

Very short-term monitoring of Romosozumab longitudinal effects in a cohort of postmenopausal women by means of Radiofrequency Echographic Multi-Spectrometry (REMS) technology

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Abstract

Background

Romosozumab/AMG785 (Evenity®, Amgen and UCB pharma, RMZ) is a sclerostin-neutralizing antibody that rapidly increases BMD, but very short-term monitoring in clinical routine is limited by specific issues of available ionizing techniques.

Aims

To assess the effectiveness of the radiation-free Radiofrequency Echographic Multi Spectrometry (REMS) for very short-term monitoring of RMZ in postmenopausal women.

Methods

Seventy-four postmenopausal women starting RMZ and 52 postmenopausal women not receiving anti-osteoporosis drugs underwent proximal femur REMS scans at baseline and after 6 months, assessing total hip (TH) and femoral neck (FN) BMD. Exploratory analyses were also performed in treatment-naïve patients and in women with ≥ 2 prior fragility fractures.

Results

After six months of RMZ, BMD significantly increased at both TH (+ 3.7%; $0.718 \pm 0.103 \text{ g/cm}^2$ vs. $0.698 \pm 0.116 \text{ g/cm}^2$; $p < 0.01$) and FN (+ 4.1%, $0.572 \pm 0.092 \text{ g/cm}^2$ vs. $0.556 \pm 0.105 \text{ g/cm}^2$; $p \leq 0.01$). In treatment-naïve patients ($n = 33$), BMD gains were larger (TH + 4.7%; FN + 4.6%), as also in women with ≥ 2 prior fractures ($n = 36$), where TH BMD increased by 4.1% and FN BMD by 4.8%. In untreated controls, no significant changes were observed at either TH (-0.8%; $p > 0.05$) or FN (-0.6%; $p > 0.05$). Weight and BMI did not change significantly over the considered 6-month interval.

Conclusions

REMS detected clinically-relevant 6-month increases in femoral BMD during RMZ therapy, while BMD remained stable in untreated controls. These findings, together with anthropometric stability, support the feasibility of REMS for very short-term follow-up in real-world settings.

Introduction

Osteoporosis is a systemic skeletal disorder characterised by reduced bone mineral density (BMD), deterioration of bone microarchitecture and compromised bone strength, leading to an increased

susceptibility to fragility fractures, which represent a major cause of morbidity, mortality and healthcare burden worldwide [1, 2]. Some pharmacological options include anabolic (teriparatide and abaloparatide) and antiresorptive (bisphosphonates and denosumab) agents. While agonists of parathyroid hormone (PTH) receptor 1, primarily promoting stem cell differentiation, bone turnover and mineral deposition that may be subsequently reabsorbed [3], the antiresorptives are largely limited to the inhibition of osteoclastic-mediated bone resorption while not adequately promoting the recovery of bone mass or the reversal of microarchitectural damage[4] These limitations have stimulated the development of new therapeutic strategies aimed at enhancing bone formation and reducing bone absorption pathways at the same time.

Romosozumab (AMG785; Evenity®, Amgen/UCB pharma; RMZ) is a humanised monoclonal IgG2 antibody that selectively inhibits sclerostin, an osteocyte-derived glycoprotein that negatively regulates bone formation through the suppression of the canonical Wnt/ β -catenin signalling pathway [5, 6]. By neutralising sclerostin, RMZ exerts a unique dual effect on bone remodelling: it markedly stimulates osteoblast-mediated bone formation while simultaneously inducing a transient reduction in bone resorption, resulting in a net anabolic effect on the skeleton [7–9]. This mechanism distinguishes RMZ from conventional antiresorptive and anabolic drugs and positions it as a cornerstone therapy for patients with imminent fracture risk.

Randomised controlled trials (FRAME, ARCH, STRUCTURE and BRIDGE) consistently showed that RMZ induces rapid and clinically meaningful BMD gains at the lumbar spine and proximal femur [10–14]. In postmenopausal women with osteoporosis, twelve months of RMZ increased BMD from baseline by 11.9–14.7% at the lumbar spine, by 5.6–8.1% at the total hip and by 4.3–7.4% at the femoral neck [14]. Furthermore, twelve months of RMZ significantly exceeded the gains achieved with alendronate or teriparatide over similar treatment durations [11, 12], showing promising results even in osteoporotic men [10]. These structural improvements translated into substantial reductions in vertebral and non-vertebral fracture risk [14].

Beyond densitometric changes, RMZ has also been shown to improve bone quality parameters (e.g., cortical thickness and trabecular microarchitecture) in studies using high-resolution peripheral quantitative computed tomography (HR-pQCT) and histomorphometry [15]. Moreover, RMZ typically produces an early rise in bone formation markers (e.g., P1NP), followed by a subsequent decline in bone resorption markers (e.g., CTX), reflecting a transient uncoupling of remodelling [11, 12].

Given its potent anabolic properties and ability to rapidly enhance skeletal strength, RMZ is commonly considered for patients with severe osteoporosis at very high fracture risk and/or recent or multiple fragility fractures, in line with international guideline recommendations and prioritisation statements [16]. However, concerns regarding potential cardiovascular risk signals reported in the ARCH trial warrant careful patient selection and individualised risk stratification [12]. Latest safety data available in literature do not substantiate these concerns and indicate a risk ratio for any adverse events compared

to placebo ranging from 0.90 to 0.98, with the cardiovascular death risk ratio ranging from 1.08 to 1.24 [17, 18].

In the current routine practice, evaluation and monitoring of treatment impact on BMD relies mainly on dual-energy X-ray absorptiometry (DXA), which usually can be performed no earlier than 18 months, so shorter follow-up may be limited by accessibility issues, radiation exposures; it is also well established that the DXA technique is susceptible to numerous technical and clinical site-specific artifacts, which may at times limit its repeatability and clinical reliability [19]. Radiofrequency Echographic Multi-Spectrometry (REMS) is a radiation-free, portable technology that estimates axial BMD from raw ultrasound signals[20, 21] and has shown good agreement with DXA [22, 23], combined with the ability of effectively avoiding the relevant artifacts [24, 25]. An increasing number of studies support the use of this technology in osteoporosis management, as a more accessible alternative to DXA [26, 27].

The present study aimed to evaluate whether proximal femur REMS can capture early (6-month) BMD changes during RMZ therapy in a real-world cohort of postmenopausal women. Secondary aims were to explore early responses according to prior osteoporosis treatment exposure and fracture burden and to contextualise observed changes against a non-treated control group.

Materials and methods

Study design and participants

This retrospective observational study was conducted at the Rheumatology Unit of “P.O. Valle D'Itria” in Martina Franca (Taranto, Italy). The study is reported in accordance with the STROBE statement for observational studies. This retrospective observational study included REMS acquisitions performed between February 2024 and November 2025. Data were retrospectively extracted from clinical records starting in December 2025. A convenience sample size of eligible patients was used for the study.

Participants received RMZ by subcutaneous injection (210 mg monthly, administered as two consecutive 105 mg injections) according to the product label. Treatment effects were evaluated by comparing proximal femur REMS BMD measurements at baseline and at the 6-month follow-up. Serum vitamin D and calcium levels were also collected at the same time points.

Inclusion criteria for the RMZ-treated cohort were Caucasian postmenopausal women with osteoporosis and a 10-year fracture risk $\geq 20\%$ (estimated using either the FRAX or the DeFRA fracture-risk assessment tool) plus at least one of the following conditions: *i*) ≥ 1 moderate or severe vertebral fracture; *ii*) ≥ 2 mild vertebral fractures; *iii*) ≥ 2 non-vertebral fragility fractures; *iv*) a femoral fragility fracture within the previous 2 years. Exclusion criteria included male sex, contraindications to RMZ (e.g., a history of cardiovascular events and/or patients deemed suitable to continue alternative effective anti-osteoporosis treatments), conditions affecting bone metabolism such as thyroid or parathyroid disorders, cancer, hormone replacement therapy, missing baseline or 6-month BMD data, and discontinuation of RMZ before the 6-month follow-up.

The negative control group included postmenopausal women who were not receiving a pharmacological anti-osteoporosis therapy and who underwent two proximal femur REMS scans 6 months apart in the same clinical setting.

All data were anonymised prior to analysis.

Ethics approval

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 was obtained from all participants.

REMS scan examination

Proximal femur BMD was measured by REMS using an EchoStation device (Echolight S.p.a., Lecce, Italy), equipped with a convex transducer (nominal frequency 3.5 MHz). The acquisition protocol has been described previously [20, 21]. Briefly, for femoral scans, the probe was aligned with the femoral head-neck axis, with the probe indicator towards the patient's face, to visualise the typical proximal femur profile (head, neck and trochanter). Once the target interfaces were identified, the operator adjusted the scan depth and focus to optimise the results and held the image for 40 s according to the indications provided by the device software. For an accurate follow-up assessment, 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 according to the training program of the device manufacturer and had at least 3 months of previous continuous experience in REMS acquisitions. Before data analysis, scan quality was always checked by three independent operators through the quality scan check features available in the medical report (i.e., appropriate setting of transducer focus and scan depth, target bone profile in the central part of the image, within the ultrasound beam focal zone and at about halfway through the image depth), who were not aware of baseline results when checking the follow-up scans.

Parameters

Total hip (TH) and femoral neck (FN) BMD and T-score values were calculated by REMS software and were included in the subsequent statistical analysis. The primary outcomes were the changes in TH and FN BMD from baseline to 6 months.

At femoral sites, REMS short-term intra-operator precision expressed as root mean square coefficient of variation (RMS-CV) is 0.32% (95% confidence interval: 0.24–0.40%), with a corresponding least significant change (LSC) value of 0.88% at the 95% confidence level [23]. For short-term inter-operator

repeatability, RMS-CV is 0.48% (95% confidence interval: 0.36–0.60%), and the corresponding LSC is 1.33% [23].

Statistical analysis

Descriptive statistics were used to summarise participant characteristics and outcome measures. Continuous variables were reported as mean $\pm$ standard deviation (SD), while categorical variables were reported as absolute and percentage frequencies. Normality of continuous variables was assessed using the Shapiro-Wilk test. Changes in demographic and anthropometric data (age, height, weight and body mass index (BMI)), biochemical parameters (serum calcium and vitamin D levels), and BMD were reported as mean differences from baseline with 95% confidence intervals (CI) and as mean percentage variations from baseline. Paired *t*-tests were used to assess statistically significant differences in anthropometric data, biochemical parameters or BMD at 6-month follow-up with respect to baseline. Exploratory subgroup analyses were performed according to variables of interest (e.g., age groups, BMI, previous osteoporosis therapies, and number of prior fractures).

All analyses and graphs were produced using R statistical software (version 4.5.2) [28]. A *p*-value < 0.05 was always considered statistically significant.

Results

Patients' characteristics

A total of 74 patients met the inclusion criteria for RMZ therapy and completed the 6-month follow-up; 52 women were included as negative controls and also completed the 6-month follow-up.

Table 1 summarises demographic, anthropometric and biochemical characteristics of the study cohorts at baseline and at 6-month follow-up for RMZ-treated patients and negative controls, respectively.

Baseline clinical characteristics of the RMZ-treated patients are reported in Table 2.

Table 1

Anthropometric and biochemical differences of Romosozumab-treated and negative control patients at baseline and 6-month follow-up. Anthropometric and demographic variables (age, height, weight and BMI) and biochemical parameters (serum calcium and vitamin D levels) are shown as mean $\pm$ standard deviation (SD). *p*-values refer to the paired Student's *t*-test (n.s. = not significant).

Romosozumab-treated patients			
Variable	Patients that started Romosozumab therapy (<i>n</i> = 74)	Patients at 6-month follow-up of Romosozumab therapy (<i>n</i> = 74)	<i>p</i>-value
Age (years)	75.18 $\pm$ 8.11	75.57 $\pm$ 8.01	< 0.001
Weight (kg)	60.23 $\pm$ 11.23	60.85 $\pm$ 10.71	n.s.
Height (cm)	153.93 $\pm$ 7.68	153.93 $\pm$ 7.68	n.s.
BMI (kg/m ²)	25.55 $\pm$ 5.38	25.83 $\pm$ 5.27	n.s.
Calcium levels (mg/dL)	9.66 $\pm$ 0.60	9.40 $\pm$ 0.50	n.s.
Vitamin D levels (ng/mL)	39.82 $\pm$ 13.63	44.26 $\pm$ 17.10	n.s.
Negative control patients			
Variable	Negative controls at baseline (<i>n</i> = 52)	Negative controls at 6-month follow-up (<i>n</i> = 52)	<i>p</i>-value
Age (years)	71.52 $\pm$ 5.14	71.95 $\pm$ 5.05	< 0.001
Weight (kg)	61.02 $\pm$ 10.30	61.48 $\pm$ 10.67	n.s.
Height (cm)	155.75 $\pm$ 6.45	155.75 $\pm$ 6.45	n.s.
BMI (kg/m ²)	25.16 $\pm$ 4.00	25.54 $\pm$ 3.96	n.s.

Table 2

Clinical characteristics of Romosozumab-treated patients at therapy initiation. Values are expressed as percentages, calculated as the number of patients divided by the total study population x 100.

Variable	Patients that started Romosozumab therapy (<i>n</i> = 74)
Patients with comorbidities (%)	29.3
Patients with 1 fracture (%)	27.0
Patients with 2 fractures (%)	25.7
Patients with ≥ 3 fractures (%)	23.0
Patients who followed an anti-osteoporosis therapy before Romosozumab (%; categories mutually non-exclusive):	55.4
• Bisphosphonates (%): 28.8	
• Denosumab (%): 26.0	
• Teriparatide (%): 12.3	
Patients who received a bone-relevant co-medication before Romosozumab (%):	35.4
• Corticosteroids (%): 29.2	
• Vitamin D (%): 4.1	
• Diuretic (%): 2.1	

Changes in BMD

In RMZ-treated patients, TH BMD exhibited a statistically significant increase of 3.7% at 6 months compared with baseline (0.718 ± 0.103 vs. 0.698 ± 0.116 g/cm²; $p < 0.01$) (Fig. 1a and Table 3). Likewise, FN BMD showed a statistically significant increase of 4.1% (0.572 ± 0.092 vs. 0.556 ± 0.105 g/cm²; $p < 0.01$) (Fig. 1b and Table 3). Notably, mean percentage changes exceeded the femoral REMS LSC (0.88%) [23].

In negative controls, no statistically significant BMD changes were observed at 6 months with respect to baseline at either TH (-0.8% ; 0.721 ± 0.088 vs. 0.727 ± 0.088 g/cm²; $p > 0.05$) or FN (-0.6% ; 0.579 ± 0.078 vs. 0.583 ± 0.078 g/cm²; $p > 0.05$) (Fig. 1c and Fig. 1d and Table 3).

Table 3

Summary of BMD levels at baseline and 6-month follow-up in Romozosumab-treated and negative control patients. Absolute differences and percentage (%) changes are reported along with the 95% confidence interval (CI). *p*-values refer to the paired Student's *t*-test (n.s. = not significant).

Romozosumab-treated patients						
Characteristic	Baseline (<i>n</i> = 74)	6 months (<i>n</i> = 74)	Difference	95% CI	<i>p</i> -value	% Variation, (95% CI)
BMD TH						
Mean (SD)	0.698 ± 0.116	0.718 ± 0.103	0.020	0.008, 0.032	< 0.01	+ 3.7 (1.6, 5.9)
BMD FN						
Mean (SD)	0.556 ± 0.105	0.572 ± 0.092	0.017	0.006, 0.027	< 0.01	+ 4.1 (1.7, 6.4)
Negative control patients						
Characteristic	Baseline (<i>n</i> = 52)	6 months (<i>n</i> = 52)	Difference	95% CI	<i>p</i> -value	% Variation (95% CI)
BMD TH						
Mean (SD)	0.727 ± 0.088	0.721 ± 0.088	-0.006	-0.016, 0.004	n.s.	-0.8 (-2.1, 0.6)
BMD FN						
Mean (SD)	0.583 ± 0.078	0.579 ± 0.078	-0.004	-0.011, 0.003	n.s.	-0.6 (-1.9, 0.6)

Interestingly, in an exploratory analysis considering only patients who did not receive any prior osteoporosis therapy before starting RMZ (treatment-naïve, *n* = 33), larger BMD increases in BMD were found at both sites: TH (+ 4.7%, 0.742 ± 0.095 vs. 0.712 ± 0.106 g/cm², *p* < 0.001; Fig. 2a) and FN (+ 4.6%, 0.595 ± 0.087 vs. 0.573 ± 0.097 g/cm², *p* < 0.01; Fig. 2b). Likewise, when considering only patients with 2 or more prior fractures (*n* = 36), a greater increase in BMD at 6 months was observed at both skeletal sites. Specifically, TH BMD increased by 4.1% (0.728 ± 0.088 vs. 0.703 ± 0.105 g/cm², *p* < 0.01; Fig. 2c), and FN BMD increased by 4.8% (0.580 ± 0.080 vs. 0.558 ± 0.094 g/cm², *p* < 0.01, Fig. 2d).

Discussion

The new humanised monoclonal IgG2 antibody known as RMZ is a sclerostin-neutralising antibody with unique dual action (increased bone formation with a transient decrease in resorption), which translates into rapid BMD gains and fracture risk reduction in pivotal trials [10–14]. However, in routine practice, early monitoring is limited by specific issues of radiation-bearing technologies like DXA. In this retrospective real-world study, we documented for the first time that REMS, a portable, radiation-free

technology with good agreement with DXA and able to effectively avoid relevant artefacts [22–25], can detect early (6-month) changes in proximal femur BMD (by + 3.7% and + 4.1% at TH and FN, respectively) in postmenopausal women undergoing RMZ therapy. These findings further strengthen the current body of evidence on REMS by demonstrating its applicability to the longitudinal monitoring of bone changes and highlighting its potential role in the safe, very short-term tracking of treatment-induced skeletal changes.

A cohort of 74 postmenopausal women was included and monitored with REMS at baseline and after 6 months of RMZ treatment. Before starting the RMZ therapy, 44.6% had never received a specific anti-osteoporosis treatment, whereas the remaining 55.4% had undergone prior osteoporosis therapies before switching to RMZ. A clinically relevant proportion had a history of previous fragility fracture(s), which were mostly located at the lumbar site, consistent with a very high-risk population eligible for RMZ according to current international guidance [16] (Table 2): 27.0% had experienced a single vertebral fracture, 25.7% had 2 fractures (with at least one being a vertebral fracture), and the remaining 23.0% suffered from 3 or more fractures (also with at least one vertebral fracture). No patient had reported prior femoral fractures.

After 6 months, REMS detected significant increases in BMD at both TH (+ 3.7%) and FN (+ 4.1%), in line with previous DXA-based real-world observational studies, showing improvements ranging from 1% to 4% at the TH and from 0.5% to 6% at the FN [29–32]. Our results are consistent with these studies, with REMS-BMD percentage changes at the FN slightly higher than those at the TH, and closely resemble both Italian [29] and Japanese observational data [30–33]. Notably, the observed BMD changes substantially exceeded the REMS LSC, providing further evidence that the detected differences are not due to measurement variability.

Furthermore, as shown in Table 1, anthropometric parameters remained stable over the 6-month interval. Therefore, the BMD increments detected by REMS at the total hip and femoral neck are more consistent with treatment-related skeletal changes over time than with anthropometric variations. This interpretation is further supported by *i*) the standardisation of acquisition settings (scan depth and focal setting at follow-up kept consistent with baseline) and *ii*) the absence of significant BMD changes in untreated controls over the same timeframe.

In fact, in contrast to RMZ-treated patients, untreated controls showed slight, non-significant BMD decreases at both TH and FN, which are consistent with literature-available information that the average rate of physiological change in femoral neck BMD in women is ~ 1% (such variation does not depend significantly on age) [34]. Therefore, these results reinforce the effectiveness of REMS technology to reliably capture RMZ-induced changes in BMD.

Interestingly, when focusing on treatment-naïve patients, the detected BMD gain was larger than in the overall population at both TH (4.7% *vs.* 3.7%) and FN (4.6% *vs.* 4.1%). This finding agrees with currently available evidence based on DXA acquisitions and further suggests the hypothesis that RMZ exerts a more rapid anabolic effect in untreated bone, through acceleration of the osteoblast activity and the

formation of novel mineral deposition [31, 35–37]. Moreover, as reported in a study investigating the relationship between FRAX and risk of first incident fracture [38], RMZ appears to provide greater clinical benefits in terms of reduced incidence of all fractures in patients with higher baseline risk, like those with a history of previous fracture(s). In line with these observations, our REMS-based study showed that RMZ therapy was associated with greater BMD gains in patients with 2 or more previous fractures (4.1% vs. 3.7% at TH, 4.8% vs. 4.1% at FN): a possible explanation for this enhanced response is that individuals with multiple prior fractures often present a more active remodelling, being therefore more responsive to anabolic stimuli [39, 40]. RMZ, through sclerostin inhibition, preferentially stimulates osteoblast activity, potentially exerting a disproportionately larger effect [41]. Therefore, in patients with multiple prior fractures, this mechanism may translate into a more rapid and measurable improvement in bone turnover and mineral deposition, which can be captured by REMS technology.

This study has also some limitations. First, its retrospective single-centre design. Second, the follow-up was limited to 6 months, capturing only the early phase of treatment effects. Moreover, REMS measurements were not paired with contemporaneous DXA for direct cross-technology comparisons. Finally, our analysis focused exclusively on BMD changes, whereas literature available evidence indicates that RMZ can also induce effects on bone quality [15, 42, 43]. In this context, further studies will incorporate REMS-derived indices of bone quality (e.g., Fragility Score) to capture skeletal changes beyond BMD alone.

Conclusion

RMZ is an innovative therapeutic option that produces a robust and unique BMD increase. This retrospective observational study assessed for the first time the effectiveness of the REMS technology to monitor the short-term effects of RMZ in a cohort of postmenopausal women, observing BMD gains of + 3.7% (TH) and + 4.1% (FN), which became larger in treatment-naïve patients (+ 4.7% and + 4.6% at TH and FN, respectively) and patients with 2 or more previous fractures (4.1% and 4.8% at TH and FN, respectively), confirming the literature-available DXA-based results. Overall, our findings support the role of REMS technology as a valuable tool for assessing the real-world short-term clinical effectiveness of RMZ in populations exhibiting a high fracture risk profile. The possibility of performing frequent radiation-free assessments may facilitate closer follow-up in clinical practice and enable a more timely evaluation of treatment response. In addition, because anthropometric parameters did not change significantly over the considered 6 months, the reported REMS BMD variations are not confounded by anthropometric changes and are consistent with actual short-term skeletal effects of therapy.

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.

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Author Contribution

Conceptualization: A.S.; Methodology: A.S., N.N.; Formal analysis and investigation: A.S., A.C., A.C., R.F., E.D.T., M.P., C.S., F.D., N.N.; Writing – original draft preparation: A.S.; Writing – review and editing: A.S., A.C., A.C., R.F., E.D.T., M.P., C.S., F.D., N.N.; Supervision: N.N..

Data Availability

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

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Figures

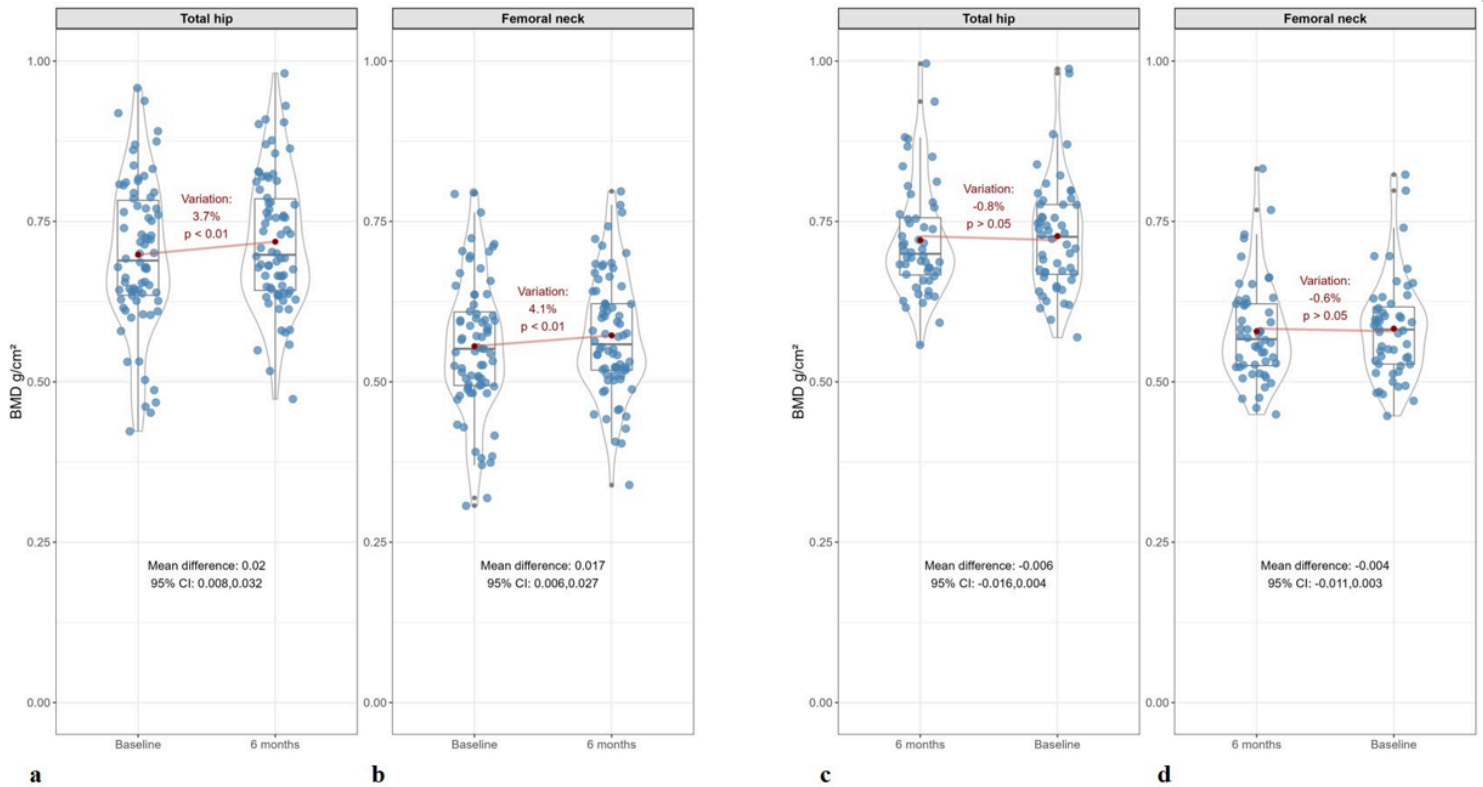


Figure 1

Changes in BMD at the total hip (TH) and femoral neck (FN) in Romosozumab-treated and negative control patients. Distribution of BMD (g/cm²) values at baseline and after 6-month follow-up at TH (a) and FN (b) in Romosozumab-treated patients and distribution of BMD (g/cm²) values at baseline and after 6-month follow-up at TH (c) and FN (d) in negative control patients. Violin plots illustrate data density, with embedded boxplots showing the median and interquartile range. Individual blue dots represent participant-level values, while red dots indicate the overall mean for each time point. Percentage changes of BMD at 6-month follow-up with respect to baseline are shown in red in each panel. Mean differences and corresponding 95% confidence intervals (CI) are also reported in each panel.

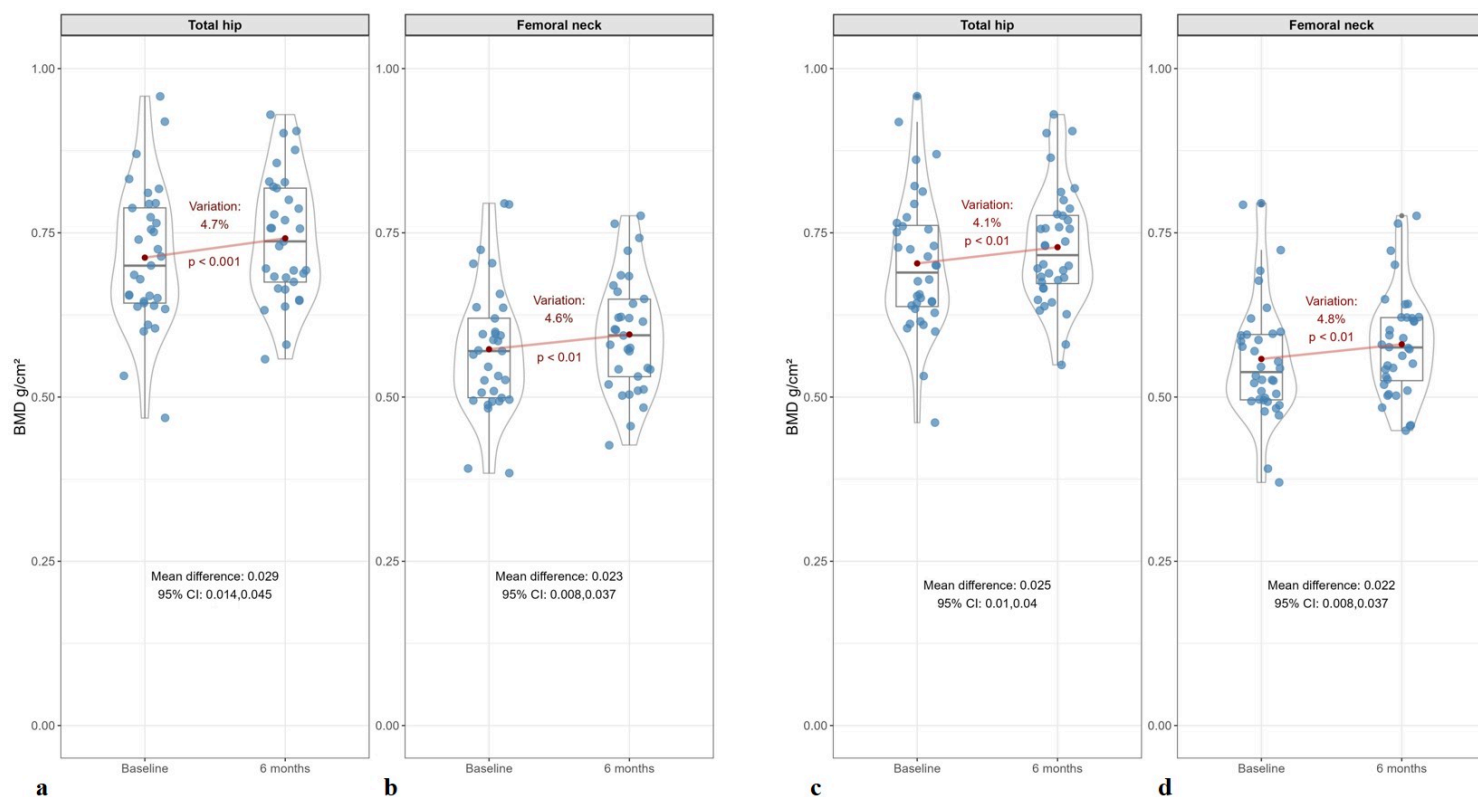


Figure 2

Changes in BMD at the total hip (TH) and femoral neck (FN) after 6 months of Romosozumab therapy in treatment-naïve patients and in patients with 2 or more prior fractures. Distribution of BMD (g/cm²) at baseline and after 6-month follow-up at TH (**a**) and FN (**b**) in treatment-naïve patients and distribution of BMD (g/cm²) at baseline and after 6-month follow-up at TH (**c**) and FN (**d**) in patients with 2 or more prior fractures. Violin plots illustrate data density, with embedded boxplots showing the median and interquartile range. Individual blue dots represent participant-level values, while red dots indicate the overall mean for each time point. Percentage changes of BMD at 6-month follow-up with respect to baseline are shown in red in each panel. Mean differences and 95% confidence intervals (CI) are also reported in each panel.