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ORIGINAL ARTICLE

Denosumab improves trabecular bone score in relationship with decrease in fracture risk of women exposed to aromatase inhibitors

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Abstract

Purpose Trabecular bone score (TBS) is a gray-level textural metric that has shown to correlate with risk of fractures in several forms of osteoporosis. The value of TBS in predicting fractures and the effects of bone-active drugs on TBS in aromatase inhibitors (AIs)-induced osteoporosis are still largely unknown. The primary objective of this retrospective study was to assess the effects of denosumab and bisphosphonates (BPs) on TBS and vertebral fractures (VFs) in women exposed to AIs.

Methods 241 consecutive women (median age 58 years) with early breast cancer undergoing treatment with AIs were evaluated for TBS, bone mineral density (BMD) and morphometric VFs at baseline and after 18–24 months of follow-up. During the study period, 139 women (57.7%) received denosumab 60 mg every 6 months, 53 (22.0%) BPs, whereas 49 women (20.3%) were not treated with bone-active drugs.

Results Denosumab significantly increased TBS values (from 1.270 to 1.323; $P<0.001$) accompanied by a significant decrease in risk of VFs (odds ratio 0.282; $P=0.021$). During treatment with BPs, TBS did not significantly change ($P=0.849$) and incidence of VFs was not significantly different from women untreated with bone-active drugs ($P=0.427$). In the whole population, women with incident VFs showed higher decrease in TBS vs. non-fractured women ($P=0.003$), without significant differences in changes of BMD at any skeletal site.

Conclusions TBS variation predicts fracture risk in AIs treated women. Denosumab is effective to induce early increase of TBS and reduction in risk of VFs.

Keywords Aromatase inhibitors · Vertebral fractures · Trabecular bone score · Denosumab · Bisphosphonates

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Introduction

Breast cancer is the most prevalent cancer worldwide [1]. Since cancer's cells can express estrogen receptors, hormone-deprivation therapies with aromatase inhibitors (AIs) are frequently used as adjuvant therapy of non-metastatic breast cancer, with favorable effects in preventing recurrences and increasing patient's survival [2, 3]. However, AIs can also induce a progressive deterioration of bone strength with consequent increased risk of fragility fractures in several subjects exposed to AI therapy [4].

Prediction of fractures in women exposed to AIs could be a challenge. Although BMD is a valid surrogate of bone strength in post-menopausal women, in several forms of secondary osteoporosis the diagnostic value of this tool is limited due to predominant alterations in bone quality that could not be captured by dual-energy X-ray absorptiometry (DXA) measurement of BMD [5]. Indeed, bone loss induced by hormone-deprivation therapies is more rapid and severe than that occurring in post-menopausal osteoporosis and bone quality is affected more than bone quality by AI therapy [6]. In this scenario, additional DXA indexes have been developed eventually to improve fracture risk prediction [7]. 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 [8]. This DXA-derived parameter shows a good correlation with vertebral microstructure [9]. As a matter of fact, usefulness of TBS as a predictive tool for fractures in post-menopausal osteoporosis has been demonstrated [10]. Similarly, TBS has been proposed as a reliable and feasible tool in characterizing the alterations in bone quality and predicting fractures in several forms of secondary osteoporosis [5]. However, the effects AIs on TBS resulted to be variable and the impact of TBS degradation on risk of fractures in this clinical setting has not been so far clarified [11–13].

Bisphosphonates (BPs) and denosumab are recommended to prevent bone loss and fractures in women treated with AIs [2, 14]. Data available in literature on therapeutic outcomes of these drugs in AI-induced osteoporosis were mainly focused on BMD and more recently on vertebral fractures (VFs), whereas data on TBS changes during BPs or denosumab therapy in women exposed to AIs are scarce and inconclusive [11–13].

In this retrospective study, reflecting real-life clinical practice, we aimed at investigating the performance of TBS in predicting VFs and the effects denosumab and BPs on TBS in women under treatment with AIs.

Materials and methods

This study followed Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines [15]. The inclusion criteria were: (1) hormone receptor-positive early breast cancer with indication to AIs (either alone or in combination to GnRH agonists) in adjuvant setting; (2) at least two out-patient visits during a 18–24-month follow-up; (3) duration of hormone-deprivation therapy < 12 months at the time of first visit; (4) availability of DXA analyses longitudinally performed by the same machine during the follow-up; (5) availability of two spine images (either by X-rays or DXA) for vertebral morphometry during the follow-up; (6) written informed consent. The exclusion criteria were: (1) bone metastases; (2) treatment with bone-active drugs (except for calcium and vitamin D) prior to and at time of first DXA examination; (3) spinal surgery; (4) renal insufficiency; (5) liver disease.

Two hundred and forty-one consecutive women with breast cancer, evaluated for skeletal health at out-patient bone clinics in the period between September 2020 and January 2023 and meeting the inclusion and exclusion criteria were retrospectively enrolled in the study. For the study purposes, all participants were assessed two times during 18–24 months of follow-up. The database was locked on February 20th 2023 and data analysis was completed by February 28th 2023.

During the study period, the therapeutic decision making for prevention of fractures was based on national guidelines, current Italian regulation for drug reimbursement, patient's preference, comorbidities and overall clinical judgment [16]. National guidelines and Italian regulation for drug reimbursement allow to treat all subjects undergoing hormone-deprivation therapies regardless of BMD and WHO Fracture Risk Assessment (FRAX) scores, but in our study treatment with bone-active drugs was decided on an individual basis when T-score was above -1.0 SD and there were not coexistent traditional major risk factors for fractures, due to controversy in defining the optimal therapeutic threshold in these specific conditions [2, 14, 16–18]. Moreover, the choice of BPs or denosumab was shared with patients who were informed about effectiveness and risk profile of each drug.

The primary aim of the study was to assess the effects of bone-active drugs (BPs and denosumab) on TBS in women treated with AIs for breast cancer. As secondary end-points, we explored the (1) association between changes in TBS and risk of VFs; (2) differences in TBS changes between denosumab and BPs.

The study was approved by the Ethics Committee of IRCCS Humanitas Research Hospital and the patients gave their informed consent to use the clinical data for research purposes.

Assessment of VFs

VFs were assessed in all 241 patients at first out-patient visit and after 18–24 months of follow-up by a quantitative morphometric assessment using DXA (Hologic Inc, USA) images (152 cases) or conventional spine X-rays radiographs (89 cases) [19, 20]. Six points were manually marked on each vertebral body to describe the vertebral shape. Anterior (Ha), middle (Hm), and posterior (Hp) vertebral heights were measured and height ratios (Ha/Hp, Ha/Hm, Hm/Hp) were calculated for each vertebra from T4 to L4. According to the quantitative morphometry method, the fractures were defined as mild, moderate, and severe based on height ratio decreases of 20–25%, 25–40%, and more than 40%, respectively [21]. Incident VFs were defined as either new fractures (the same vertebrae from no VF at baseline to any grade of VF at follow-up) or progression of pre-existing VFs (from mild to moderate/severe VFs or from moderate to severe VFs between baseline and the follow-up). Spine deformity index (SDI) was calculated by summing the score of each VF after the grade of the fracture (score 1, 2, or 3 for mild, moderate, and severe fractures, respectively) was assigned [22]. Assessment of VFs was retrospectively performed by two observers, who were blinded to the identity of patients.

DXA measurement of BMD and TBS

All subjects were evaluated at the time of first out-patient visit and after 18–24 months of follow-up by DXA (Hologic Inc, USA) measurement of BMD at lumbar spine, femoral neck and total hip. BMD was expressed as T-score, comparing the results with those obtained in a gender-matched Caucasian population at the peak of bone mass [23]. A T-score less than or equal to − 2.5 SD at the hip or spine was defined as osteoporosis, whereas osteopenia was defined as a T-score between − 1 and − 2.5 SD.

TBS was measured in all subjects using lumbar spine DXA images. Based on results of a meta-analysis, subjects were categorized as with degraded TBS when the values were ≤ 1.230 [24].

Assessment of FRAX score

The fracture risk was assessed in 230 women with age ≥ 40 years by the FRAX tool (FRAX® tool) using the online calculator (www.shef.ac.uk/FRAX) with the information collected at the first visit. The calculation of FRAX score was performed including BMD values of women and considering AI therapy as a cause of secondary osteoporosis [25].

Measurement of body mass index (BMI)

BMI was defined by the individual's weight in kilograms divided by the square of their height in meters. Underweight, overweight and obese were defined by BMI < 18.5 kg/m^2, 25–30 kg/m^2 and ≥ 30 kg/m^2, respectively.

Assessment of vitamin D status

Hypovitaminosis D was defined by serum 25-hydroxy-vitamin D [25(OH)-vitamin D] below 30 ng/ml [26]. Measurement of 25(OH)-vitamin D was not centralized using commercial kits.

Statistical analysis

Normally distributed continuous data, as assessed by Kolmogorov–Smirnov's test, were presented as mean and 95% confidence interval (95% CI) of the mean, whereas non-normally distributed data were presented as median and range. Categorical data were presented as number and percentage. Unpaired and paired normally distributed data were compared using *t*-test and ANOVA, with Bonferroni's corrections. Non-normally distributed parameters were compared by Wilcoxon's, Mann–Whitney's and Kruskal–Wallis' tests, for paired, un-paired and multiple comparisons, respectively. Unpaired and paired frequencies were compared using the Chi-square and McNemar's tests, respectively. Determinants of incident VFs were assessed by univariate logistic regression analysis. All risk factors significantly associated with incident VFs in the univariate analysis were then submitted to multivariate logistic regression analyses taking into account the first end-point of the study and the minimal guidance criterion of ten events per variable [27]. A $P < 0.05$ was considered as significant.

Data availability

The datasets generated and analyzed during the current study are available in the ZENODO repository.

Results

Baseline

Ninety-five women (39.4%) were in early post-menopausal phase (< 5 years), and the mean age of the subjects in the whole population was 58.7 years (95% CI 57.2–60.2; range: 30–81). At time of the first visit, all women with estrogen receptor-positive breast cancer were treated with AIs (in combination with gonadotropin-releasing hormone agonist in 35 cases) for less than 12 months, with 79 women

(32.8%) being also treated with adjuvant chemotherapy and 29 women (12.0%) also receiving trastuzumab (Table 1).

At time of the first visit, 66 women (27.4%) had osteoporosis, whereas osteopenia and normal BMD at all skeletal sites were found in the remaining 111 (46.1%) and 64 (26.6%) women, respectively. At this time-point, morphometric VFs were diagnosed in 29 women (12.0%), with a median SDI of 2 (range: 1–3). No significant difference in prevalent VFs was found between evaluations performed on DXA and spine X-ray images (11.2% vs. 13.5%; $P=0.597$). TBS was degraded in 84 women (34.9%), the prevalence being higher in subjects with morphometric VFs as compared to those without VFs (69.0% vs. 30.2%; $P<0.001$).

At time of the first visit, all 241 women were taking cholecalciferol already prescribed by the oncologists after diagnosis of breast cancer. In 132 women, cholecalciferol was combined with calcium carbonate (120 cases) or calcium citrate (12 cases). At this time, hypovitaminosis D was diagnosed in 97 out of 241 women notwithstanding vitamin D supplementation. After the first visit at the out-patient bone clinic, 72 women with persistent hypovitaminosis increased their cholecalciferol doses, whereas in 25 women with hypovitaminosis D cholecalciferol was replaced with calcifediol. The remaining 144 women continued with unchanged cholecalciferol doses.

After the first visit, 139 women (57.7%) started denosumab 60 mg subcutaneously every 6 months, 53 (22.0%) were treated with BPs, 48 with oral BPs (alendronate 70 mg/week or risedronate 35 mg/week or risedronate 75 mg for two consecutive days/month) and 5 with intravenous zoledronate [5 mg/12 months], whereas 49 women (20.3%) were not treated with bone-active drugs because of patient preference, contraindications and/or clinical judgment.

Women treated with BPs were significantly older than those treated with denosumab ($P=0.011$) and those who were not treated with bone-active drugs ($P=0.030$) (Table 1). No significant differences in baseline BMI, BMD at any skeletal site, TBS, FRAX score, prevalent VFs and adjuvants therapies for breast cancer were found among the three therapeutic groups (Table 1).

Effects of bone-active drugs on skeletal end-points

The median range of follow-up was 18 months (range 18–24). During follow-up, treatment with denosumab induced a significant increase in lumbar spine, femoral neck

Table 1 Baseline clinical and demographical data of 241 women with breast cancer under treatment with aromatase inhibitors, stratified according to treatment with bone-active drugs

Variables	Whole population	Stratification based on treatment with bone-active drugs			*P*-values
		Untreated	Denosumab	BPs	
Cases	241	49	139	53	0.009
Age (years)	58.7 (57.2–60.2)	57.1 (53.1–60.8)	57.6 (55.6–59.6)	63.2 (60.2–66.2)*	
BMI (Kg/m^2)	25.0 (24.4–25.5)	25.2 (23.7–26.6)	24.6 (23.8–25.3)	25.8 (24.7–26.9)	0.243
Chemotherapy (*n*°/%)	79 (32.8%)	23 (46.9%)	39 (28.1%)	17 (32.1%)	0.053
Trastuzumab (*n*°/%)	29 (12.0%)	7 (14.3%)	15 (10.8%)	7 (13.2%)	0.776
Early menopause (*n*°/%)	95 (39.4%)	23 (46.9%)	62 (44.6%)	10 (18.9%)*	0.002
Prevalent VFs (*n*°/%)	29 (12.0%)	4 (8.2%)	19 (13.7%)	6 (11.3%)	0.586
FRAX score for major Fx[a]	7.5 (6.69–8.30)	6.5 (4.9–8.1)	7.8 (6.7–8.8)	7.9 (5.9–9.8)	0.411
LS BMD (gr/cm^2)	0.924 (0.904–0.944)	0.958 (0.916–1.001)	0.904 (0.877–0.931)	0.944 (0.907–0.980)	0.059
FN BMD (gr/cm^2)	0.689 (0.674–0.704)	0.719 (0.682–0.757)	0.679 (0.666–0.698)	0.688 (0.657–0.722)	0.095
TH BMD (gr/cm^2)	0.827 (0.812–0.843)	0.848 (0.811–0.884)	0.812 (0.793–0.831)	0.849 (0.815–0.884)	0.055
BMD categories					
Normal BMD (*n*°/%)	64 (26.6%)	16 (32.7%)	36 (25.9%)	12 (22.6%)	0.061
Osteopenia (*n*°/%)	111 (46.1%)	26 (53.1%)	56 (40.3%)	29 (55.7%)	
Osteoporosis (n°/%)	66 (27.4%)	7 (14.3%)	47 (33.8%)	12 (22.6%)	
TBS	1.276 (1.260–1.291)	1.302 (1.261–1.343)	1.270 (1.248–1.291)	1.269 (1.243–1.294)	0.253
Degraded TBS (*n*°/%)	84 (34.9%)	14 (28.6%)	52 (37.4%)	18 (34.0)	0.530

Continuous un-paired data were presented as mean and 95% confidence interval (CI) of the mean, and the comparisons were performed by ANOVA and Bonferroni's correction. Categorical data were presented as number of cases and percentages.

BMD Bone mineral density, *BMI* body mass index, *BPs* bisphosphonates, *FN* femoral neck, *FRAX* WHO fracture risk assessment, *FX* fracture, *LS* lumbar spine, *TBS* trabecular bone score, *TH* total hip, *VFs* vertebral fractures

*$P<0.05$ vs. women treated with denosumab and those untreated with bone-active drugs

[a]Evaluated in 230 out of 241 enrolled women with age ≥ 40 years

and total hip BMD, while treatment with BPs reached a significant increase only in total hip BMD. Patients who were not treated with bone-active drugs had a significant decrease of BMD at all skeletal sites (supplemental Table 1).

During follow-up, treatment with denosumab induced a significant increase in TBS values (from 1.270, 95% CI 1.248–1.291 to 1.323, 95% CI 1.300–1.346; $P < 0.001$) (Fig. 1) with a significant decrease in the number of subjects with degraded TBS (from 52/139 to 37/139; $P = 0.001$) (Fig. 2). Conversely, TBS values decreased significantly ($P = 0.009$) in subjects who were not treated with bone-active drugs, whereas they did not change significantly ($P = 0.849$) in subjects treated with BPs (Fig. 1).

During follow-up, 17 women (7.1%) experienced incident VFs. The incidence of VFs was significantly higher in women untreated with bone-active drugs as compared to those treated with denosumab (14.3% vs. 3.6%; $P = 0.008$), whereas the difference vs. women treated with BPs was not significantly different (14.3% vs. 9.3%; $P = 0.427$). Incident VFs was significantly higher in obese and overweight women as compared to those with normal BMI (14.7% vs. 9.2% vs. 2.9%; obese vs. overweight vs. normal BMI, respectively; $P = 0.040$). No significant difference in incident VFs was found among women with baseline osteoporosis vs. those with osteopenia or normal BMD ($P = 0.311$). Women with incident VFs showed higher decrease in TBS during the follow-up (Fig. 3a) as compared to women who did not fracture, without significant differences in changes of BMD at lumbar spine (Fig. 3b) and total hip (Fig. 3c). In the univariate logistic regression analysis, risk of incident VFs

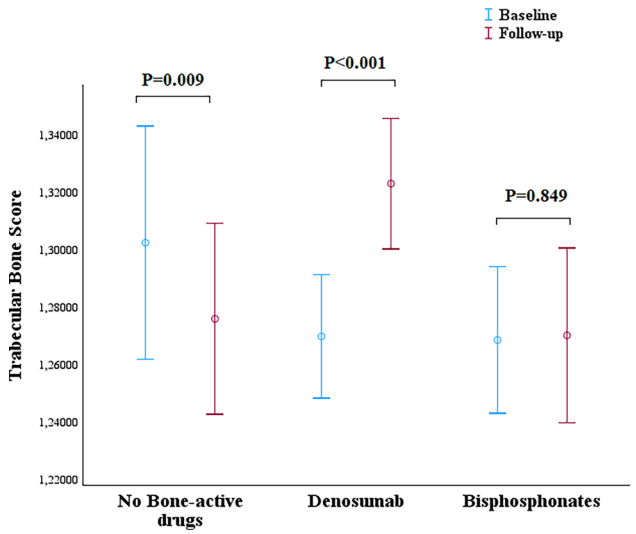

Fig. 1 Effects of bisphosphonates and denosumab on trabecular bone score in women exposed to aromatase inhibitors therapy and followed up for 18–24 months. Data were presented as mean and 95% confidence interval of the mean and comparisons were performed by *t*-test for paired data

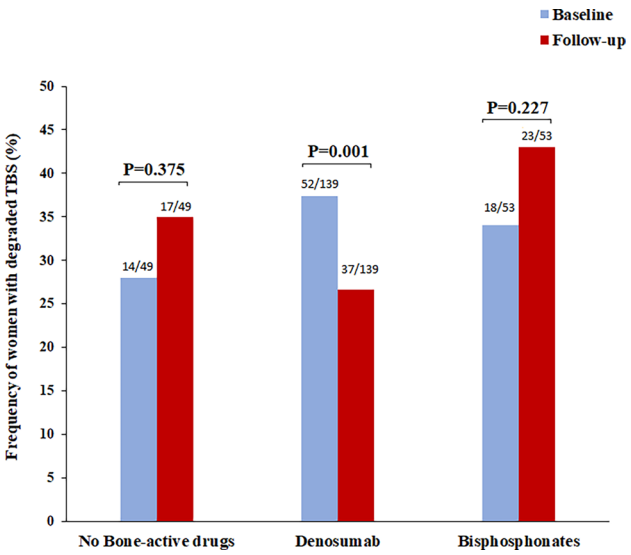

Fig. 2 Effects of bisphosphonates and denosumab on frequency of degraded trabecular bone score in women exposed to aromatase inhibitors therapy and followed up for 18–24 months. Data were presented as percentages and comparisons were performed by McNemar test

was significantly associated with higher BMI, pre-existing VFs and greater decrease in total hip BMD and TBS during the follow-up, and resulted to be significantly decreased by denosumab treatment (Table 2). In the multivariate analyses, decrease in TBS maintained the significant association with risk of incident VFs independently of BMI, pre-existing VFs, denosumab treatment and change in total hip BMD (Table 2).

At follow-up, all women had serum 25(OH)-vitamin D values above 30 ng/ml.

Discussion

In this retrospective study reflecting the real-life clinical practice, decrease in TBS was significantly associated with high risk of incident VFs during only 2 years of treatment with AIs in women with early breast cancer, independently of age, BMI, pre-existing fractures and changes in BMD. Treatment with denosumab induced concomitant increase in TBS and decrease in incident VFs, whereas BPs did not induce relevant effects on these therapeutic outcomes.

VFs are the hallmark of both primary and secondary osteoporosis and they represent the most frequent fragility fractures with relevant impact on quality of life and risk of future fractures [28, 29]. Our study confirms that VFs are a frequent and early complication of AI therapy and provides a further evidence that fractures could occur even in women with baseline normal BMD and low FRAX score [7, 18, 30]. Indeed, prediction of fractures in women exposed

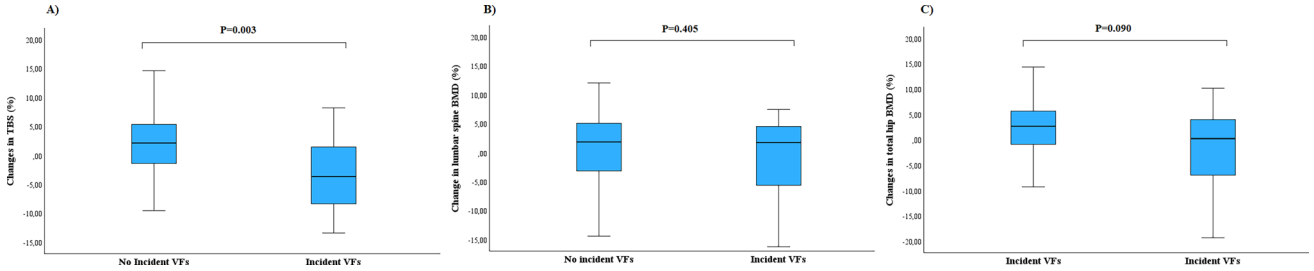

Fig. 3 Changes in trabecular bone score (TBS) (**A**), bone mineral density (BMD) at lumbar spine (**B**) and total hip (**C**) in women exposed to aromatase inhibitors therapy stratified according to incident vertebral fractures (VFs). Data are presented as median, 25th and 75th percentile and range and comparisons were performed by Mann–Whitney's test

to AIs could be a challenge and the optimal therapeutic threshold has not been so far defined [17, 18]. Our study suggests that TBS might be used as a tool for identifying subjects at higher risk of VFs during the first years of AI therapy. In fact, TBS decreased early in women exposed to AIs and the TBS changes significantly correlated with the risk of morphometric VFs independently of other potential determinants of fractures, such as older age and pre-existing fractures.

There is evidence that anti-resorptive drugs can induce favorable effects on TBS concomitantly to the increase in BMD and reduction of fracture risk in women with postmenopausal osteoporosis [31–34]. In women exposed to AI therapy, treatment with oral BPs was shown to prevent the impairment of TBS induced by hormone-deprivation therapy [35, 36]. Consistently, in our study, oral BPs enabled to maintain stable TBS values during 2-year treatment with AIs, counteracting the negative effects of hormone-deprivation therapy on bone quality (i.e., TBS decreased significantly in women not treated with bone-active drugs). However, the favorable effect of oral BPs was not accompanied by a significant decrease in risk of VFs, likely because a longer follow-up could be required for the anti-fracture effectiveness of these drugs [37]. Noteworthy, the effects of denosumab resulted to be more clinically relevant than oral BPs. In fact, denosumab induced significant improvement in TBS in close relationship with decrease in risk of VFs. The effect of denosumab on TBS is consistent with previous observation that parameters of bone structure and elasticity as evaluated by phalangeal quantitative ultrasound of bone improved during treatment with this drug in women exposed to AIs for breast cancer [12]. The effect on bone quality, that is expected for anabolic drugs, seems indeed to be peculiar of denosumab in the context of anti-resorptive drugs. Specifically, denosumab may preserve trabecular microstructure by preventing plate perforation and preserving axially aligned trabeculae [38]. Denosumab may further improve trabecular microstructure by preserving modeling-based bone formation despite its potent inhibition of remodeling [39]. Interestingly, these effects of denosumab on bone quality occurred in our women after only 18–24 months of treatment, consistent with the hypothesis that this drug enables to reduce the imminent risk of fracture [37].

In the general population, low BMI is a well-recognized risk factor for fractures while higher BMI might have a beneficial effect [40]. Conversely, in our women under AI therapy, most of VFs occurred in overweight or obese cases. This result is in agreement with previous studies reporting high prevalence of VFs in women with high body fat mass under AI therapy [41, 42], consistent with the hypothesis that increased adiposity might produce invariably detrimental effects on the skeleton exposed to AI therapy due to annihilation of estrogen production induced by the inhibitory action of the drugs on aromatase enzyme in adipose tissue [17]. Therefore, overweight/obese subjects from being protected in basal conditions become at high risk of bone fragility fractures after starting AIs. It is interesting to note that the negative predictive effect of BMI on fracture risk is maintained even in a population treated with bone resorption inhibitors.

This study has some limitations. The lack of a control group of women not treated with AIs did not allow to clarify whether anti-resorptive drugs maintain in the AI-induced osteoporosis the same effectiveness already reported in post-menopausal osteoporosis. The study was retrospective but DXA evaluations of TBS were performed by the same machine. Moreover, the study was observational and adjudication process of treatment was not randomized but physician dependent. However, the study was designed to provide information on TBS changes during treatment with bone-active drugs in the real-life clinical practice. The assessment of VFs was performed by two methods, but as already demonstrated by others [43], we did not find differences between assessment of VFs on DXA and spinal radiographs images. Patients were followed up for 24 months or less, not allowing to investigate the long-term effects of AIs and bone-active drugs on TBS. Another limitation of study was the lack of data on biochemical markers of bone turnover which might have been useful in identifying early subjects with more severe

Table 2 Logistic regression analyses evaluating the determinants of incident vertebral fractures (VFs) in women under treatment with aromatase inhibitors

Variables	Univariate			Multivariate#1		Multivariate#2		Multivariate#3		Multivariate#4	
	ORs	CI 95%	*P*-values	ORs	*P*-values	ORs	*P*-values	ORs	*P*-values	ORs	*P*-values
Age	1.041	0.996–1.089	0.078								
Baseline BMI	**1.115**	1.008–1.233	0.034							**1.127**	0.037
Baseline osteoporosis	3.168	0.672–14.930	0.145								
Baseline degraded TBS	1.308	0.445–3.845	0.626								
Baseline FRAX score for major Fx	1.676	0.576–4.873	0.343								
Baseline VFs	**8.593**	2.998–24.629	< 0.001					**11.814**	< 0.001		
Treatment with denosumab	**0.282**	0.096–0.828	0.021			0.494	0.242				
Changes in LS BMD during follow-up	0.973	0.899–1.052	0.492								
Changes in TH BMD during follow-up	**0.912**	0.847–0.982	0.014	0.935	0.082						
Changes in TBS during follow-up	**0.864**	0.785–0.951	0.003	**0.876**	0.01	**0.888**	0.025	**0.864**	0.002	**0.868**	0.003

All risk factors significantly associated with incident VFs in the univariate analysis were then submitted to multivariate logistic regression analyses taking into account the minimal guidance criterion of ten events per variable [27]. Values in bold referred to statistically significant odds ratios (ORs)

BMD Bone mineral density, *BMI* body mass index, *CI* confidence intervals, *Fx* fractures, *FRAX* WHO fracture risk assessment, *FX* fracture, *LS* lumbar spine, *ORs* odds ratios, *TBS* trabecular bone score, *TH* total hip, *VFs* vertebral fractures

bone loss, guiding the choice of anti-osteoporotic drugs and monitoring the therapeutic effectiveness [44, 45]. Lack of information on body composition did not allow to investigate the relationship between TBS and visceral adiposity that could induce direct negative effects on bone quality especially in the context of hormone deprivation [46, 47]. Moreover, the missing data on body composition and regional distribution of fat and lean mass do not allow to exclude a possible interference of regional soft tissue noise on the DXA images and eventually in the gray-level texture [48]. Indeed, there is recent evidence that denosumab can improve TBS in post-menopausal osteoporosis even when the parameter was corrected by regional soft tissue thickness [49].

In conclusion, this study showed for the first time how in real-life clinical practice, TBS variations correlate with fracture risk in women treated with AIs, and denosumab is effective to induce a clinically relevant increase in TBS associated with a significant reduction in risk of VFs after only 2-year follow-up. These findings provide a strong rationale for including DXA measurement of TBS in the diagnostic and therapeutic workup of women exposed to estrogen-deprivation therapies.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40618-023-02174-5.

Declarations

Conflict of interest The authors declare the following competing financial interests: Dr Pedersini received consultancy fees from Roche, Novartis, Eli Lilly, Daiichi Sankyo, Gilead, Eisai, Accord, outside the submitted work; Dr. Torrisi received research grants from Pfizer, consultancy fees from MSD and lecture fees from Pfizer, Eli Lilly, EISAI and Genomic Health outside the submitted work; Dr. Vena received grants from IBSA Pharmaceutical outside the submitted work; Dr. Zambelli received consultancy fees from Roche, Novartis, Pfizer, Eli Lilly & Co., AstraZeneca, Genomic Health outside the submitted work; Dr. Bossi received research grants from Novo-Nordisk, Eli Lilly, Bayer, Sanofi Italia and advisory board and consultancy fees from MSD, Alfasigma, Boehringer Ingelheim, Astra Zeneca, Mundipharma Italia, Pfizer outside the submitted work; Dr. Lania received grants from Pfizer and consultancy fees from Ipsen, 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. Mazziotti received consultancy fees from Novartis, Ipsen, Eli Lilly and lecture fees from Amgen and Abiogen, outside the submitted work.

Ethical approval and Research involving human participants and/or animals The study was approved by the Ethics Committee of IRCCS Humanitas Research Hospital.

Consent to participate The study was conducted in accordance with the Declaration of Helsinki, and all participants gave their written informed consent.

Informed Consent No Informed Consent.

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