



Adiposity Excess and Vertebral Fractures in Patients With Breast Cancer Taking Aromatase Inhibitors

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Abstract

IMPORTANCE Aromatase inhibitors (AIs) profoundly suppress estrogen synthesis and accelerate bone loss in postmenopausal women with early breast cancer (EBC). Although body mass index (BMI)-defined obesity has been considered protective for skeletal health, emerging evidence suggests a paradoxical association with fracture risk.

OBJECTIVE To evaluate whether fat mass percentage (FM%) greater than 40.8%, measured by dual-energy x-ray absorptiometry (DXA), is associated with vertebral fracture (VF) progression in patients with EBC receiving AIs.

DESIGN, SETTINGS, AND PARTICIPANTS This retrospective cohort study included consecutive postmenopausal women with EBC (stages I-III) recruited in a single referral center between September 2014 and June 2024. All patients received adjuvant endocrine therapy and underwent serial DXA assessments. Patients treated with tamoxifen or with major comorbidities affecting skeletal fragility were excluded.

EXPOSURES Body composition and bone fragility parameters evaluated by DXA at baseline and at 18, 24, and 30 months.

MAIN OUTCOMES AND MEASURES Adiposity excess was defined as FM% greater than 40.8%, and VF progression was defined as new incident fractures and/or worsening by at least 1 Genant grade at a previously fractured vertebral level. Their association was evaluated using a joint model; time-dependent associations were evaluated using extended Cox regression. Secondary analyses explored associations with bone mineral density, trabecular bone score (TBS), appendicular lean mass index (ALMI), and traditional fracture risk factors.

RESULTS A total of 769 White women (median [range] age, 63 [30-87] years; median [range] BMI, 24.6 [15.6-46.1]) entered the study. During follow-up, 69 patients (9.0%) experienced VF progression. FM% greater than 40.8% was independently associated with increased VF progression (adjusted hazard ratio [HR], 2.00; 95% CI, 1.44-2.82; $P < .001$). Higher ALMI (HR, 0.38; 95% CI, 0.22-0.65; $P < .001$) and BMD (HR, 0.79; 95% CI, 0.66-0.94; $P = .01$) were associated with lower risk of VF progression.

CONCLUSIONS AND RELEVANCE In this retrospective cohort study of patients with EBC receiving AIs, adiposity excess was identified as a novel fracture risk factor, whereas higher muscle mass was protective. These findings support incorporating body-composition assessment into fracture-risk evaluation and preventive strategies for patients undergoing AI therapy.

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Key Points

Question Is a high fat mass percentage associated with vertebral fracture progression in patients with stage I to III breast cancer receiving aromatase inhibitors?

Findings In this cohort study of 769 women with early breast cancer, fat mass percentage greater than 40.8% was independently associated with a 2-fold higher risk of vertebral fracture progression.

Meaning These findings suggest that fat mass assessment should be incorporated into fracture risk stratification for this population, identifying a high-risk subgroup that body mass index alone would miss.

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Introduction

Aromatase inhibitor (AI) therapy in postmenopausal women with hormone receptor-positive early breast cancer (EBC)^{1,2} induces profound estrogen deprivation, accelerating bone loss and increasing fracture risk.³⁻⁵ Vertebral fractures (VFs) are a key manifestation of bone fragility,^{6,7} consistent with evidence that aromatase activity and estrogen levels remain closely correlated with bone mineral density (BMD) in postmenopausal women, even when reduced.^{8,9}

International guidelines recommend baseline assessment of fracture risk factors (eg, prior fractures, family history of osteoporosis) using the fracture risk assessment tool (FRAX) and periodic BMD evaluation by dual-energy x-ray absorptiometry (DXA).¹⁰⁻¹⁴ However, both measures¹⁵ may underestimate fracture risk in patients receiving AIs, as they do not capture qualitative bone deterioration from estrogen depletion.^{16,17}

Low body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) is an established fracture risk factor,^{10,13} whereas obesity has variable skeletal effects through mechanical loading, peripheral estrogen production, and inflammatory signaling.^{18,19} Excess adipose tissue is associated with increased estrogen activity, with likely protective effects on bone and muscle.²⁰ In women receiving AIs, however, growing evidence suggests a paradoxical link between adiposity and skeletal fragility.^{21,22} An Italian multicenter study found that obesity, defined as BMI of 30 or greater, was associated with more than a 3-fold higher VF risk in women with EBC undergoing hormone deprivation.²³ BMI nonetheless inadequately reflects body composition,^{20,21} whereas DXA-measured fat mass (FM) provides greater accuracy.^{24,25}

We previously showed that DXA-assessed FM was directly associated with VF risk in postmenopausal women treated with AIs.²⁶ Confirmation in larger cohorts with longer follow-up is needed, considering dynamic changes in body composition during AI treatment.

This study aimed to examine whether DXA-assessed adiposity excess (ie, fat mass percentage [FM%] >40.8%) represents an independent risk factor for VF progression—defined as incident VFs and/or worsening of a preexisting VF—in patients with EBC receiving AIs. We hypothesized that adiposity excess would be associated with greater VF risk beyond conventional skeletal fragility measures. Secondary analyses assessed associations with FRAX score, densitometric parameters, and additional body composition indices.

Methods

This retrospective, single-center longitudinal cohort study enrolled White women with histologically confirmed EBC (stage I-III, no bone metastasis) receiving adjuvant endocrine therapy with AIs or a luteinizing hormone-releasing hormone agonist plus AIs or tamoxifen, from September 2014 to June 2024. The study was approved by the ethics committee of Brescia, Italy (protocol NP3270), and all participants provided written informed consent per the Declaration of Helsinki.²⁷ This report complies with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.²⁸

Patients with significant comorbidities affecting skeletal fragility (chronic corticosteroid use, hypercortisolism, hyperthyroidism, chronic kidney failure) or prior tamoxifen treatment were excluded. Eastern Cooperative Oncology Group scores of 0 to 1 and estimated life expectancy of more than 18 months were required. All patients included in this analysis had at least 2 DXA scans, at baseline and at 24 months (± 6 months) (eFigure 1 in [Supplement 1](#)). DXA measurements (using Hologic QDR-4500W instrumentation, software version 9.03) were analyzed by dedicated radiologists (M.R. and D.F.) who were blinded to patients' clinical information and DXA scan's time point. Bone fragility parameters included BMD (in grams per centimeter squared), T scores (classified per World Health Organization criteria as normal, osteopenic, or osteoporotic), and trabecular bone score (TBS), a textural index automatically derived from a DXA lumbar spine scan that evaluates local gray-level variations with an experimental variogram of 2-dimension projections. Morphometric VFs

were identified through quantitative morphometric analysis of DXA images and classified according to the Genant classification as follows: mild (20%-25% reduction in vertebral height ratio), moderate (26%-40% reduction), or severe (>40% reduction). VF progression was defined as the occurrence of either a new VF (transition from no fracture to any Genant grade fracture) or worsening of a preexisting VF, defined as an increase of at least 1 Genant grade at a vertebral level already fractured at the previous assessment (from mild to moderate or severe, or from moderate to severe), between baseline and follow-up.

The following DXA parameters of body composition were evaluated: FM (expressed in grams and as a percentage of total weight); lean body mass (in grams); lean mass index (LMI, calculated as total lean mass divided by height squared); trunk-to-appendicular fat ratio; fat mass index (FMI, calculated as total FM divided by height squared); android-fat percentage; gynoid-fat percentage; android-to-gynoid fat ratio; and appendicular lean mass index (ALMI, lean mass from arms plus legs divided by height squared). Consistent with the body composition-based framework proposed by the European Society for Clinical Nutrition and Metabolism and the European Association for the Study of Obesity, adiposity excess was defined as a FM% greater than 40.8%.²⁹ This threshold was selected because it has been previously associated with increased all-cause mortality in a large population-based study³⁰ and because no validated FM%-specific cutoffs for fracture risk are currently available in this population. FM% was assessed at baseline and during Als, and patients were classified as having excess adiposity if the threshold was exceeded at any assessment. Smoking status was classified as never, previous, and current smoker; alcohol intake as 12 g/d or less and greater than 12 g/d; physical activity as mild, moderate, and intense; and family history of fractures as the presence of osteoporotic fractures in at least 1 first-degree relative.

The primary objective was to evaluate the association between FM% greater than 40.8%, at any assessment, and VF progression, after adjustment for known fracture risk factors, such as age, prior fractures, personal or family history of fractures, BMI, and DXA parameters of bone fragility (eg, BMD, T-score, and TBS). Secondary analyses explored associations between VF progression and additional body composition measures (lean mass, ALMI, ALMI-to-FM% ratio, FMI, LMI, trunk-to-appendicular fat ratio). In an exploratory analysis, fat distribution parameters (android and gynoid fat percentage, android:gynoid ratio) were also assessed.

Bone-targeting agents (BTAs, denosumab or bisphosphonates) were prescribed alongside Als at the discretion of treating physicians. The decision was based on current available international guidelines for the management of cancer treatment-induced bone loss and aromatase inhibitor-associated bone loss and Italian drug reimbursement regulations.^{12,13,31-33} Detailed prescribing criteria are reported in the eMethods in [Supplement 1](#).

Statistical Analysis

Data were described using mean and SD or median and range for quantitative variables and as counts and percentages for qualitative variables. The event of interest was defined as the occurrence of a new VF or worsening of an existing one.

The multivariable model investigating the association between FM% greater than 40.8% and the risk of the event of interest was built using subject matter knowledge on the potential covariates and their hypothesized relationships. This is represented using a directed acyclic graph to identify the minimal adjustment set (**Figure 1**).

The risk of event was modeled using a joint model.³⁴ This approach simultaneously analyzes longitudinal data (eg, repeated body composition biomarkers) and time-to-event data (eg, fracture event or progression); by linking the 2 models through shared random effects, the framework accounts for the association between biomarkers' trajectory and event risk. It also mitigates bias from measurement error (in body composition biomarkers) and handles missing values under plausible assumptions, yielding more reliable inference than a complete-case analysis or extended Cox models. Joint models were fitted in a bayesian framework using the JMBayes2 R package³⁴ (4 chains, 6500 iterations each), with convergence checked via trajectory plots and the Gelman-Rubin

statistic ($\hat{R}$).³⁵ The obesity (FM% >40.8%) longitudinal model included time, age, and weight using a binomial family; the BMD longitudinal model included time, drug use, their interaction, weight, and age; the ALMI model accounted for time, age, and weight; the TBS model included time, BTA use, their interaction, weight, and age; the BMI model considered time and age; and models for BMD, ALMI, and BMI used a t-distribution family to account for the variable kurtosis.

Additional analyses were performed using an extended Cox model for time-varying covariates (a complete-case approach, not imputing missing data). A Kaplan-Meier curve was used to display the conditional association of FM% greater than 40.8% with VF progression, derived from the multivariable extended Cox model: estimated survival curves were first computed for each participant accounting for covariate values, then averaged with weighting to obtain an overall estimate per obesity level.

All hypothesis tests were performed assuming a 2-sided 5% significance level. All the analysis was performed using R version 4.5.2 (R Project for Statistical Computing).

As post hoc sensitivity analyses, FM% was modeled as a continuous variable to assess the association across its full range. Additionally, the analysis was repeated in patients with normal BMI (<25 or <30) to evaluate the role of excess adiposity independent of BMI.

Results

Patient Characteristics

The present analysis included 769 postmenopausal White women with EBC with a median (range) age of 63 (30-87) years and median (range) BMI of 24.6 (15.6-46.1) (Table 1). All patients underwent DXA assessments at baseline and after 24 ± 6 months of AI therapy.

Overall, 547 patients (72.0%) were taking BTAs, 74 (9.9%) had prevalent VFs at baseline, and no patients reported major traumatic falls or fractures during follow-up. At baseline, 185 of 630 patients (29.4%) were classified as having excess adiposity; and 100 of 445 (22.5%) who did not have obesity at baseline exceeded the threshold at subsequent assessments, so that 350 of 755 (46.4%) were identified as having excess adiposity at least once during the study (Table 1 and Table 2; eTable 1 and eTable 2 in Supplement 1).

Figure 1. Directed Acyclic Graph Showing the Assumed Causal Structure of the Model

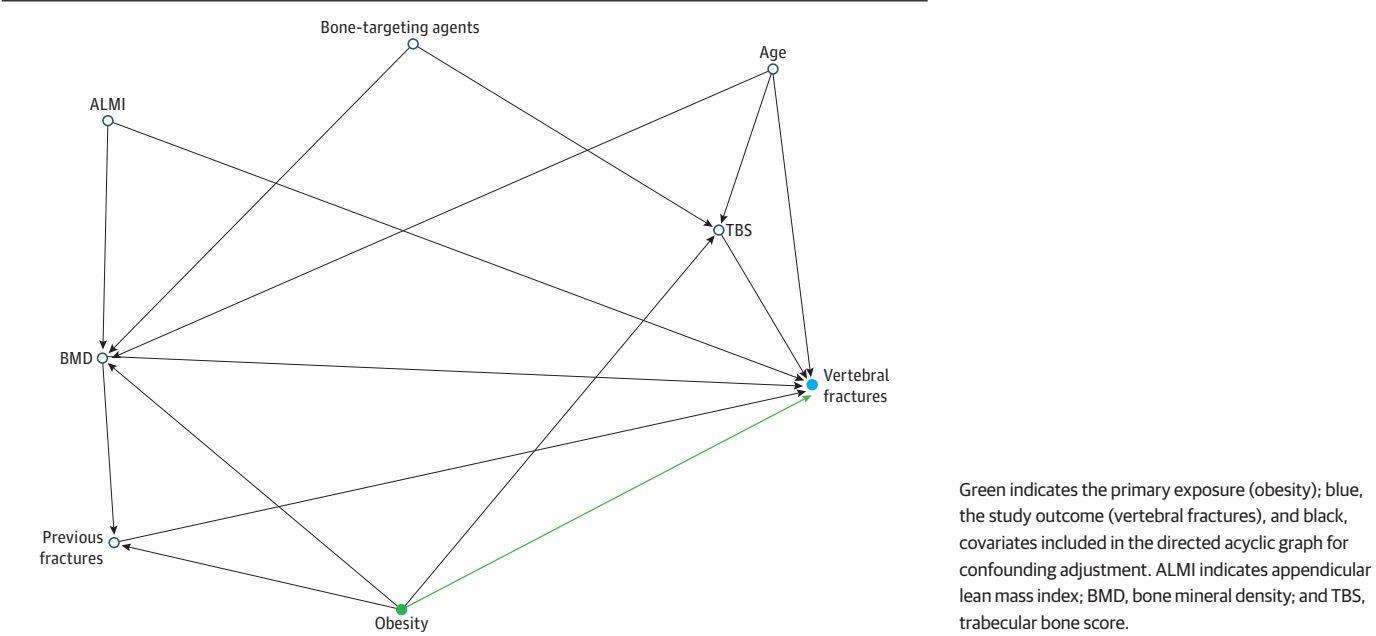


Table 1. Baseline Clinical and Pathological Characteristics of the Study Population

Characteristic	No. with data	Participants, No. (%) (N = 769)
Age, median (range), y	769	63 (30-87)
Height, median (range), m	766	1.61 (1.43-1.79)
Body weight, median (range), kg	762	64.00 (42.00-130.00)
BMI, median (range)	762	24.60 (15.60-46.10)
Menopausal status		
Premenopausal or perimenopausal	766	178 (23.2)
Postmenopausal		588 (76.8)
Previous clinical fractures		
Yes	767	165 (22.0)
No		602 (78.0)
Family history of fractures		
Yes	759	97 (13.0)
No		662 (87.0)
Smoking status		
Yes	767	205 (26.7)
No		562 (73.3)
Alcohol consumption		
Yes	767	190 (24.8)
No		577 (75.2)
Tumor stage		
T1	767	531 (69.2)
T2-T4		236 (30.8)
Nodal status		
N0	766	463 (60.4)
N1-N3		303 (39.6)
Histological type		
Ductal	768	562 (73.2)
Lobular		137 (17.9)
Other		69 (8.9)
Grading		
G1	760	40 (5.3)
G2-G3		720 (94.7)
Ki-67, median (range), %	767	22 (0-90)
ERBB2 status		
Positive	768	102 (13.3)
Negative		666 (86.7)
Type of surgery		
QUART	547	358 (65.4)
Mastectomy		189 (34.6)
Lymph node management		
SLNB	546	425 (77.8)
AD with or without SLNB		121 (22.2)
Radiotherapy		
Yes	547	366 (66.9)
No		181 (33.1)
(Neo)adjuvant chemotherapy		
Yes	769	290 (37.7)
No		479 (62.3)

(continued)

Table 1. Baseline Clinical and Pathological Characteristics of the Study Population (continued)

Characteristic	No. with data	Participants, No. (%) (N = 769)
Endocrine therapy		
AI	769	640 (83.2)
LHRHa with AI		114 (14.9)
LHRHa with tamoxifen		15 (1.9)
Bone-targeting agents ^a		
Yes	763	547 (72.0)
No		216 (28.0)
Type of bone-targeting agents ^a		
Bisphosphonates	547	143 (26.1)
Denosumab		404 (73.9)

Abbreviations: AD, axillary dissection; AI, aromatase inhibitors; BMI, body mass index calculated as weight in kilograms divided by height in meters squared; LHRHa, luteinizing hormone-releasing hormone agonist; QUART, quadrantectomy; SLNB, sentinel lymph node biopsy.

^a Bone-targeting agents were subsequently prescribed based on baseline densitometric characteristics and fracture risk factors.

Table 2. Baseline Densitometric and Body Composition Parameters of the Study Population

Characteristic	No. with data	Participants, median (range) (N = 769)
Total BMD, g/cm ²	652	1.02 (0.60 to 1.86)
Lumbar spine BMD, g/cm ²	760	0.91 (0.49 to 1.41)
Lumbar T-score	761	−1.20 (−5.20 to 3.30)
FRAX major fractures, %	756	5.90 (<0.01 to 33.90)
FRAX hip fracture, %	756	1.10 (<0.01 to 20.30)
DXA classification, No. (%)		
Normal	762	207 (27.0)
Osteopenia		382 (50.0)
Osteoporosis		176 (23.0)
Vertebral fractures		
Yes	767	74 (9.9)
No		675 (90.1)
SDI	749	0.21 (0.00 to 7.00)
FM, g	630	24.00 (8.00 to 60.00)
FM%	630	38.00 (17.00 to 54.00)
Lean body mass, g	598	38.90 (26.40 to 60.90)
Android fat, %	451	39.00 (13.00 to 57.00)
Gynoid fat, %	449	40.60 (18.30 to 56.90)
Android:gynoid fat ratio	450	0.92 (0.39 to 1.42)
Trunk:appendicular fat ratio	567	0.98 (0.41 to 1.98)
LMI	628	14.73 (11.09 to 22.09)
ALMI	604	6.00 (4.19 to 9.77)
FMI	630	9.40 (3.10 to 25.10)
TBS	391	1.29 (0.91 to 1.55)
Obesity (FM% >40.8%), No. (%)		
Yes	630	185 (29.4)
No		445 (70.6)

Abbreviations: ALMI, appendicular lean mass index; BMD, bone mineral density; DXA, dual x-ray absorptiometry; FM, fat mass; FMI, fat mass index; FRAX, Fracture Risk Assessment Tool (major osteoporotic fractures); LMI, lean mass index; SDI, Spinal Deformity Index; TBS, trabecular bone score.

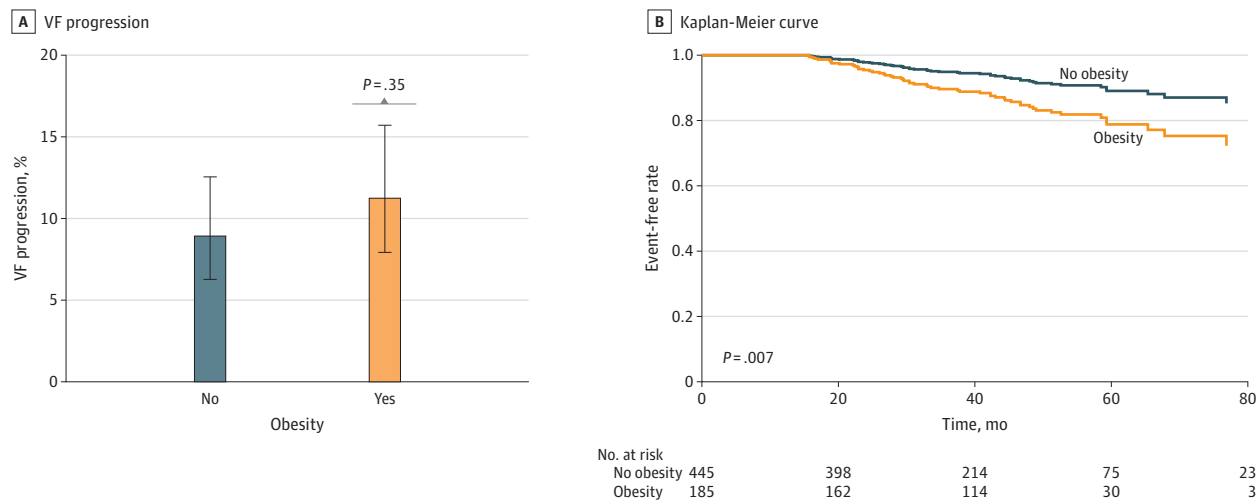
eFigure 2 in Supplement 1 illustrates the limited agreement between FM% and BMI in our population. A threshold of BMI less than 30 failed to identify excess fat mass (FM% >40.8%) in 28.9% of measurements, while FM% of 40.8% or less was observed in only 3.6% of measurements with BMI of 30 or greater.

Factors Associated With VF Progression According to Univariate and Multivariable Analyses

With a median (IQR) follow-up of 45.64 (27.07-59.39) months, VF progression occurred in 69 of 769 patients (9.0%), with most events occurring within the first 30 months (33 patients) or between 31 and 60 months (28 patients). eFigure 3 in Supplement 1 illustrates the cumulative incidence of VF progression over time. VF progression occurred in 29 of 258 patients with excess adiposity at baseline (11.2%), compared with 29 of 325 without excess adiposity (8.9%) ($P = .35$) (Figure 2A). Kaplan-Meier estimates of event-free survival (Figure 2B) demonstrated a significantly shorter time to VF progression among patients with excess adiposity vs those without ($P = .007$).

In univariable extended Cox models (eTable 3 in Supplement 1), older age (hazard ratio [HR], 1.20; 95% CI, 1.09-1.32; $P < .003$), a history of prior clinical fractures (HR, 1.89; 95% CI, 1.15-3.11; $P = .01$), and FM% greater than 40.8% (HR, 2.04; 95% CI, 1.24-3.37; $P = .01$) were associated with a higher risk of VF progression. In contrast, higher BMD was associated with lower risk of VF progression (HR, 0.81; 95% CI, 0.67-0.98; $P = .04$). BMI itself was not significantly associated with VF progression (HR, 1.04; 95% CI, 0.99-1.08; $P = .10$). To evaluate these factors together while using all available repeated measurements over time, we fit a multivariable joint model (Table 3). FM% greater than 40.8% remained independently associated with VF progression after adjustment for the other variables in the joint model. Specifically, comparing patients with a very low vs a very high probability of having obesity (from approximately 1% to approximately 99%), the risk of VF progression was doubled (HR, 2.00; 95% CI, 1.44-2.82; $P < .001$). Sensitivity analyses modeling FM% as a continuous variable confirmed a consistent positive association with vertebral fracture risk (current FM%: HR, 1.36; 95% CI, 0.98-1.92; $P = .06$; cumulative FM%: HR, 1.45; 95% CI, 1.04-2.05; $P = .03$), with log relative hazard increasing across higher FM% values (eTable 4A, eTable 4B, and eFigure 4 in Supplement 1).

Figure 2. Vertebral Fracture (VF) Progression According to Obesity Status Defined by Fat Mass Percentage



Obesity was defined as a fat mass percentage greater than 40.8%.

Table 3. Factors Associated With Vertebral Fracture Progression in Multivariable Analysis (Joint Model)^a

Factors	HR (95% CI)	P value
Age (per 5-y increase)	0.97 (0.77-1.20)	.77
Obesity	2.00 (1.44-2.82)	<.001
Previous clinical fractures (baseline)	1.53 (0.88-2.63)	.13
BMD (0.1 g/cm ² -unit increment)	0.79 (0.66-0.94)	.01
ALMI	0.38 (0.22-0.65)	<.001

Abbreviations: ALMI, appendicular lean mass index; BMD, bone mineral density; HR, hazard ratio.
^a A total of 746 participants and 66 events were included in the model.

In the joint model (Table 3), prior fractures were not significantly associated with VF progression after adjustment (HR, 1.53; 95% CI, 0.88-2.63; $P = .13$). Higher BMD remained associated with a lower risk of VF progression (HR, 0.79; 95% CI, 0.66-0.94; $P = .01$), and higher ALMI was associated with reduced VF progression risk (HR, 0.38; 95% CI, 0.22-0.65; $P < .001$). Conversely, higher FM%-to-ALMI ratio values were associated with an increased risk of VF progression (current FM%: HR, 1.39; 95% CI, 1.01-1.90; $P = .04$), supporting the previous findings (eTable 5 in [Supplement 1](#)).

To further validate these findings, we performed a multivariable extended Cox regression analysis including time-varying covariates (eTable 3 in [Supplement 1](#)). This analysis confirmed the results of the joint model, identifying excess adiposity (HR, 2.77; 95% CI, 1.30-5.93; $P = .01$), lower BMD (HR, 0.69; 95% CI, 0.51-0.94; $P = .03$), and older age (HR, 1.28; 95% CI, 1.05-1.57; $P = .001$) as significantly associated with VF progression. Due to the high number of missing TBS values, we fitted an additional model where TBS showed no association with VF progression (HR, 0.97; 95% CI, 0.62-1.49; $P = .88$); all other covariates, including FM% greater than 40.8%, showed consistent estimates (eTable 6 in [Supplement 1](#)).

In addition, among women with BMI less than 25 and excess fat mass (FM% >40.8%), the hazard of VF progression was markedly increased (HR, 6.63; 95% CI, 1.93-21.85; $P < .001$), after adjustment for age, prior fractures, and BMD (eTable 7A in [Supplement 1](#)). Considering BMI less than 30 with FM% greater than 40.8%, the association was no longer significant (HR, 1.92; 95% CI, 0.87-7.51; $P = .21$) (eTable 7B in [Supplement 1](#)).

Discussion

In this large retrospective cohort study, adiposity excess was independently associated with more than a 2-fold increased risk of VF progression, inconsistent with the traditional paradigm that high BMI is protective for bone health in women receiving adjuvant AI therapy.^{11,13} Adipose tissue represents the main source of estrogens through aromatase enzyme in postmenopausal women.³⁶ However, excess adiposity promotes chronic low-grade inflammation, increased marrow adiposity, and metabolic dysregulation, that may impair bone quality independently of BMD.²¹ In previous analyses by our group, fat mass was associated with VF onset^{26,37} without identifying a specific high-risk subgroup, a gap now addressed by the present study.

The observed positive association between obesity and fracture risk contrasts with current international guidelines, which identify low BMI as a major risk factor for fragility fractures.^{12,13} This discrepancy reflects important differences in the pathophysiology of bone fragility between women treated with Als and postmenopausal osteoporosis: in postmenopausal women, enhanced aromatase activity in adipose tissue sustains circulating estrogen levels, thereby supporting BMD and partially counterbalancing adiposity-related impairment of bone quality. Conversely, in women undergoing AI therapy, aromatase inhibition abolishes this protective mechanism by markedly suppressing estrogen production, allowing BMD loss and adiposity-related bone quality deterioration to act synergistically. As a result, women with overweight and obesity become paradoxically more susceptible to fracture.³⁸

The paradoxical association of FM with fracture risk in women with EBC receiving Als compared with untreated postmenopausal women was previously reported in our cross-sectional study.³⁷ In the present study, adiposity excess was defined using an FM% threshold of 40.8%, an internationally validated cutoff associated with increased all-cause mortality.^{29,30} In our study, 46% of patients exceeded this threshold at least once, and this subgroup showed an approximately 2-fold higher fracture risk. Adiposity excess was also associated with earlier vertebral fracture occurrence, suggesting a role in accelerating skeletal deterioration. Furthermore, one-third of patients with FM% greater than 40.8% had a BMI less than 30, demonstrating that BMI substantially underestimates fat mass burden in this population and would fail to identify a clinically meaningful proportion of high-risk patients.

Among traditional fracture risk factors, as expected, age and previous fractures were both associated with VFs, whereas BMD appeared to have a protective role. Baseline TBS, an index of bone microarchitecture reflecting bone quality,¹⁷ was not significantly associated with incident VFs, consistent with recent results in women with EBC undergoing hormone deprivation therapy.³⁹ Of note, ALMI—a measure of upper and lower limb musculature—emerged as independently associated with lower risk of VF in the multivariable joint model, supporting the role of muscle tone and the importance of its maintenance by physical activity. The exploratory analysis did not reveal any association of fat distribution (gynoid, android, or android:gynoid ratio) with fracture risk.

Strengths and Limitations

The strengths of this study include the large number of patients who were enrolled and followed up at the same center. Additionally, the central evaluation of DXA parameters and VFs were carried out by the same radiologists.

This study also has limitations. The main limitation lies in its retrospective design. Another limitation was related to the use of BTAs in most women included in the study, leading to a relatively lower incidence of VFs than expected for a population at high risk of fractures.⁴⁰ Instead, use of glucagon-like peptide 1 (GLP-1) and GLP-1/gastric inhibitory polypeptide receptor agonists was not systematically recorded; their potential confounding effects on body composition warrant evaluation in future studies.⁴¹ A further limitation is that circulating estradiol was not measured during AI therapy; such data, requiring high-sensitivity mass spectrometry,^{8,42} could have clarified whether incomplete aromatase suppression, particularly in women with obesity, modulates fracture risk. Another limitation is the lack of data on visceral adiposity, which has been specifically associated with osteoporosis and fragility fractures⁴³⁻⁴⁵; nevertheless, our findings suggest that excess adiposity, regardless of fat distribution, may adversely affect skeletal health during AI-induced estrogen deprivation.

Conclusions

In this retrospective single-center longitudinal cohort study, adiposity excess was independently associated with a more than 2-fold increased risk of VF progression in postmenopausal women with EBC. These findings highlight FM%-based assessment as a clinically relevant measure for fracture risk stratification, identifying high-risk patients who would be missed by BMI alone. Additionally, higher ALMI was inversely associated with fracture risk, supporting the role of muscle preservation through physical activity in this population.

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SUPPLEMENT 1.

eTable 1. Baseline Clinicopathological, Densitometric, and Body Composition Characteristics by Obesity Status, Classified According to Occurrence of FM% Greater Than 40.8% at Any Assessment During Follow-Up

eTable 2. Clinicopathological, Densitometric and Body Composition Characteristics of the Study Population at Baseline, 18 Months, 36 Months, and 5 Years of Follow-Up

eTable 3. Univariable and Multivariable Analyses of Factors Assessed for Association With Vertebral Fracture Progression (Extended Cox Model With Time-Varying Covariates; Complete-Case Analysis)

eTable 4. Factors Associated With Vertebral Fracture Progression in Multivariable Analysis (Joint Model), Considering Current FM% as a Continuous Variable and Considering the Cumulative Effect of FM% as a Continuous Variable

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- eTable 6. Factors Associated With Vertebral Fracture Progression in Multivariable Analysis Including Trabecular Bone Score (Joint Model)
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- eFigure 1. Study Flow Diagram of Patient Selection
- eFigure 2. Correlation Between Fat Mass Percentage and Body Mass Index in the Study Population
- eFigure 3. Cumulative Incidence of New Vertebral Fractures or Worsening of Preexisting Fractures, Over Time (Extended Cox Model)
- eFigure 4. Log Relative Hazard of Vertebral Fracture Events as a Function of Fat Mass Percentage, Estimated From the Joint Longitudinal Model
- eMethods.

SUPPLEMENT 2.
Data Sharing Statement