.88 (0.36)	1.85 (0.40)	0.904
FS subperiosteal width *(cm)*	2.95 (0.23)	2.95 (0.21)	2.90 (0.22)	0.225
FS Z *(cm³)*	2.27 (0.39)	2.25 (0.39)	2.16 (0.33)	0.059
Neck shaft angle (NSA)	125.9 (4.9)	127.1 (6.1)	126.5 (5.1)	0.180
Hip axis length (HAL) *(cm)*	103.2 (6.1)	102.7 (6.4)	102.7 (5.9)	0.777

AI: aromatase inhibitors; BMD: bone mineral density; TBS: trabecular bone score, BSI: bone strain index; HSA: hip structural analysis; NN: narrow neck; BR: buckling ratio; CSA: cross-sectional area; CSMI: cross-sectional moment of inertia; Z: modulus; IT: inter-trochanteric; FS: femoral shaft.
[a] Kruskal-Wallis test.

fractures were found in some bone geometry parameters: however, differences were noted between AIDen- and AIDen+. Specifically, AIDen- fractured patients showed higher values of BR (both IT and FS), lower cortical thickness (IT 0.35 vs 0.39 cm respectively; FS 0.48 vs 0.54 cm), and higher FS endocortical width (2.06 vs 1.85 cm). Conversely, CSA and CSMI in both IT area (4.32 vs 4.69 cm^2 and 11.59 vs 13.26 cm^4) and FS area (3.52 vs 3.92 cm^2; 2.91 vs 3.33 cm^4) decreased according to the presence of VFs in the AIDen+ population. Among the changes in these variables according to VFs, only femoral BSI, total and neck, in the AI naïve group, maintained a statistical significance after Bonferroni correction. The ROC curves of variables showing a statistically significant variation in relation to the absence or presence of VFs demonstrated overall low diagnostic accuracies. The areas under the curve (AUCs), in fact, varied between 0.61 and 0.68 in AI-naive patients and between 0.64 and 0.68 and between 0.65 and 0.74 in AI treated ones with and without denosumab, respectively (Figs. S1–S3, supplementary materials).

5. Discussion

In this study, a high number of textural, structural and geometric bone variables were analyzed in three groups of postmenopausal EBC patients, which were either AI-naive or assessed during AI therapy with or without denosumab. As expected, parameters associated with greater bone fragility, such as BMD and T-score, progressively decreased from AI-naive to AIDen- and AIDen+, since these data reflect the fact that treatment with AI increases bone fragility and patients assigned to denosumab therapy in addition to AIs had characteristics of greater skeletal fragility than those who received AI alone. As regard as bone geometry and structural parameters, a progressive decrease was observed for CSA and CSMI assessed at femoral NN, IT and FS but at lesser extent, likely reflecting the favorable effects of denosumab on bone quality and strength. The structural and geometric parameters, however, showed a non-univocal pattern in relation to the presence of VFs, an undoubted indicator of skeletal fragility in the three groups of patients. BMD and T-score showed significantly lower values in patients with VFs compared to those not fractured in the group of AI-naive patients but not in AI-treated ones. This observation is not new and further confirms the poor role of BMD in predicting the fracture risk associated with AI treatment already shown in other studies (Pedersini et al., 2019; Mazziotti et al., 2022; Dalla Volta et al., 2020). BSI, a new bone fragility parameter, has been shown to correlate well with VFs in AI-naive patients but not in AI-treated patients. These data confirm that the mechanisms underlying bone fragility in postmenopausal women differ from those of AI-treated EBC patients. This difference affects the

Table 2
Bone parameters of study participants stratified according to occurrence of fractures. Data are reported by mean (standard deviation).

	AI-naive			AI-treated without denosumab			AI-treated with denosumab		
Bone parameters	Not fractured (n = 264)	Fractured (n = 41)	p	Not fractured (n = 149)	Fractured (n = 38)	p	Not fractured (n = 92)	Fractured (n = 26)	p
Femoral neck BMD *(g/cm²)*	0.70 (0.11)	0.67 (0.10)	0.091	0.69 (0.08)	0.67 (0.11)	0.237	0.67 (0.10)	0.66 (0.09)	0.399
Femoral neck T-score	−1.34 (1.01)	−1.53 (1.06)	0.260	−1.43 (0.70)	−1.60 (1.01)	0.234	−1.60 (0.94)	−1.74 (0.79)	0.515
Total hip BMD *(g/cm²)*	0.84 (0.12)	0.77 (0.10)	**0.001**	0.83 (0.10)	0.80 (0.11)	0.165	0.81 (0.11)	0.79 (0.09)	0.243
Total hip T-score	−0.86 (0.96)	−1.38 (0.79)	**0.001**	−0.96 (0.79)	−1.21 (0.97)	0.097	−1.05 (0.92)	−1.29 (0.76)	0.238
TBS	1.23 (0.12)	1.21 (0.10)	0.542	1.23 (0.09)	1.19 (0.11)	0.081	1.25 (0.10)	1.22 (0.14)	0.354
Femoral neck BSI	1.70 (0.35)	1.93 (0.45)	**<0.001**[a]	1.76 (0.39)	1.88 (0.83)	0.197	1.83 (0.36)	1.76 (0.41)	0.440
Femoral total BSI	1.43 (0.26)	1.60 (0.33)	**<0.001**[a]	1.47 (0.27)	1.58 (0.65)	0.131	1.51 (0.27)	1.49 (0.31)	0.836
Total BMD *(g/cm²)*	0.93 (0.17)	0.90 (0.17)	0.209	0.91 (0.14)	0.90 (0.14)	0.790	0.90 (0.13)	0.85 (0.13)	0.065
Total T-score	−1.01 (1.56)	−1.33 (1.51)	0.224	−1.26 (1.27)	−1.37 (1.31)	0.653	−1.32 (1.19)	−1.83 (1.14)	0.057
Total *Z*-score	0.69 (1.64)	0.61 (1.67)	0.785	0.49 (1.37)	0.76 (1.27)	0.284	0.24 (1.21)	0.09 (1.26)	0.584
Lumbar total BSI	2.08 (0.58)	2.24 (0.77)	0.101	2.24 (0.61)	2.25 (0.64)	0.951	2.07 (0.53)	2.21 (0.59)	0.266
Narrow neck (NN) area									
NN BR	11.33 (2.50)	12.57 (3.29)	0.059	11.33 (2.58)	11.57 (4.29)	0.754	11.60 (2.95)	11.71 (3.06)	0.892
NN CSA *(cm²)*	2.77 (0.47)	2.75 (0.42)	0.908	2.72 (0.31)	2.58 (0.45)	0.117	2.68 (0.42)	2.52 (0.33)	0.159
NN CSMI *(cm⁴)*	2.52 (0.69)	2.70 (0.69)	0.301	2.48 (0.55)	2.26 (0.59)	0.122	2.41 (0.55)	2.20 (0.59)	0.154
NN cortical thickness *(cm)*	0.17 (0.03)	0.16 (0.03)	0.276	0.17 (0.02)	0.17 (0.03)	0.594	0.17 (0.03)	0.16 (0.02)	0.465
NN endocortical width *(cm)*	2.94 (0.29)	**3.10** (0.38)	**0.037**	2.94 (0.32)	2.85 (0.32)	0.281	2.94 (0.30)	2.87 (0.35)	0.364
NN subperiosteal width *(cm)*	3.29 (0.27)	3.43 (0.35)	**0.045**	3.28 (0.30)	3.18 (0.28)	0.207	3.28 (0.26)	3.19 (0.32)	0.242
NN Z *(cm³)*	1.34 (0.29)	1.37 (0.26)	0.755	1.33 (0.22)	1.25 (0.26)	0.177	1.31 (0.26)	1.20 (0.19)	0.107
Inter-trochanteric (IT) area									
IT BR	8.57 (1.62)	9.69 (2.54)	**0.011**	8.62 (1.56)	9.94 (3.68)	**0.014**	8.75 (1.84)	9.02 (2.02)	0.592
IT CSA *(cm²)*	4.84 (0.83)	4.67 (0.85)	0.417	4.80 (0.73)	4.45 (0.89)	0.077	4.69 (0.70)	4.32 (0.54)	**0.040**
IT CSMI *(cm⁴)*	13.86 (3.48)	14.35 (3.86)	0.581	13.87 (3.74)	12.42 (4.14)	0.139	13.26 (3.05)	11.59 (2.57)	**0.040**
IT cortical thickness *(cm)*	0.40 (0.07)	0.37 (0.08)	0.147	0.39 (0.06)	0.35 (0.07)	**0.011**	0.39 (0.07)	0.37 (0.06)	0.266
IT endocortical width *(cm)*	4.78 (0.38)	4.99 (0.49)	**0.042**	4.84 (0.48)	4.83 (0.41)	0.894	4.79 (0.49)	4.67 (0.46)	0.335
IT subperiosteal width *(cm)*	5.58 (0.39)	5.73 (0.43)	0.133	5.63 (0.47)	5.53 (0.39)	0.388	5.57 (0.45)	5.40 (0.42)	0.173
IT Z *(cm³)*	4.19 (0.92)	4.20 (1.03)	0.986	4.16 (0.93)	3.77 (1.10)	0.105	4.04 (0.85)	3.61 (0.69)	0.056
Femoral shaft (FS) area									
FS BR	2.94 (0.69)	3.44 (1.02)	**0.007**	2.92 (0.70)	3.45 (1.26)	**0.012**	2.98 (0.76)	3.15 (0.86)	0.405
FS CSA *(cm²)*	4.01 (0.56)	3.85 (0.58)	0.253	4.00 (0.53)	3.82 (0.62)	0.184	3.92 (0.54)	3.52 (0.34)	**0.005**
FS CSMI *(cm⁴)*	3.48 (0.81)	3.65 (0.87)	0.405	3.44 (0.76)	3.52 (0.90)	0.703	3.33 (0.71)	2.91 (0.52)	**0.022**
FS cortical thickness *(cm)*	0.54 (0.10)	0.49 (0.11)	0.067	0.54 (0.11)	0.48 (0.09)	**0.033**	0.53 (0.12)	0.49 (0.11)	0.168
FS endocortical width *(cm)*	1.87 (0.34)	2.06 (0.44)	**0.035**	1.85 (0.36)	2.06 (0.31)	**0.019**	1.85 (0.40)	1.86 (0.41)	0.962
FS subperiosteal width *(cm)*	2.94 (0.22)	3.04 (0.28)	0.092	2.93 (0.21)	3.02 (0.19)	0.076	2.92 (0.22)	2.84 (0.22)	0.150
FS Z *(cm³)*	2.27 (0.39)	2.27 (0.39)	0.965	2.26 (0.38)	2.22 (0.45)	0.718	2.20 (0.34)	1.98 (0.24)	**0.016**
Neck shaft angle (NSA)	125.89 (4.81)	126.39 (5.68)	0.686	126.80 (5.96)	128.21 (6.96)	0.368	126.23 (5.29)	127.41 (4.12)	0.392
Hip axis length (HAL) *(cm)*	102.85 (5.95)	106.22 (6.46)	**0.026**	102.41 (6.49)	104.11 (5.88)	0.296	103.19 (6.17)	100.65 (4.26)	0.111

AI: aromatase inhibitors; BMD: bone mineral density; TBS: trabecular bone score, BSI: bone strain index; NN: narrow neck; BR: buckling ratio; CSA: cross-sectional area; CSMI: cross-sectional moment of inertia; Z: modulus; IT: inter-trochanteric; FS: femoral shaft.
Bold means the p-value is statistically significant.
[a] Still significant after Bonferroni Correction.

predictor parameters of fracture risk, which are different in the two groups. In this context, our study provided convincing evidence that treatment with AIs does not alter bone geometry in women with EBC. Consistently, most of the bone geometry parameters known to be associated with fragility fractures in the general population (Ulivieri and Rinaudo, 2021), as well as in our naïve women with EBC, were not significantly associated with VFs in women with EBC treated with AIs. As a matter of fact, the ROC analysis suggested that evaluation of bone geometry might not improve the accuracy in predicting fractures in women exposed to AI treatment. One could argue that this result might be influenced by the changes in body composition induced by AI therapy (Pedersini et al., 2019; Monteverdi et al., 2021). Indeed, there is evidence that increase in body fat can be associated with better hip geometry (Maïmoun et al., 2021). It is known that the bone quality parameters are more accurate than the bone quantity ones in determining the fracture risk in AI-treated patients. However, they generally have a lower BMD than AI-naïve patients (Pedersini et al., 2019; Monteverdi et al., 2021; Mazziotti et al., 2022). TBS, a parameter of altered bone quality, has not been shown to vary in relation to the presence of VFs in our study, and this finding raises doubts about its role in the clinical assessment of fracture risk, despite a previous study found an association between TBS and fractures in AI-treated EBC patients (Catalano et al., 2019).

Bone health management in EBC patients treated with AIs frequently includes bone resorption inhibitors to prevent fracture risk. However, women treated with these drugs also suffer from fractures, albeit to a lesser extent. Identifying risk factors in women treated with denosumab or bisphosphonates is an interesting topic for future research.

Denosumab was shown to improve bone geometric parameters and mechanical properties at proximal femur in women with post-menopausal osteoporosis, with effects that were greater than bisphosphonates at the intertrochanteric and shaft sites (Beck et al., 2008). Consistent with these findings, in our women with EBC treated with denosumab, prevalent VFs were associated with smaller CSA and CSMI (both in IT and FS area). These data suggest that, although bone geometry did not allow to predict fractures with high accuracy, measurement of some parameters of femur structures during denosumab treatment might help the clinicians to identify subjects poorly responding to the anti-resorptive therapy.

In conclusion, in this study different bone geometry parameters have shown an association with VFs in patients treated with AI plus or minus denosumab. These data suggest a different pathophysiology of bone fragility in these patients and the potential need to tailor the choice of fracture risk parameters depending on whether patients taking AIs to receive concomitant denosumab or not. However, the tested parameters revealed a low diagnostic accuracy and their role in predicting the VF risk in the 3 group of patients considered in this study is uncertain.

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CRediT authorship contribution statement

Rebecca Pedersini, Deborah Cosentini. Alfredo Berruti: Conceptualization, Methodology, Software, Data curation, Writing- Original draft preparation, reviewing and editing.

Davide Farina, Ulivieri Fabio Massimo, Mazziotti Gherardo, Vito Amoroso: Supervision.

Edda Lucia Simoncini, Pierluigi di Mauro, Filippo Maffezzoni, Laini Lara, Monteverdi Sara: Resources, Investigation.

Manuel Zamparini, Luca Rinaudo; Software, Validation;

Declaration of competing interest

Dr. Pedersini received consultancy fees from Novartis, Eli Lilly, Amgen, Gilead, Daichi Sankyo, Roche, Eisai, Seagen. Dr. Mazziotti received consultancy fees from Novartis, Ipsen, Eli Lilly and lecture fees from Amgen and Abiogen, outside the submitted work. Dr. Vena received grants from IBSA Pharmaceutical outside the submitted work. Dr. Berruti reports receiving grants and personal fees from Janssen Cilag, grants and personal fees from Astellas, and personal fees from Bayer outside the submitted work. Dr. Ulivieri is scientific coordinator in Tecnologie Avanzate s.r.l. Bone Strain Index Project. Eng. Luca Rinaudo is technical manager in Tecnologie Avanzate s.r.l. Bone Strain Index Project. All other authors declare no conflict of interest.

Data availability

The data that has been used is confidential.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bonr.2023.101654.

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