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RESEARCH ARTICLE

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The potential effect of romosozumab on perioperative management for instrumentation surgery

Koji Ishikawa[1,2] | Soji Tani[1] | Tomoaki Toyone[1] | Koki Tsuchiya[1] | Tomoko Towatari[1] | Yusuke Oshita[3,4] | Ryo Yamamura[1] | Kazuki Wada[1,4] | Takashi Nagai[1,5] | Toshiyuki Shirahata[6] | Katsunori Inagaki[1] | Kudo Yoshifumi[1]

[1]Department of Orthopaedic Surgery, School of Medicine, Showa University, Tokyo, Japan

[2]Department of Orthopaedic Surgery, Duke University, Durham, North Carolina, USA

[3]Department of Orthopaedic Surgery, Showa University Northern Yokohama Hospital, Yokohama, Kanagawa, Japan

[4]Department of Orthopaedic Surgery, Yamanashi Red Cross Hospital, Fujikawaguchiko, Yamanashi, Japan

[5]Department of Rehabilitation Medicine, School of Medicine, Showa University, Tokyo, Japan

[6]Department of Orthopaedic Surgery, Showa University Koto Toyosu Hospital, Tokyo, Japan

Correspondence
Koji Ishikawa, Department of Orthopaedic Surgery, School of Medicine, Showa University, Building No. 6, Room 517, 1-5-8 Hatanodai, Shinagawa, Tokyo 142-8666, Japan.
Email: koji.ishikawa@med.showa-u.ac.jp

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Abstract

Background: Age-related changes in bone health increase the risk for complications in elderly patients undergoing orthopedic surgery. Osteoporosis is a key therapeutic target that needs to be addressed to ensure successful instrumentation surgery. The effectiveness of pharmacological interventions in orthopedic surgery, particularly the new drug romosozumab, is still unknown. We aim to evaluate the effect of 3-month romosozumab treatment on biomechanical parameters related to spinal instrumentation surgery, using the Quantitative Computed Tomography (QCT)-based Finite Element Method (FEM).

Methods: This open-labeled, prospective study included 81 patients aged 60 to 90 years, who met the osteoporosis criteria and were scheduled for either romosozumab or eldecalcitol treatment. Patients were assessed using blood samples, dual-energy absorptiometry (DXA), and QCT. Biomechanical parameters were evaluated using FEM at baseline and 3 months post-treatment. The primary endpoints were biomechanical parameters at 3 months, while secondary endpoints included changes in regional volumetric bone mineral density around the pedicle (P-vBMD) and vertebral body (V-vBMD).

Results: Romosozumab treatment led to significant gains in P-vBMD, and V-vBMD compared to eldecalcitol at 3 months. Notably, the romosozumab group showed greater improvements in all biomechanical parameters estimated by FEM at 3 months compared to the eldecalcitol group.

Conclusion: Romosozumab significantly increased the regional vBMD as well as biomechanical parameters, potentially offering clinical benefits in reducing postoperative complications in patients with osteoporosis undergoing orthopedic instrumentation surgery. This study highlights the novel advantages of romosozumab treatment and advocates further research on its effectiveness in perioperative management.

KEYWORDS
aging, biomechanics, imaging, osteoporosis

1 | INTRODUCTION

Recent medical advancements have significantly increased life expectancy, leading to a rise in the number of aged patients undergoing surgeries.[1–3] The significant shift in the aging population highlights osteoporosis as an enormous problem in orthopedic surgery due to its impact on postoperative complications.[4–6]

Osteoporosis, a global health concern, is not only an essential therapeutic target for extending healthspan, but also lifespan.[7–9] Recent research has further investigated the links of osteoporosis with orthopedic surgery, aiming to optimize operative outcomes.[10–13] Specifically, if instrumentation spinal surgery is indicated, adequate risk stratification, including bone health, is advocated to ensure optimal and safe outcomes, since bone fragility exacerbates postoperative complications such as loosening, junctional failure, and cage subsidence, potentially resulting in revision surgery. Indeed, previous studies have reported that 25%–60% of patients with osteoporosis experienced postoperative complications, even following successful instrumentation surgery.[14–16]

While dual-energy absorptiometry (DXA) is a reliable method for assessing bone health, recent findings indicate that regional volumetric bone mineral density (vBMD) around an implant, as measured by QCT, demonstrates stronger correlations with both intraoperative screw fixation and postoperative complications, including screw loosening and cage subsidence, compared to areal bone mineral density (aBMD) assessed by DXA.[6,17,18] Furthermore, Keaveney et al. demonstrated the superiority of CT-based biomechanical analysis over BMD testing alone in terms of predicting reoperation following spinal instrumentation surgery.[5] Thus, a multidisciplinary approach including bone health assessment of the regional BMD in the vertebra as well as biomechanical analysis is recommended prior to surgery to an ensure optimal and safe outcome.

Pharmacologic therapy could play an important role in perioperative bone management for facilitating bone health, but its effectiveness for orthopedic implant surgery has not been systematically investigated.[12,19] The potential advantages of osteoporosis treatments, such as teriparatide and bisphosphonates, for instrumentation surgery have been previously reported, particularly in addressing issues like screw loosening and adjacent vertebral fractures.[17,19–22] Although the contribution of BMD to cage subsidence is described, to the best of our knowledge, there is no study examining the effects of osteoporosis treatment for cage subsidence.[18] A significant challenge in clinical biomechanical implant analysis, particularly during pharmacological interventions, is the inability to conduct damage or destruction analysis. This type of analysis is commonly applied in conventional biomechanical research through animal or cadaver studies. Our recent in silico biomechanical analysis using Finite Element Method (FEM) challenges these limitations, and showed that a 12-month course of denosumab treatment (an anti-RANKL antibody) is potentially beneficial for reducing postoperative screw loosening following spinal instrumentation surgery.[17] This study lays the groundwork for understanding the impact of osteoporosis treatment on optimizing outcomes in instrumentation surgery. However, considering the onset of postoperative complications within the initial few months after surgery, there is a pressing need for treatments that show benefits quickly following administration.[16]

Romosozumab may offer a solution to this issue, given that previous reports have shown its potential to increase BMD shortly after treatment administration in terms of both imaging and bone biopsy assessment.[23–25] Thus, we aim to evaluate the effects of a 3-month romosozumab treatment on spinal instrumentation surgery using QCT-based FEM. In this study, all patients receiving romosozumab were given prophylactic drugs (active vitamin D and/or calcium) to prevent hypocalcemia, as reported in clinical trial.[26] Consequently, the potential effects of eldecalcitol on bone quality were evaluated in the control group (eldecalcitol alone). We have extended our earlier FEM methods to cover analysis for the risk of cage subsidence, a major complication that occur in 5%–50% of cases following surgery and is linked with negative clinical outcomes.[18] Here, we first demonstrated the potential secondary benefits of short-term romosozumab treatment in improving bone health and reducing postoperative complications in patients with osteoporosis undergoing spinal instrumentation surgery.

2 | METHODS

2.1 | Study subjects

This was an open-labeled prospective study of ambulatory patients 60 to 90 years of age who met the osteoporosis criteria.[27] Between March 2019 and March 2021, 226 patients who met the criteria for

severe osteoporosis and were scheduled for Romosozumab (Romo) or Eldecalcitol (ELD) treatment were assessed for inclusion. A total of 81 patients participated in the present study. The exclusion criteria included patients with illnesses affecting bone and calcium metabolism or bone disorders other than osteoporosis, any malignant conditions, fresh fracture, severe renal dysfunction, or a history of cardiovascular events. To prevent the artifacts caused by implants in imaging analysis, we also excluded patients who had experienced or were scheduled for spinal surgery. The patients were divided into two groups based on their treatment (Romo: 69 patients, ELD: 12 patients). Patients with romosozumab received daily eldecalcitol (0.75 μg) and/or calcium (400–800 mg) to avoid hypocalcemia, except for four patients. These four exceptions were decided by physicians based on their baseline serum calcium levels to prevent hypercalcemia. The medication compliance related to eldecalcitol and calcium was assessed at each visit and it was confirmed that all patients consumed >90% of the drugs over the course of the study. The study was approved by the Institutional Review Board of Yamanashi Red Cross Hospital and was conducted in accordance with the precepts of the Declaration of Helsinki. All patients provided informed consent before participation.

2.2 | Assessments

We measured the spine-areal BMD (spine-aBMD) using DXA (L1-4) (Hologic QDR series: Hologic, Waltham, MA) at baseline and 6 months. All DXA measurements were analyzed by a radiologist at a central site. The regional vBMD around the pedicle (P-vBMD) and vertebral body (V-vBMD) as well as biomechanical parameters were measured by QCT-based FEM at baseline and 3 months. The intra- and inter-observer coefficients of variation of BMD assessments have been previously described.[6,17,28] Blood samples, including serum levels of TRACP-5b and total-P1NP, were assessed at baseline and then at 3 and 6 months following treatment. The primary endpoints were the biomechanical parameters at 3 months. Secondary endpoints included the changes in regional vBMD and bone turnover markers throughout the study.

2.3 | Three-dimensional vBMD

The details of the measurement of vBMD have been described in previous studies.[6,17,29,30] CT data were acquired with Revolution EVO ES (GE healthcare) using predefined scanning conditions (x-ray energy, 120 kV; x-ray current, SD20; rotation speed, 0.8 s/rot; beam pitch, 0.984; slice thickness, 2.5 mm; reconstruction intervals, 2.5 mm). For QCT scanning, a phantom (Mindways, Austin, TX, USA) was placed underneath the patients for BMD calibration, thereby ensuring measurement quality throughout the study. The vBMD at the vertebral body and pedicle (reference vertebra L4) was measured using 3D finite element model created by MECHANICAL FINDER (Research Center of Computational Mechanics; version 10.0, Tokyo, Japan) (Figure 1; Figure S1). For the FEM vertebral, the 2 mm mesh size was selected based on the mesh size assessment (Figure S2). We selected the L vertebra if the vertebra had a grade 2 or 3 fracture by using a semiquantitative method.[31]

2.4 | Finite Element Methods

Biomechanical parameters related to spinal instrumentation including compression strength (CS), pullout strength of the screw (POS), and cage subsidence strength (CSS) were evaluated by QCT-based FEM using MECHANICAL FINDER. The FEM modeling methods were based on previous studies and are shown in Figure 1, Table S1, and Movies S1–S4.[17,32] Briefly, finite element models of the L4 vertebrae were constructed from the CT data and examined for the CS (Movie S2). Then, a pedicle screw and cage were placed as in spinal fusion surgery to evaluate POS and CSS, with zero friction at the

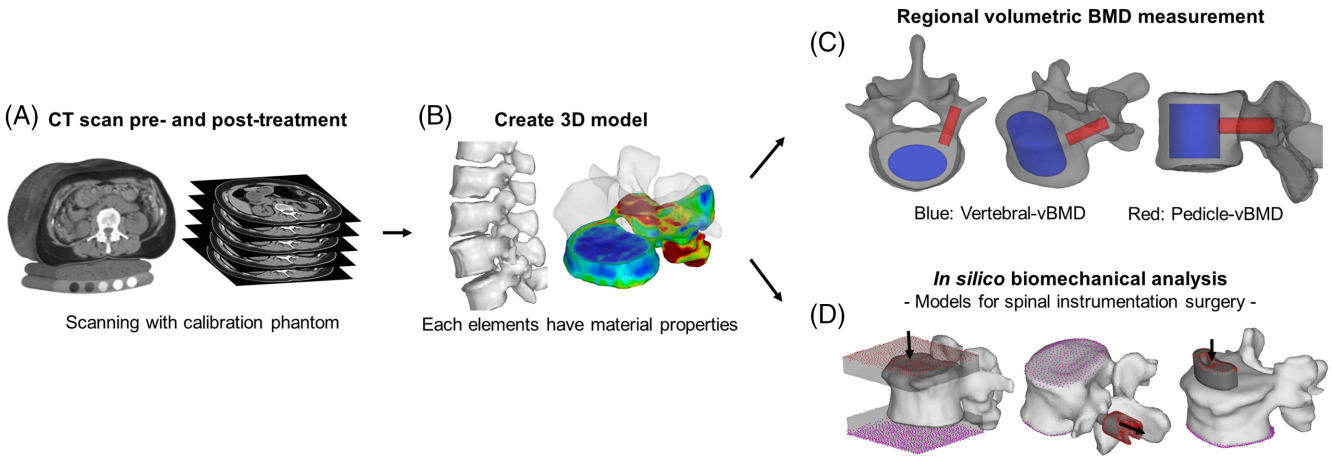

FIGURE 1 Overview of in silico drug assessment for instrumentation surgery. The proposed framework for drug assessment in instrumentation surgery. (A) CT scans, pre- and post-treatment, with a calibration phantom for quality longitudinal measurements. (B) Creation of the 3D (dimensional) vertebral models from the CT data. (C) Regional 3D v-BMD measurements provide accurate BMD assessment. (D) Biomechanical evaluations of surgical-related parameters using the finite element method.

vertebrae-implant interfaces (Movies S3 and S4).[17] In the CSS model, a banana-shaped PEEK (polyetheretherketone) cage, which was created using Metasequoia 4 (tetraface Inc., Tokyo, Japan), was set 4-mm behind the anterior edge of the upper endplate vertebrae according to the spinal fusion surgery so as to assess the risk of cage subsidence. A compressive displacement was applied to the cage at the cranial end of the vertebrae at ramped displacement increments of 0.02 mm/step. The predicted CCS was identified by a rapid decrease in the force-displacement curve or a rapid increase in the failure elements. The detailed finite element models and materials properties are provided in Table S1.

2.5 | Statistical analysis

Fisher's exact test and the Mann–Whitney *U* test were used to compare differences between the two groups. Dunn's test was used for multiple comparisons. The correlations between each parameter were determined using Spearman's rank coefficients. Statistical analyses were performed using Stat Flex Ver. 6 (Artech, Tokyo). All statistical tests were two tailed and results with *p*-values<0.05 were considered statistically significant.

3 | RESULTS

3.1 | Patients and baseline demographics

Sixty-six patients in the Romo-group (66/69 patients, 95.7%) and 10 patients in the ELD-group (10/12 patients, 83.3%) completed the 6 months study follow-up (Romo: 66/69 [95.7%], ELD: 10/12 [83.3%], p = ns) (Figure S3). The reasons for the discontinued study were as follows; loss of motivation (one patient in Romo, two patients in ELD), hospital administration related to vascular event (one patient in Romo), death unrelated to treatment (one patient in Romo). Table 1 shows the demographics and baseline characteristics of the groups. Serum TRACP-5b and P1NP were higher in the ELD group, presumably due to a difference in the prior treatment history, but the difference was not significant. BMD measured by DXA and QCT was equivalent in the two groups.

3.2 | Safety

The patients observed to undergo adverse events were 21 (30.4%) in the Romo and no patients in the ELD (Figure S4). Injection-site reactions such as redness, tenderness and swelling were reported by 16 patients (23.2%) in Romo group. These reactions were well recognized at the initial injection (50.0%). Among the patients who had injection-site reactions, five patients (7.3%) experienced these reactions multiple times during the study (Figure S5). One (1.5%) patient had hypocalcemia and one (1.5%) patient had hypercalcemia in the Romo group, both of which were of mild severity and asymptomatic. Gastroenteritis was observed in one (1.5%) patient. Two (2.9%) patients in the Romo group had severe adverse events including one stroke and one death leading to treatment discontinuation.

3.3 | Changes in bone turnover markers showed dual effects of romosozumab

The changes in the total P1NP and TRACP-5b levels are shown in Figure S6. In the Romo group, the P1NP level reached its highest value at 3 months ($p < 0.001$, vs. Baseline), followed by a gradual decrease at 6 months. Percentage changes from baseline of total P1NP was higher in the Romo group compared to the ELD group at 3 and 6 months (all $p < 0.001$). The P1NP level decreased significantly over the course of the study in the ELD group (3 months; $p < 0.01$, 6 months; $p < 0.01$, vs. baseline). The TRACP-5b levels decreased significantly in both groups at 3 and 6 months, and there was no significant difference between groups.

3.4 | Greater increases in regional BMD in Romo group

The median percentage changes from baseline in aBMD by DXA at 6 months was 6.61% (Q1/Q3: 2.62/12.7) in the Romo group and 0.91% (0.25/2.06) in the ELD group ($p < 0.001$) (Figure S7A). The 3D-modeling of the vertebrae demonstrates the heterogeneity of the vertebral BMD that is undetectable by DXA measurement (Figure 2A). The difference between the groups observed at 6 months was already identifiable in the regional BMD measurement at 3 months (Figure 2B–E). The Romo group exhibited significantly greater increases in regional BMD including the vertebral body and pedicle at 3 months compared to the ELD group (V-vBMD; Romo vs. ELD: 10.43% [4.39/16.77] vs. 1.54% [−4.45/2.48], $p < 0.001$ and P-vBMD; 12.75% [4.94/18.08] vs. 2.22% [−0.35/5.13], $p < 0.001$) (Figure 2F). Remarkably, treatment with romosozumab resulted in noticeable BMD increases not only within the inner pedicle region (corresponding to ROI of the P-vBMD) but also on the cortical surface of the inner pedicle (Figure 2B,D,E). Similarly, the BMD around the endplate, the corresponding area for cage placement in spinal fusion surgery, increased following romosozumab treatment (Figure 2D,E). In treatment-naïve patients, while the results were consistent, the group differences were more evident (aBMD: 9.05% [5.13/14.4] vs. 0.95% [0.57/2.56], $p < 0.001$, V-vBMD: 12.84% [5.75/20.88] vs. 1.33% [−5.37/2.11], $p < 0.0001$, and P-vBMD: 12.75% [4.94/17.49] vs. 1.22% [−0.44/5.30], $p < 0.001$) (Figure 2G; Figure S7B).

3.5 | Significant improvement in biomechanical parameters in the Romo group

Greater gains in the percentage changes from baseline were observed in the Romo group than in the ELD group in all of the biomechanical parameters (CS: 11.49% [2.04/22.55] vs. 0.74% [−2.85/6.89], pullout strength: 20.00% [9.09/33.33] vs. 0.00% [0.0/10.00], CSS: 11.19%

TABLE 1 Baseline patient characteristics.

Parameters	All	Romo	ELD
Age (years)	76.0 (70.0/81.3)	77.0 (70.0/82.3)	70.0 (75.0/66.5)
Male (%)	5 (6.9)	4 (5.8)	1 (8.3)
BMI	21.5 (19.6/23.4)	21.3 (19.5/23.1)	23.2 (21.5/24.6)
Fracture history (%)	51 (63.0)	46 (56.8)	5 (41.7)
Smoking (%)	5 (6.2)	3 (4.3)	2 (16.7)
Alcohol (%)	4 (4.9)	3 (4.3)	1 (8.3)
Prior treatment			
None	45 (55.6)	34 (49.3)	11 (91.7)
Bisphosphonate	11 (13.6)	11 (15.9)	0 (0)
SERM	3 (3.7)	3 (4.3)	0 (0)
Denosumab	10 (12.3)	10 (14.5)	0 (0)
Teriparatide	12 (14.8)	11 (15.9)	1 (8.3)
Blood samples			
Albumin levels (g/dL)	4.3 (4.1/4.5)	4.3 (4.1/4.5)	4.4 (4.2/4.6)
Corrected calcium levels (mg/dL)	9.4 (9.1/9.5)	9.4 (9.2/9.5)	9.2 (9.0/9.5)
Phosphorus levels (mg/dL)	3.6 (3.2/4.1)	3.6 (3.2/4.1)	3.6 (3.5/4.0)
eGFR (mL/min/1.73 m^2)	66.0 (55.0/74.0)	66.0 (54.8/74.0)	68.5 (61.5/75.0)
Bone metabolic markers			
Total-P1NP (μg/mL)	58.6 (31.3/86.2)	55.0 (29.2/81.0)	74.1 (58.6/115.4)
TRACP-5b (mU/dL)	453.0 (287.3/571.3)	428.0 (268.8/560.5)	536.5 (453.0/689.0)
Bone mineral density			
Spine—aBMD (g/cm^2)	0.75 (0.67/0.83)	0.75 (0.66/0.83)	0.77 (0.73/0.85)
Vertebral—vBMD (mg/cm^3)	77.5 (59.5/91.7)	76.8 (57.5/91.0)	79.3 (76.2/95.7)
Pedicle—vBMD (mg/cm^3)	126.1 (93.1/145.0)	122.4 (92.3/143.1)	138.0 (109.4/154.8)

Note: There were no statistical differences between groups for any of the parameters. The data shown are the median (interquartile ranges [IQR]; Q1/Q3) or *n* (%). The data shown as *n* or *n* (%) were analyzed by Fisher's exact test. The data presented as median IQR were analyzed by Mann–Whitney *U* test.
Abbreviations: aBMD, areal bone mineral density; BMI, bone mass index; eGFR, estimated glomerular filtration rate; SERM, selective estrogen receptor modulator; total-P1PN, total N-terminal propeptide of type 1 procollagen; TRACP-5P, tartrate-resistant acid phosphatase type 5 protein; vBMD, volumetric bone mineral density.

[3.08/25.31] vs. −0.55% [−6.36/4.30], $p < 0.01$, $p < 0.001$, $p < 0.001$, respectively) (Figure 3D). These results were bolstered by the distribution of yield risk and crushed element, which further illustrates the significant improvement following romosozumab treatment (Figure 3A–C). The findings are consistent when compared with treatment-naïve patients (CS: 13.60% [1.81/24.1] vs. 2.50% [−3.74/7.21], pullout strength: 20.00% [0.00/33.33] vs. 0.0% [0.0/8.89], CSS: 18.27% [3.26/28.11] vs. −1.97% [−6.61/4.38], $p < 0.01$, $p < 0.01$, $p < 0.001$, respectively) (Figure 3D). Collectively, these findings suggest a potential contribution of 3 months of romosozumab treatment to the reduction of postoperative complications in instrumentation surgery.

3.6 | Regional vBMD had the most significant correlations with biomechanical parameters

Local areal contribution around the implant, as displayed in each biomechanical analysis in Figure 3, led us to examine the correlation between biomechanical parameters with various BMD assessments. The correlations between the BMD and biomechanical parameters are summarized in Table 2. While the aBMD demonstrated mild or no correlations with the biomechanical parameters, the strongest correlations were observed with the regional vBMD across all parameters in both groups.

4 | DISCUSSION

Despite the longstanding recognition through intensive research of osteoporosis as a risk factor for postoperative complications in orthopedic instrumentation surgery, these complications persist as a primary concern and critical priority for surgeons. This challenge is becoming more prominent with the worldwide increase in the aged population.[33,34]

One significant limitation of biomechanical implant analysis for drug assessments in clinical practice is the inability to conduct damage or destruction analysis, a method traditionally applied in animal and cadaver research.[35,36] This issue, therefore, presents a difficulty for surgeons when they are trying to determine the effectiveness of

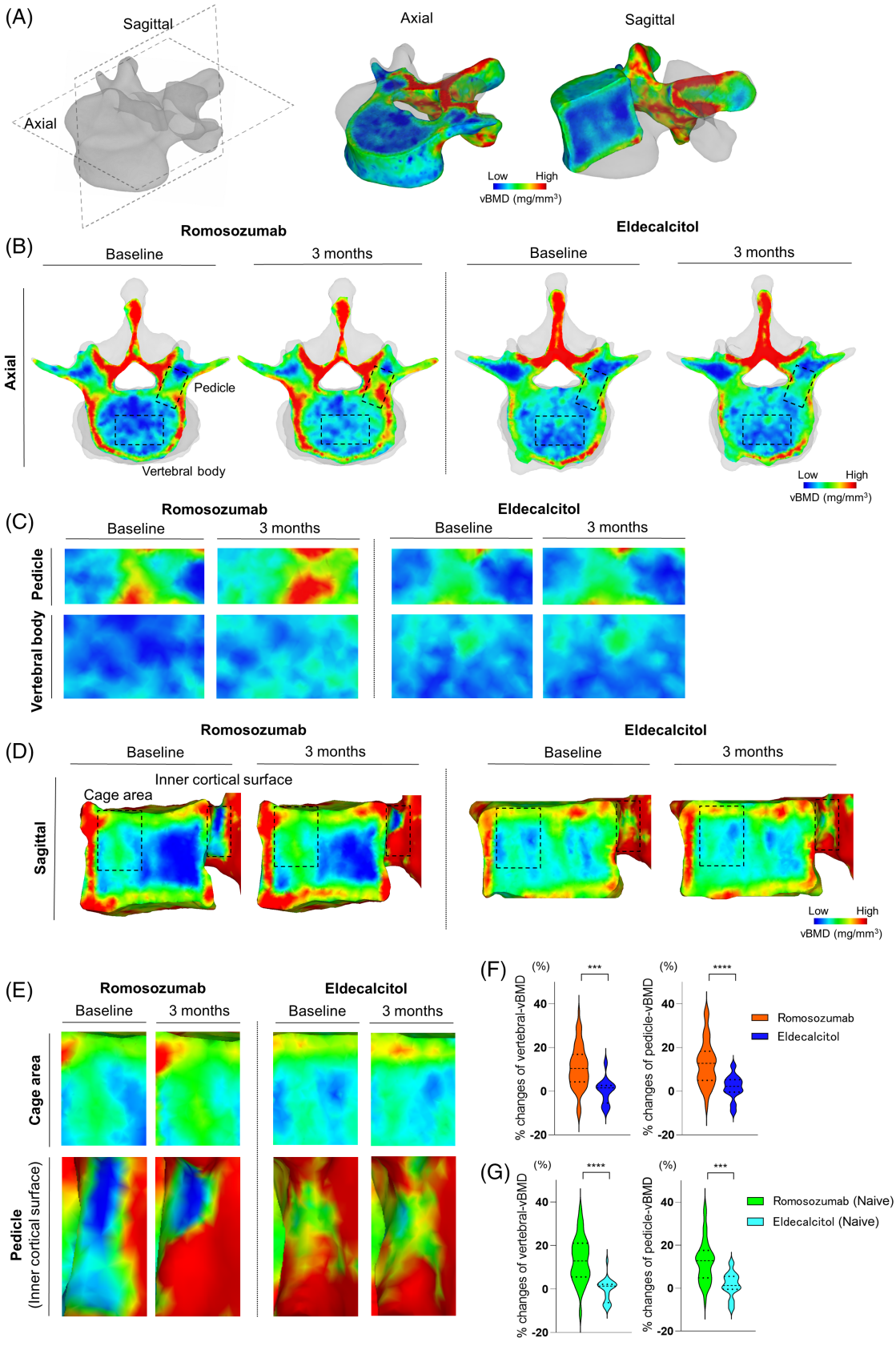

FIGURE 2 Legend on next page.

osteoporosis treatments in mitigating postoperative complications. Our in silico biomechanical analysis, utilizing patient QCT data collected during treatment, could offer novel insights into the field of osteoporosis treatment and implant research.

In this study, the effects of romosozumab, as previously described at 6 months, were already evident at 3 months, confirmed by regional vBMD in both the vertebral body and pedicle.[25,26,37] Remarkably, this change began soon after treatment administration, associated with

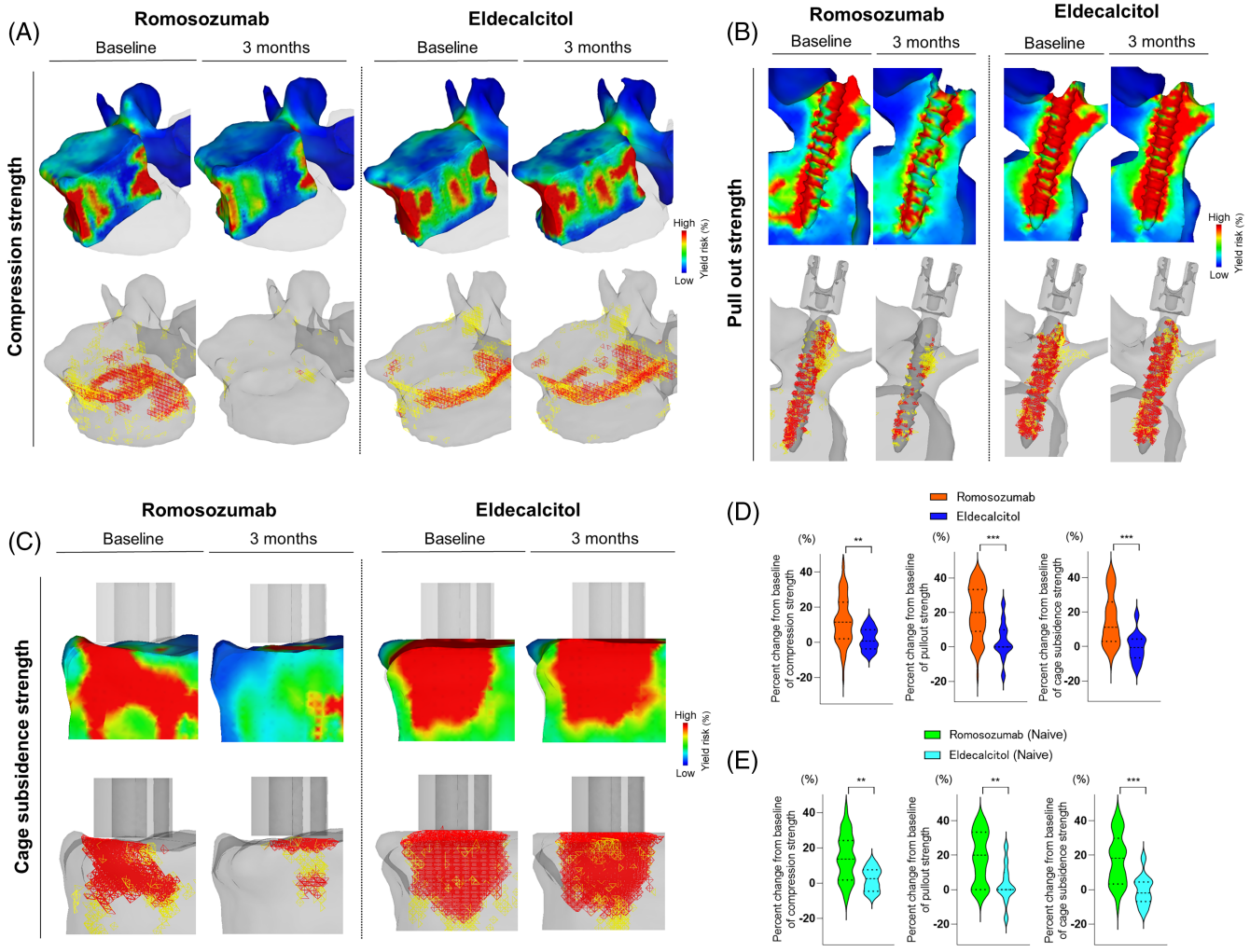

FIGURE 3 Romosozumab resulted in improvement in all the biomechanical analyses. (A) Representative images illustrating the CS analysis under a 3500 N load, following treatment. The upper images depict the distribution of yield risk (%), while the lower images show the distribution of elements associated with high-risk crushing (yield elements [yellow] and compressive failure elements [red]) both at baseline and 3 months. High yield risk and an increase in crushed elements suggest the potential risk of vertebral fracture. (B) Representative images showing the pullout strength analysis results when a 200 N force was applied to extract the screw. The upper images depict the distribution of yield risk (%), while the lower images show the distribution of elements associated with high-risk crushing. High yield risk and an increase in crushed elements suggest a potential risk of screw loosening. (C) Representative images illustrating the cage subsidence strength when a load of 400 N was applied. The upper images depict the distribution of yield risk (%), while the lower images show the distribution of elements associated with high-risk crushing. High yield risk and an increase in crushed elements suggest a potential risk of cage subsidence. (D, E) Percentage changes in biomechanical parameters between groups following 3 months of treatment. Data are expressed as medians (interquartile ranges). Differences between groups were analyzed using Mann–Whitney *U* test. $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$.

FIGURE 2 Romosozumab rapidly increases vBMD in the vertebral body and pedicle. (A) Image illustrating the 3D model of the vertebrae and dimensions in both the axial and sagittal views. Color map representing the distribution of bone mineral density (mg/mm^3). (B) Representative axial images of BMD distribution at baseline and 3 months. (C) Enlarged images of the axial view of the pedicle and vertebral body showing the improvement in BMD with romosozumab treatment in both the pedicle and vertebral body. (D) Representative sagittal images of BMD at baseline and 3 months. (E) Enlarged images of the sagittal view of the cage's corresponding area and inner cortical region of the pedicle, showing the BMD increase with romosozumab. (F, G) Percentage changes of vertebral-vBMD and pedicle-vBMD between groups following 3 months of treatment. Data are expressed as medians (interquartile ranges). Differences between groups were analyzed using Mann–Whitney *U* test. $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$; $^{****}p < 0.0001$. vBMD, volumetric bone mineral density.

TABLE 2 The regional vBMD is well correlated with the biomechanical parameters.

		Vertebral strength		Pullout strength		Cage subsidence strength	
	Baseline	***r***	***p***	***r***	***p***	***r***	***p***
All	Spine-aBMD (g/cm²)	0.2640	0.0180	0.2926	0.0080	0.1103	n.s
	Vertebral-vBMD (mg/cm^3)	0.6387	<0.0001	0.5096	<0.0001	0.6108	<0.0001
	Pedicle-vBMD (mg/cm^3)	0.5253	<0.0001	0.6706	<0.001	0.3463	0.0017
Romo	Spine-aBMD (g/cm²)	0.2959	0.0143	0.3409	0.0042	0.1145	n.s
	Vertebral-vBMD (mg/cm^3)	0.6706	<0.0001	0.4814	<0.0001	0.5635	< 0.0001
	Pedicle-vBMD (mg/cm^3)	0.5342	<0.0001	0.6253	<0.0001	0.2814	0.0201
ELD	Spine-aBMD (g/cm²)	0.1191	n.s	−0.0424	n.s	0.1189	n.s
	Vertebral-vBMD (mg/cm^3)	0.4308	n.s	0.1414	n.s	0.8531	0.0004
	Pedicle-vBMD (mg/cm^3)	0.4308	n.s	0.9188	<0.0001	0.6573	0.0202
		Vertebral strength		**Pullout strength**		**Cage subsidence strength**	
	Baseline	***r***	***p***	***r***	***p***	***r***	***p***
All	Vertebral-vBMD (mg/cm^3)	0.7106	<0.0001	0.5470	<0.0001	0.6294	<0.0001
	Pedicle-vBMD (mg/cm^3)	0.5805	<0.0001	0.6946	<0.0001	0.3896	0.0004
Romo	Vertebral-vBMD (mg/cm^3)	0.7474	<0.0001	0.5324	<0.0001	0.6177	< 0.0001
	Pedicle-vBMD (mg/cm^3)	0.5854	<0.0001	0.6658	<0.0001	0.3421	0.0043
ELD	Vertebral-vBMD (mg/cm^3)	0.8392	0.0006	0.7874	0.0024	0.8392	0.0006
	Pedicle-vBMD (mg/cm^3)	0.4755	n.s	0.8647	0.0003	0.7413	0.0006

Note: Correlations of the biomechanical parameters and BMD measured by DXA (aBMD) and QCT (vBMD). The biomechanical parameters exhibited significant correlations with each BMD measurement and showed a stronger correlation with the regional vBMD measured by QCT.
Abbreviations: aBMD, areal bone mineral density; vBMD, volumetric bone mineral density.

improvements in FEM-estimated biomechanical parameters such as vertebral CS, screw pullout strength, and CSS. It is noteworthy that these parameters are closely linked with common postoperative complications, suggesting the potential benefits of romosozumab for perioperative management. The enhancement in both BMD and FEM-estimated parameters is likely attributed to the dual mechanisms of romosozumab, namely, the enhancement of bone formation and reduction of bone resorption, as demonstrated by the evaluation of bone turnover markers.[38–40]

Several strategies have been proposed for managing osteoporosis in patients undergoing spinal surgery, with a broad consensus emphasizing the need for preoperative bone health assessment.[11–13] If poor bone health condition is detected, initiation of pharmacological treatment is recommended. Moreover, considering the risk of postoperative complications in patients with osteoporosis, Lubelski and colleagues suggest postponing surgery in order to strengthen the bone prior to the procedure.[12] In the light of potential risk reduction post-surgery shortly after the treatment administration in this study, romosozumab may emerge as a valuable preoperative therapeutic option. This is particularly significant, given that the effectiveness of most osteoporosis therapies is typically not recognized until 1 or 2 years after treatment.

Limitations in DXA's capacity to predict future fractures and post-surgical complications, arising from factors like BMD heterogeneity in the vertebra, osteophyte formation, articular facet hypertrophy, and aortic calcification, are further supported in the present study.[5,6,41]

We found that all of the biomechanical parameters exhibit their strongest correlations with vBMD around the implant. This implies a significant contribution of region-specific vBMD in postoperative complications. As potential DXA limitations like overestimation of BMD is prevalent in patients with a spinal disorder, evaluation of regional vBMD might yield more clinical utility in assessing the risk of surgery.

Previous studies on the effects of romosozumab showed increases in both cortical BMD and cortical thickness.[23,42] Genant et al. reported that most significant changes in the cortical area predominantly occur in the endocortical region.[43] Furthermore, histomorphometry analysis of bone biopsies from a clinical trial showed that the anabolic effect in the initial 2 months of romosozumab treatment mainly arises on the endocortical surface, leading to a 18.3% increase in the mineralizing surface compared to a 4.1% increase in the trabecular bone.[24,44] Even though we did not scrutinize parameters related to the cortical and endocortical area due to their ambiguous definition and the limited resolution of imaging studies, we did find that the vBMD in the pedicle responded more favorably to treatment than in the vertebral area. These insights could potentially support previously mentioned studies, given that the region of interest for P-vBMD presumably includes the endocortical area, whereas V-vBMD mainly comprises trabecular bone.

Consistent with a previous report, romosozumab was generally well tolerated, with no new safety findings observed.[25] The most frequently observed adverse events were injection site reactions, which some patients experienced multiple times. While two severe events were noted, the frequency of these events was similar to previous studies.[25,26] Although safety concerns, including cardiovascular risk, were raised by romosozumab when compared with alendronate, this risk was not observed in a placebo-controlled trial.[25,40,45] In addition, recent studies have shown that romosozumab is not associated with an increased rate of adverse events, regardless of levels of kidney function.[46] Nevertheless, careful assessment, including the risk of a cardiovascular event, is desired prior to romosozumab initiation. Moreover, the safety profiles of osteoporosis treatment need to be assessed in the perioperative setting.

This study has several limitations. First, this is a non-randomized, open-label design, which was necessitated by the differential effectiveness of each drug in preventing fractures, particularly among patients with relatively severe osteoporosis. Therefore, we initially recommended romosozumab over eldecalcitol for all patients. Consequently, patient choice followed expert consultation, leading to a disparity in the number of patients in each group. The small sample size of the ELD group may explain the lack of treatment effectiveness and the weak correlation between BMD and partial biomechanical analysis. However, romosozumab treatment demonstrated an improvement in biomechanical parameters compared to baseline, irrespective of the comparison with the eldecalcitol group. Another limitation was the small samples size, affecting our power to detect differences between groups. However, the romosozumab groups exhibited significant improvement in primary outcomes, and the sample size was relatively large compared to previous implant-related FEM studies.[17,32] In addition, although FEM have been validated in earlier study, our FEM model could not fully mimic the clinical situation.[32] For instance, while we used vertical loading for the compression model, actual loading is affected by spinal alignment and various activities that can cause fractures. Finally, we were unable to evaluate bone fusion and reoperation rates, one of the endpoints of spinal instrumentation surgery. Nonetheless, both the rigid screw fixation and reduced cage subsidence were potentially facilitated by romosozumab, and thus could beneficially contribute to bone fusion. Further study is warranted to support this notion.

The strengths of this study include the use of a variety of complementary imaging modalities to evaluate the effect of romosozumab on instrumentations surgery, yielding consistent and complementary results. Throughout our novel biomechanical approach, we first established the impact of instrumentation surgery based on the region-specific BMD alternations observed following romosozumab treatment. Such assessments are often a challenge for traditional biomechanical methods, particularly when drugs are involved in the clinical setting. While the present findings highlight a unique benefit of romosozumab for patients with osteoporosis undergoing instrumentation surgery, it is imperative to standardize a multidisciplinary approach, including osteoporosis assessment and treatment, prior to implantation surgery in order to maximize the chance of securing long-term success.

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CONFLICT OF INTEREST STATEMENT

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ORCID

Koji Ishikawa https://orcid.org/0000-0003-3689-5662

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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