Longitudinal monitoring of denosumab-associated bone changes by REMS in postmenopausal women with ER-positive breast cancer receiving aromatase inhibitors

Aging Clinical and Experimental Research https://doi.org/10.1007/s40520-026-03402-7

Article in Press

Longitudinal monitoring of denosumab-associated bone changes by REMS in postmenopausal women with ER-positive breast cancer receiving aromatase inhibitors.

Received: 30 March 2026

Accepted: 8 April 2026

Published online: 20 April 2026

Cite this article as: Caffarelli C., Forcignanò R., Muratore M. *et al.* Longitudinal monitoring of denosumab-associated bone changes by REMS in postmenopausal women with ER-positive breast cancer receiving aromatase inhibitors.. *Aging Clin Exp Res* (2026). https://doi.org/10.1007/s40520-026-03402-7

Carla Caffarelli, Rosachiara Forcignanò, Maurizio Muratore & Stefano Gonnelli

Title: Longitudinal monitoring of denosumab-associated bone changes by REMS in postmenopausal women with ER-positive breast cancer receiving aromatase inhibitors. .

Authors: Carla Caffarelli[1]*, Rosachiara Forcignanò[2]§, Maurizio Muratore[3]§, Stefano Gonnelli[1].

§equal contributors listed in alphabetical order.

Affiliations:

[1]Department of Medicine, Surgery and Neuroscience, University of Siena, Italy

[2]O.U. of Oncology “Vito Fazzi” Hospital, ASL-LE, Lecce, Italy

[3]O.U. of Rheumatology, “Galateo” Hospital, San Cesario di Lecce, ASL-LE, Lecce, Italy

***Correspondence:** Carla Caffarelli (carlacaffarelli04@gmail.com)

Abstract

Background: Adjuvant endocrine therapy is the treatment for estrogen-receptor (ER)-positive breast cancer (BC). Aromatase inhibitors (AIs) reduce recurrence risk but accelerate bone loss and fracture risk. Denosumab (DmAb), an antiresorptive agent, shows promise in mitigating these effects.

Aims: To assess the short-term effects of DmAb and AIs on bone health in ER-positive BC patients using Radiofrequency Echographic Multi-Spectrometry (REMS) compared with DXA.

Methods: Post-menopausal BC patients receiving AIs who were referred for osteoporosis assessment were retrospectively identified and classified into 2 groups according to routine clinical management: patients receiving DmAb (Group A) or any anti-osteoporotic treatment (Group B). Bone health was evaluated at baseline (T0) and after 6 (T1), 12 (T2), and 18 months (T3). DXA was performed at T0 and T2, while REMS was also performed at T1 and T3.

Results: 364 patients were included in the study. Group B showed a progressive decline in spine and femoral BMD, detected at all time points. Conversely, Group A exhibited significant BMD improvements at both skeletal sites, observed at all time points. Over 18 months, lumbar spine REMS-BMD decreased of -3.92%±0.88% ($p<0.0001$) in Group B and increased by 5.28%±0.73% ($p<0.0001$) in Group A. Comparable trends were observed at the femoral site.

Conclusions: This study, for the first time, quantifies the short-, medium- and long-term AIs effects on bone loss and the positive impact of DmAb on bone density recovery without radiation exposure. These findings support REMS as a reliable tool for longitudinal monitoring of treatment response in patients receiving anti-osteoporosis therapy.

Keywords: Breast cancer; REMS; follow-up; Denosumab; Aromatase inhibitors; Radiofrequency Echographic Multi-Spectrometry.

Introduction

Adjuvant endocrine therapy is widely recognized as the standard treatment for hormone receptor-positive early-stage breast cancer (BC) [1, 2]. Specifically, aromatase inhibitors (AIs) are the preferred option for the treatment of post-menopausal women with oestrogen-receptor positive (ER+) BC [3], due to their ability to inhibit peripheral oestrogen production. AIs are often used either as an alternative to tamoxifen (which blocks oestrogen action) or in sequence following tamoxifen treatment [4, 5].

However, a notable side effect of AIs is their potential to negatively impact bone health. AIs by significantly lowering circulating oestrogen levels accelerate bone resorption at a rate estimated at 2- to 4-fold higher than the physiological resorption rate seen during menopause [3, 6–8]. As a result, women on AIs face an increased risk of fracture. In fact, BC patients have a hospitalization rate for osteoporotic fractures (such as hip, spine, and wrist fractures) of 1.25 times higher (95% CI: 1.23–1.28) than the general population [9], and real-world studies show that up to 18–20% of women on AIs may experience a fracture after 5 years of treatment [7, 10]. This elevated fracture risk is an immediate concern during active cancer treatment, particularly for patients already undergoing other therapies. Effective prevention and monitoring of these bone-related side effects are crucial in comprehensive treatment management, especially for patients with curable disease and long-life expectancies.

Several antiresorptive treatments have proven effective in preventing and managing the bone health issues associated with aromatase inhibitors. Clinical studies have provided strong evidence that subcutaneous denosumab (DmAb) 60 mg, administered every six months alongside vitamin D3 supplementation, significantly helps prevent fractures and increases bone mineral density (BMD) in BC patients undergoing adjuvant AI therapy [1, 2, 11, 12].

Bone health is typically assessed using densitometric techniques that measure BMD at key axial sites, such as the proximal femur and/or lumbar spine (LS). The results are expressed as T-scores, which compare the patient's BMD of a healthy young population. The World Health Organization (WHO) defines a T-score between -2.5 and -1.0 as osteopenia, indicating reduced bone density [13] between normal levels and osteoporosis. Osteoporosis, a more severe condition, is diagnosed when the T-score is ≤ -2.5, signifying very low BMD and compromised bone micro-architecture [14]. BMD is commonly measured using dual-energy X-ray absorptiometry (DXA), a X-ray-based technology.

For patients undergoing AIs therapy, which can cause significant changes in BMD over a short period, it is crucial to accurately assess both the absolute BMD value and the rate of BMD loss. To achieve this, repeated examinations are needed, with the frequency of assessments varying depending on individual risk factors and clinical circumstances. [7, 15]. Currently, there is still no broad consensus on the optimal timing for monitoring, although it is generally agreed that a minimum one-year interval between two consecutive DXA measurements is required to differentiate real BMD changes from the inherent precision errors of the DXA system. Furthermore, when evaluating short-term precision at the femoral neck *in vivo* using the Hologic DXA system, the coefficient of variation (%CV) and least significant change (%LSC) values were found to be 1.49% and 4.12%, respectively [16]. The best precision results reported so far for total spine measurements in a female population with an average age of 60 years, using the Hologic DXA system, showed %CV and %LSC values between 0.7%-0.8% and 2.0-2.1% [17]. Additionally, the presence of osteoarthritis or aortic calcification may lead to falsely elevated BMD measurements when using DXA [18].

In the last years, Radiofrequency Echographic Multi-Spectrometry (REMS) has emerged as an effective, non-ionizing method for assessing bone density at axial sites. REMS calculates BMD, and T-score values, by processing raw ultrasound signals obtained through echographic scans of the lumbar

vertebrae and/or femoral neck [19, 20]. This technology has demonstrated high short-term precision, with a low variability, precisely %CV of 0.32% and a %LSC of 0.88% at the femoral site. Similarly, for the lumbar spine, the %CV is 0.38% and %LSC is 1.05% [19]. Recent studies have confirmed the efficacy of REMS for short-term monitoring of bone health. Notably, Pisani et al., 2023 [21] showed that REMS could identify frail individuals and predict fracture risk over a 5-year follow-up, while Ramirez Zegarra et al., (2024) and Arechavaleta-Velasco et al., (2025) demonstrated its ability to monitor bone changes over a 6-month period, from the first to the third trimester of pregnancy [22, 23]. Similarly, REMS ability was also demonstrated in follow-up on patients with type 2 diabetes mellitus [24]. When comparing the REMS BMD T-scores with those obtained from DXA, a strong correlation was observed at both the lumbar spine ($r = 0.94$, $p < 0.001$) and femoral neck ($r = 0.93$, $p < 0.001$) [19].

This study aimed to assess the short-, medium- and long-term effects of DmAb on bone health, in post-menopausal women with ER-positive BC treated with AIs, who were referred for osteoporosis assessment, comparing the results obtained using REMS technology with those obtained using DXA.

Materials and methods

Study design and participants

This retrospective observational study was conducted as a collaboration between the Galateo Hospital in San Cesario di Lecce (Lecce, Italy) and the Oncology Department of the Vito Fazzi Hospital (Lecce, Italy). The study protocol received approval from the Ethics Committee (ID: 2258/11), and all participants provided written informed consent upon enrolment.

This retrospective observational study included follow-up acquisitions performed between January 2018 and March 2025. Data were retrospectively

analyzed starting in June 2025. The study is reported in accordance with the STROBE statement for observational studies.

A total of 416 ER-positive BC patients eligible for adjuvant AI therapy, who were referred for osteoporosis assessment on axial reference sites were recruited. All the patients received Vitamin D3 and calcium supplementation according to standard clinical practice. On the basis of medical prescription, subjects who received 60 mg of DmAb therapy every 6 months were included in Group A while in the Group B, the subjects who did not receive anti-osteoporotic treatment were included. Denosumab was prescribed according to predefined clinical criteria (e.g., risk factors, clinician judgement).

The initial DXA and REMS scans were performed before the start of AI therapy, establishing the baseline BMD at time T0. Follow-up measurements were taken at 6 months (T1), 12 months (T2) and 18 months (T3) after AIs initiation.

At T2, both DXA and REMS were performed, whereas at T1 and T3 only REMS was performed (see Figure 1), as DXA is not suitable for short-term follow-up. [25].

Exclusion criteria were: significant deambulation impairments; a BMI > 40 kg/m^2; AIs therapy starting before the trial inclusion.

Ethics approval

This study was approved by the local ethic committee and internal review board, and it was conducted in accordance with the ethical standards of the Declaration of Helsinki (1964). Informed consent was obtained from all participants

Procedures

Bone mineral density at the lumbar spine and proximal femur was measured using a Discovery W scanner (QDR Series, Hologic, Waltham, MA, USA) for DXA scans, while REMS echographic scans were performed using an EchoStation device (Echolight S.p.a., Lecce, Italy), equipped with a convex transducer operating at the nominal frequency of 3.5 MHz. To ensure the accuracy of the DXA measurements, all scans were independently reviewed by two different experienced operators to eliminate potential errors related to patient positioning, data analysis, presence of artefacts, and inaccurate post-processing, as highlighted in recent studies [26].
Additionally, quality control procedures were implemented for all REMS reports to verify the correct transducer depth and focus selection [19].

DXA and REMS acquisitions

The DXA scans were performed following standard clinical protocols. For the femur scans, the patient's leg was positioned straight on the table, with the femoral shaft aligned parallel to the vertical edge of the image. The leg was then internally rotated by 15° to 25°, using a dedicated positioning device to ensure accuracy. For the spinal scans, the patient's hip and knee were both fixed at 90° angle.
For REMS, the echographic scan of the lumbar spine was performed by acquiring ultrasound images of the L1-L4 vertebrae, with the convex probe placed on the patient's abdomen. For femoral scans, the convex probe was positioned parallel to the femoral neck, with the probe indicator facing the patient. Once the target bone interface was visualized, the operator adjusted the scan depth and focus to optimize the results. For an accurate follow-up assessment, REMS acquisition parameters (*i.e.*, scan depth and focal settings) were kept consistent with baseline for each patient. All acquisitions were performed by operators who had received the specific training and had at least 3 months of previous continuous experience in REMS acquisitions.

Outcomes

The outcome of this study was to monitor the effects of AIs and DmAb on bone status in BC patients by means of both conventional annual DXA monitoring and follow-up scans performed every 6 months with REMS technology, to provide a more accurate short-term assessment.

Statistical analysis

To determine the sample size, calculation was performed following to the guidelines by the University of Wisconsin School of Medicine and Public Health, assuming a 95% confidence interval. The methodology used for estimating the sample size is based on a quantitative variable. The formula used for the calculation is:

$$\text{Sample size} = \frac{(Z_{1-\alpha/2})^2 \bullet SD^2}{d^2}$$

where:

- $Z_{1-\alpha/2}$ (standard normal variate) = 1.96 (for a 95% Confidence Interval, $p < 0.05$;
- SD (Standard deviation of the variable) = expected BMD Standard Deviation, 0.11 g/cm^2;
- d (Absolute error or precision) = 1.33% of the expected BMD mean value, based on Rodriguez-Sanz's study, which reported an average BMD loss of 0.018 g/cm^2 per year [15].

Writing these values into the formula, the required sample size per group was calculated as 143 patients, resulting in a total sample size of 286 patients. To account for potential dropouts (due to DmAb treatment interruption, death, absence of informed consent or exam inaccuracies), the total sample size was rounded up to 416 patients.

Continuous variables were reported as mean ± standard deviation (SD) or with interquartile ranges (25th and 75th quartiles) and normality was assessed using the Shapiro-Wilk test. Paired t-tests were used to assess statistically significant differences in BMD. Exploratory subgroup analyses were performed according to variables of interest (body mass index, BMI). All analyses and graphs were produced using MedCalc® Statistical Software version 22.021 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2024). A *p*-value < 0.05 was always considered statistically significant.

Results

A total of 416 BC patients (aged 40-71 year; with a BMI ranging from 15 to 35 kg/m^2) eligible for AIs therapy were screened for densitometric assessment. Out of 416 screened patients, 52 did not sign the informed consent to participate in the study.

The remaining 364 patients were included and classified into two groups. Group A (n = 189) received AIs plus denosumab (60 mg every six months), while Group B (n = 175) received AIs only (see Figure1).

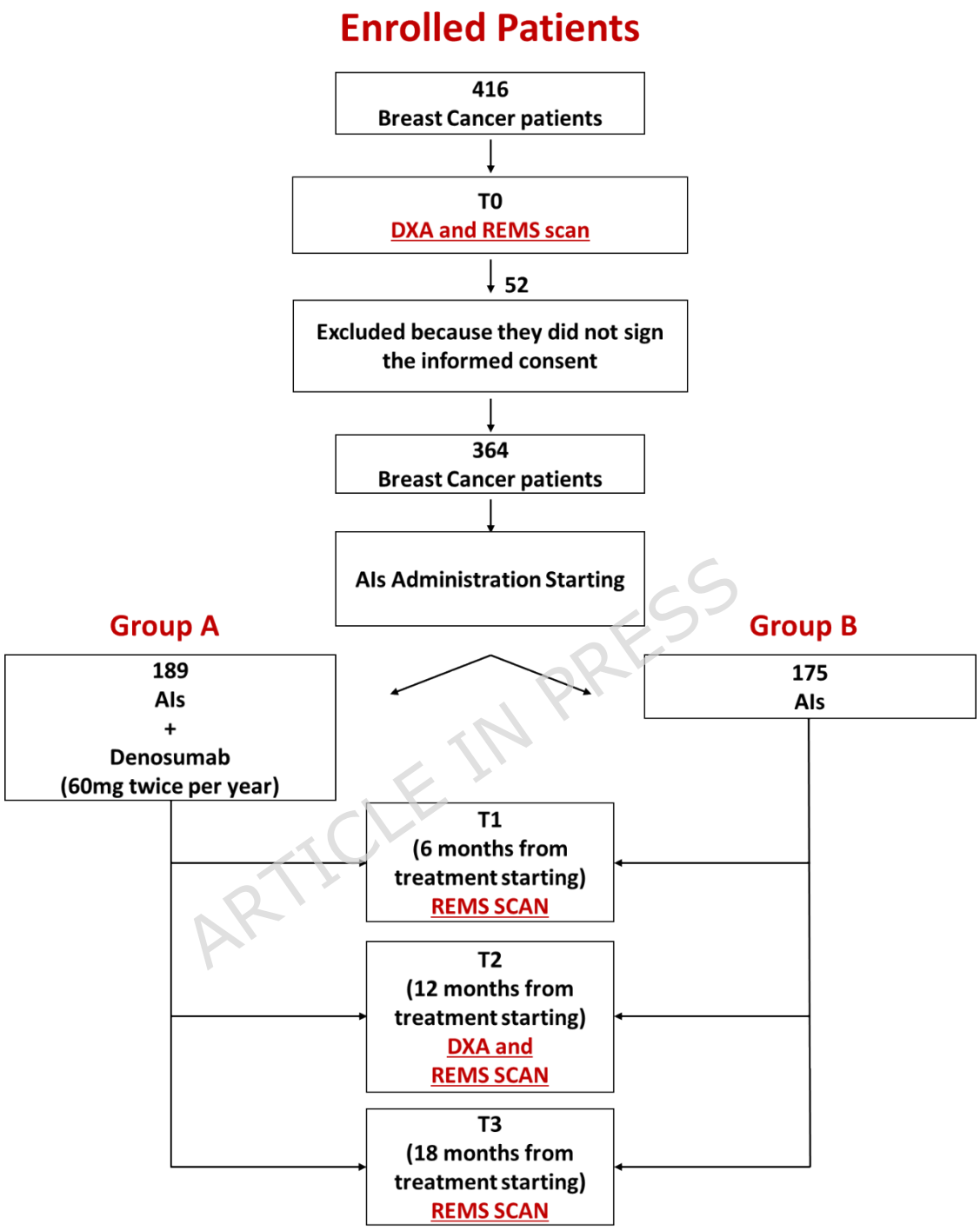

Figure 1. operative study protocol and participant flow.

Group A consisted of 189 subjects with a mean age of 58.5 ± 4.6 y, while Group B included 175 patients with a mean age of 57.8 ± 4.5 y. The baseline characteristics of the patients were reported in Table 1.

Table 1. Baseline demographic and clinical characteristics of participants in Group A and Group B.

Variable	Group B	Group A	*p*-value
n	175	189	n.a.
Age [years] (mean ± SD)	57.8 ± 4.5	58.5 ± 4.6	
Body-mass index [kg/m^2] (mean ± SD)	27.0 ± 5.5	26.4 ± 6.2	
DXA T-score			
LS	-1.9 ± 1.2	-1.9 ± 1.2	0.68
Femoral neck	-1.8 ± 1.0	-1.7 ± 1.0	0.21
REMS T-score			
LS	-1.8 ± 1.3	-1.9 ± 1.2	0.63
Femoral neck	-1.8 ± 1.0	-1.7 ± 1.0	0.92

Table 2 reports the percentage change values and interquartile ranges (25th and 75th quartiles) between the two time points for both techniques. The percentage change was provided for both Group A, and Group B, for both femur and spine measurements, respectively.

Table 2. Percentage changes in femoral neck (FN) and lumbar spine (LS) bone mineral density (BMD) measured by DXA and REMS in Group A and Group B. FN = femoral neck; LS = lumbar spine.

		DXA			REMS		
Site	**Scan delta**	**Group B**	**Group A**	***p***	**Group B**	**Group A**	***p***
FN	**T1-T0**				-0.86 (-1.28 - -0.37)	0.83 (0.51 – 1.13)	<0.0001

	T2-T1				-0.65 (-1.01 - -0.29)	0.90 (0.49 – 1.27)	<0.0001
	T2-T0	-1.21 (-2.04 - -0.48)	1.84 (0.84 – 2.55)	<0.0001	-1.50 (-2.08 - -0.90)	1.74 (1.35 – 2.07)	<0.0001
	T3-T2				-1.41 (-2.19 - -0.62)	0.90 (0.43 – 1.32)	<0.0001
	T3-T1				-2.05 (-2.83 - -1.35)	1.81 (1.40 – 2.22)	<0.0001
	T3-T0				-2.89 (-3.51 - -2.26)	2.65 (2.39 – 2.90)	<0.0001
LS	**T1-T0**				-1.21 (-1.77 - -0.65)	1.92 (1.04 – 2.80)	<0.0001
	T2-T1				-1.12 (-1.67 - -0.54)	2.19 (1.17 – 3.16)	<0.0001
	T2-T0	-2.11 (-3.35 - -0.84)	3.86 (2.76 – 4.86)	<0.0001	-2.34 (-2.91 - -1.77)	4.16 (3.57 – 4.72)	<0.0001
	T3-T2				-1.61 (-2.64 - -0.69)	1.08 (0.44 – 1.68)	<0.0001
	T3-T1				-2.73 (-3.52 - -1.94)	1.91 (1.04 – 2.81)	<0.0001
	T3-T0				-3.92 (-4.50 - -3.28)	5.28 (4.77 – 5.78)	<0.0001

At time T0, the average difference in BMD evaluated at the LS using both DXA and REMS techniques was not statistically significant (p = 0.57 for Group B and p = 0.40 for Group A).

At time T1, Group B showed an initial BMD decrease measured with REMS, resulting in a total decline of -1.21% ± 0.78% ($p < 0.0001$). In contrast, Group A showed a significant BMD increase of 1.92% ± 1.07% ($p < 0.0001$), due to the antiosteoporosis treatment with DmAb.

At T2, the following results were observed for LS (see Figure 2, lumbar spine scans): Group B displayed a further BMD decrease compared to T0, amounting to -2.11% ± 1.65% ($p < 0.0001$) according to DXA and -2.34% ± 0.87% ($p < 0.0001$) based on REMS measurements. In contrast, Group A demonstrated a corresponding BMD increase of 3.86% ± 1.53% ($p < 0.0001$) by DXA and 4.16% ± 0.78% ($p < 0.0001$) by REMS. The average difference

in BMD change measured at T2 by the two techniques was not significant (p = 0.22 for Group B and p = 0.13 for Group A), . At time T3, Group B exhibited a further BMD decline, resulting in a total decrease of -3.92% ± 0.88% (p < 0.0001) compared to T0 values. On the other hand, in Group A, DmAb treatment led to an additional BMD increase, culminating in a total BMD increase of 5.28% ± 0.73% (p < 0.0001) over the same 18-month period.

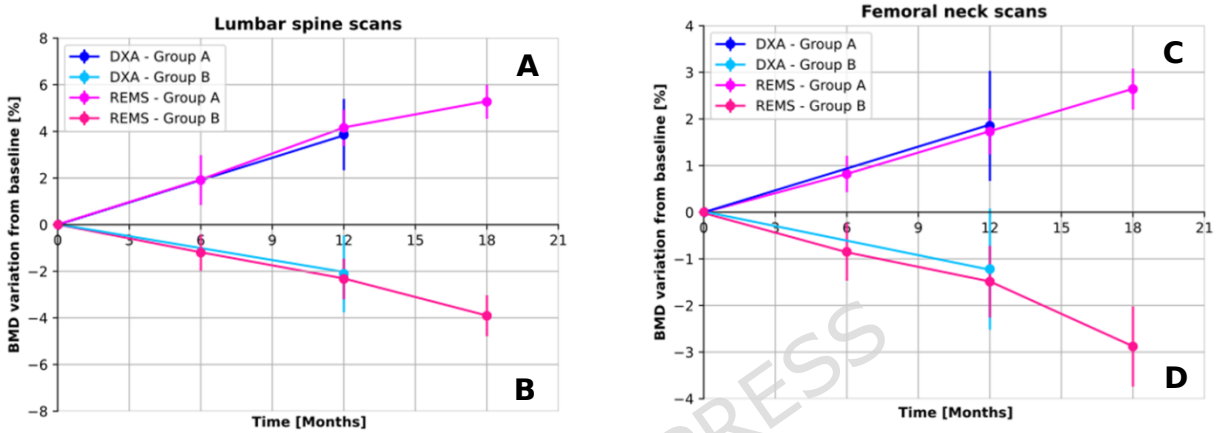

Figure 2 – Lumbar Spine and Femoral Neck scans:
Lumbar spine scans: Effect of DmAb and AIs on the mean percentage changes in BMD.
(A) Percentage change in lumbar spine BMD for Group A, as measured by DXA and REMS.
(B) Percentage change in lumbar spine BMD for Group B, as measured by DXA and REMS.
Femoral neck scans: Effect of DmAb and AIs on mean percentage changes in BMD.
(C) Percentage change in femoral neck BMD for Group A, treated with DmAb, as measured by DXA and REMS.
(D) Percentage change in femoral neck BMD for Group B, treated with AIs, as measured by DXA and REMS.

Similar results were observed for femoral neck BMD (see Figure 2, femoral neck scans). At time T0, , the average difference in BMD obtained by DXA and REMS techniques was not statistically significant (p = 0.30 for Group B and p = 0.23 for Group A).

At time T1, Group B showed an initial BMD decrease measured with REMS, resulting in a total reduction of -0.86% ± 0.62% (p < 0.0001). In contrast,

Group A demonstrated a first BMD increase of 0.83% ± 0.12% ($p < 0.0001$) due to DmAb treatment.

At T2, Group B exhibited a BMD reduction of -1.21% ± 1.30% ($p < 0.0001$) measured by DXA, and a similar decrease of -1.50 ± 0.77% ($p < 0.0001$) according to REMS. In Group A, a BMD increase of 1.84% ± 1.18% ($p < 0.0001$) and 1.74% ± 0.49% ($p < 0.0001$) was detected by DXA and REMS, respectively. As expected, the difference between the average BMD changes measured by the two techniques at T2 was not significant ($p = 0.08$ for Group B and $p = 0.17$ for Group A).

At T3, Group B showed a total BMD decrease of -2.89% ± 0.86% ($p < 0.001$) over the entire treatment period, while Group A showed a total BMD increase of 2.65% ± 0.44% ($p < 0.001$) over the same period.

When all subjects were stratified into two groups based on their BMI (under-/normal-weight and overweight/obese), Group B showed a reduction in BMD values at both the femur and spine, as measured by DXA (T0 and T2) and REMS (T0, T1, T2 and T3). (Similarly, Group A demonstrated an increase in BMD values at both the femur and spine, measured by both DXA and REMS, at each time point. Table 3 presents the mean percentage change values and standard deviation, adjusted for BMI, between two time points for both measurement techniques.

Table 3. Mean percentage changes in lumbar spine and femoral neck measurements stratified by BMI category (under-/normal-weight, overweight/obese) assessed by DXA and REMS in Group A and Group B.

	SPINE		**FEMORAL NECK**	
	DXA			
	under-/normal-weight	***Overweight/obese***	***under-/normal-weight***	***Overweight/obese***
Group B (T0-T2)	-2.1±1.7%	-2.1±1.6%	-1.3±1.3%	-1.1%±1.3
Group A (T0-T2)	3.8±1.5%	4.0±1.6%	1.9±1.1%	1.8±1.2%

	REMS			
Group B (T0-T1)	-1.1±0.7	-1.3±0.9	-0.9±0.6	-0.9±0.6
Group B (T0-T2)	-2.2±0.8	-2.4±0.9	-1.5±0.8	-1.5±0.8
Group B (T0-T3)	-3.8±0.8	-4.0±0.9	-2.8±0.8	-2.9±0.9
Group A (T0-T1)	1.9±1.1	1.9±1.0	0.8±0.4	0.8±0.4
Group A (T0-T2)	4.1±0.8	4.2±0.7	1.8±0.5	1.7±0.5
Group A (T0-T3)	5.3±0.8	5.3±0.7	2.7±0.5	2.6±0.4

Discussion

The data obtained in this study demonstrate that, although BMD declined over time in Group B (both at the spine and femoral neck) due to the effect of AIS, in Group A the treatment with DmAb resulted in a significant recovery of BMD, showing a substantial increase in bone mass at all time points compared to baseline.

The evaluation of the effects of AIs on BC patients at T2, assessed using two different techniques, revealed a decrease in BMD relative to baseline at both the LS and femoral site. These findings were consistent with the evidence provided by Santen RJ., [5] which documents a uniform BMD reduction of approximately −3.0% to −5.4% in the LS and −2.0% to −4.0% in the hip at 2 years follow-up in response to AIs. Additionally, the results of the present study are aligned with other research [27, 28] indicating that changes in BMD were most pronounced at the LS, likely due to the high sensitivity of trabecular bone in the vertebral body to hormonal alterations. The exploratory subgroup analysis found that overweight and obese patients experienced a greater loss of BMD, supporting the findings of Lloyd et al., [29] who reported that women with elevated BMI lost BMD more rapidly than

those with normal-weight [29]. Interestingly, although obesity was generally associated with higher trabecular bone mass and lower volumetric BMD due to adipose tissue [30], this may make overweight and obese BC patients more responsive to hormonal changes, as observed in the LS data.

The results obtained from patients treated with DmAb at T3 also support the findings of several studies, which report BMD increases of about 5.9% in the LS and approximately 3.0% in the hip following 2 years of DmAb therapy [1]. Additionally, these finding support REMS technology, known for its high precision and repeatability, [19], not only as an accurate method for diagnosing osteoporosis but also as a valuable tool for longitudinal monitoring bone mass changes and risk of fractures over short-, medium-, and long-term periods. Moreover, when compared to DXA, REMS showed comparable results, as already evidenced in literature [19, 31]

This study represents the first evaluation of the short-term (6 months), medium-term (12 months), and the long-term (18 months) effects of AIs administration on bone loss, as well as the impact of DmAb treatment on bone density recovery, in BC patients using REMS technology, supporting its feasibility in longitudinal monitoring. While previous studies have demonstrated the effect of AIs and DmAb after at least 12 months of treatment using DXA, this study offers new insights: 1) AIs induce bone loss within 6 months of treatment starting, and 2) adjuvant DmAb administration leads to significant and measurable BMD recovery at every 6-month follow-up point, effectively mitigating the bone loss associated with AIs therapy. Major limitations of the study were: the failure to assess the different effects of various AIs on bone; the lack of monitoring of bone quality through the REMS Fragility Score parameter.

Conclusion

Given the global aging population, it is anticipated that more and more individuals will be affected by both osteoporosis and cancer, which

underscores the growing need for reliable monitoring of the effects of anti-cancer therapies on bone health and, consequently, fracture risk. Thus, short-, medium- and long-term follow-up assessments are crucial for accurately monitoring bone loss rates to ensure that the most appropriate pharmacological therapy is provided for each patient. The use of non-ionizing REMS technology supports longitudinal monitoring in AIs-treated BC patients, thereby facilitating earlier detection of bone loss.

In conclusion, monitoring BMD reduction due to AIs therapy and the assessing of the protective effects of DmAb on lumbar and femoral BMD variations highlight the importance of regular bone health monitoring during hormone-ablative therapy administration. This approach is vital for primary prevention in BC patients and underscores the need of early diagnosis and personalized anti-osteoporotic treatments to support the medical community in managing bone health during cancer treatment.

Author contribution. Conceptualization: S.G., M.M.; Methodology: M.M, R.F.; Formal analysis and investigation: All the authors, Writing – original draft preparation: C.C; Writing – review and editing: all the authors.; Supervision: S.G.

Funding. No funding was received for conducting this study.

Data availability. All relevant data will be available upon reasonable request and under a dedicated agreement to the corresponding author.

Declarations

Conflict of interest. Nothing to declare.

Statement of human and animal rights. This study was approved by the Ethics Review Board of the participating hospital, and it was conducted in accordance with the ethical standards of the Declaration of Helsinki (1964).

Informed consent. Informed consent for participation and publication has been obtained from all the participants included in the study.

References

1. Gnant M, Pfeiler G, Dubsky PC, et al (2015) Adjuvant denosumab in breast cancer (ABCSG-18): a multicentre, randomised, double-blind, placebo-controlled trial. The Lancet 386:433–443. https://doi.org/10.1016/S0140-6736(15)60995-3
2. Scaturro D, de Sire A, Terrana P, et al (2022) Early Denosumab for the prevention of osteoporotic fractures in breast cancer women undergoing aromatase inhibitors: A case-control retrospective study. J Back Musculoskelet Rehabil 35:207–212. https://doi.org/10.3233/BMR-210012
3. Dell'Aquila E, Armento G, Iuliani M, et al (2020) Denosumab for cancer-related bone loss. Expert Opin Biol Ther 20:1261–1274. https://doi.org/10.1080/14712598.2020.1814731
4. Burstein HJ, Lacchetti C, Anderson H, et al (2019) Adjuvant Endocrine Therapy for Women With Hormone Receptor–Positive Breast Cancer: ASCO Clinical Practice Guideline Focused Update. Journal of Clinical Oncology 37:423–438. https://doi.org/10.1200/JCO.18.01160
5. Santen RJ (2011) Effect of Endocrine Therapies on Bone in Breast Cancer Patients. J Clin Endocrinol Metab 96:308–319. https://doi.org/10.1210/jc.2010-1679
6. Cheung AM, Tile L, Cardew S, et al (2012) Bone density and structure in healthy postmenopausal women treated with exemestane for the primary prevention of breast cancer: a nested substudy of the MAP.3 randomised controlled trial. Lancet Oncol 13:275–284. https://doi.org/10.1016/S1470-2045(11)70389-8
7. Hadji P, Aapro MS, Body J-J, et al (2017) Management of Aromatase Inhibitor-Associated Bone Loss (AIBL) in postmenopausal women with hormone sensitive breast cancer: Joint position statement of the IOF,

CABS, ECTS, IEG, ESCEO, IMS, and SIOG. J Bone Oncol 7:1–12. https://doi.org/10.1016/j.jbo.2017.03.001

8. Shapiro CL (2021) Bone-modifying Agents (BMAs) in Breast Cancer. Clin Breast Cancer 21:e618–e630. https://doi.org/10.1016/j.clbc.2021.04.009

9. Colzani E, Johansson AL V, Liljegren A, et al (2014) Time-dependent risk of developing distant metastasis in breast cancer patients according to treatment, age and tumour characteristics. Br J Cancer 110:1378–1384. https://doi.org/10.1038/bjc.2014.5

10. Ouchi Y, Nakatsukasa K, Sakaguchi K, et al (2021) The effect of denosumab in breast cancer patients receiving adjuvant aromatase inhibitors: 36-month results. J Bone Miner Metab 39:224–229. https://doi.org/10.1007/s00774-020-01138-6

11. Ellis GK, Bone HG, Chlebowski R, et al (2008) Randomized Trial of Denosumab in Patients Receiving Adjuvant Aromatase Inhibitors for Nonmetastatic Breast Cancer. Journal of Clinical Oncology 26:4875–4882. https://doi.org/10.1200/JCO.2008.16.3832

12. Galvano A, Scaturro D, Badalamenti G, et al (2019) Denosumab for bone health in prostate and breast cancer patients receiving endocrine therapy? A systematic review and a meta-analysis of randomized trials. J Bone Oncol 18:100252. https://doi.org/10.1016/j.jbo.2019.100252

13. Karaguzel G, Holick MF (2010) Diagnosis and treatment of osteopenia. Rev Endocr Metab Disord 11:237–251. https://doi.org/10.1007/s11154-010-9154-0

14. Professor Kanis JA, Melton LJ, Christiansen C, et al (1994) The diagnosis of osteoporosis. Journal of Bone and Mineral Research 9:1137–1141. https://doi.org/10.1002/jbmr.5650090802

15. Rodríguez-Sanz M, Prieto-Alhambra D, Servitja S, et al (2016) AI-related BMD variation in actual practice conditions: A prospective cohort study. Endocr Relat Cancer 23:303–312. https://doi.org/10.1530/ERC-16-0025

16. Messina C, Acquasanta M, Rinaudo L, et al (2021) Short-Term Precision Error of Bone Strain Index, a New DXA-Based Finite Element Analysis Software for Assessing Hip Strength. Journal of Clinical Densitometry 24:330–337. https://doi.org/10.1016/j.jocd.2020.10.013

17. Bandirali M, Messina C, Di Leo G, et al (2013) Bone mineral density differences between femurs of scoliotic patients undergoing dual-

energy X-ray absorptiometry. Clin Radiol 68:e511–e515. https://doi.org/10.1016/j.crad.2013.03.028

18. Albano D, Agnollitto PM, Petrini M, et al (2021) Operator-Related Errors and Pitfalls in Dual Energy X-Ray Absorptiometry: How to Recognize and Avoid Them. Acad Radiol 28:1272–1286. https://doi.org/10.1016/j.acra.2020.07.028

19. Di Paola M, Gatti D, Viapiana O, et al (2019) Radiofrequency echographic multispectrometry compared with dual X-ray absorptiometry for osteoporosis diagnosis on lumbar spine and femoral neck. Osteoporosis International 30:391–402. https://doi.org/10.1007/s00198-018-4686-3

20. Diez-Perez A, Brandi ML, Al-Daghri N, et al (2019) Radiofrequency echographic multi-spectrometry for the in-vivo assessment of bone strength: state of the art—outcomes of an expert consensus meeting organized by the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO). Aging Clin Exp Res 31:1375–1389. https://doi.org/10.1007/s40520-019-01294-4

21. Pisani P, Conversano F, Muratore M, et al (2023) Fragility Score: a REMS-based indicator for the prediction of incident fragility fractures at 5 years. Aging Clin Exp Res. https://doi.org/10.1007/s40520-023-02358-2

22. Ramirez Zegarra R, Degennaro V, Brandi ML, et al (2024) Longitudinal changes of the femoral bone mineral density from first to third trimester of pregnancy: bone health assessment by means of non-ionizing REMS technology. Aging Clin Exp Res 36:31. https://doi.org/10.1007/s40520-023-02677-4

23. Arechavaleta-Velasco F, Diaz-Cueto L, Rosales-Ortiz S (2025) Maternal Bone Mineral Density Changes during Pregnancy: A Longitudinal Prospective Study Using Radiofrequency Echographic Multi-Spectrometry. J Womens Health 34:1365–1373. https://doi.org/10.1177/15409996251372853

24. Al Refaie A, Baldassini L, Mondillo C, et al (2024) Glucagon-like Peptide-1 Receptor Agonists and Diabetic Osteopathy: Another Positive Effect of Incretines? A 12 Months Longitudinal Study. Calcif Tissue Int 115:160–168. https://doi.org/10.1007/s00223-024-01240-1

25. El Maghraoui A, Achemlal L, Bezza A (2006) Monitoring of Dual-Energy X-ray Absorptiometry Measurement in Clinical Practice.

Journal of Clinical Densitometry 9:281–286. https://doi.org/10.1016/j.jocd.2006.03.014

26. Messina C, Bandirali M, Sconfienza LM, et al (2015) Prevalence and type of errors in dual-energy x-ray absorptiometry. Eur Radiol 25:1504–1511. https://doi.org/10.1007/s00330-014-3509-y

27. Conde DM, Costa-Paiva L, Martinez EZ, Pinto-Neto AM (2012) Low Bone Mineral Density in Middle-Aged Breast Cancer Survivors: Prevalence and Associated Factors. Breast Care 7:121–125. https://doi.org/10.1159/000337763

28. Pedersini R, Amoroso V, Maffezzoni F, et al (2019) Association of Fat Body Mass With Vertebral Fractures in Postmenopausal Women With Early Breast Cancer Undergoing Adjuvant Aromatase Inhibitor Therapy. JAMA Netw Open 2:e1911080. https://doi.org/10.1001/jamanetworkopen.2019.11080

29. Lloyd JT, Alley DE, Hawkes WG, et al (2014) Body mass index is positively associated with bone mineral density in US older adults. Arch Osteoporos 9:175. https://doi.org/10.1007/s11657-014-0175-2

30. Sukumar D, Schlussel Y, Riedt CS, et al (2011) Obesity alters cortical and trabecular bone density and geometry in women. Osteoporosis International 22:635–645. https://doi.org/10.1007/s00198-010-1305-3

31. Cortet B, Dennison E, Diez-Perez A, et al (2021) Radiofrequency Echographic Multi Spectrometry (REMS) for the diagnosis of osteoporosis in a European multicenter clinical context. Bone 143:115786. https://doi.org/10.1016/j.bone.2020.115786