Original Article
Yonsei Med J 2026 Jun;67(6):492-501
https://doi.org/10.3349/ymj.2025.0325
Yonsei Medical Journal
YMJ
pISSN: 0513-5796 · eISSN: 1976-2437

# Bone Bridge Effect for the Treatment of Acute Osteoporotic Vertebral Compression Fractures: A Multistrategic Approach Using an Anabolic Agent

Ja-Yeong Yoon[1], Sung-Min Kim[2], Seong-Hwan Moon[3], Hak-Sun Kim[3], Kyung-Soo Suk[3], Si-Young Park[3], Ji-Won Kwon[3], and Byung Ho Lee[3]

[1]Department of Orthopaedic Surgery, Chungnam National University Sejong Hospital, Sejong;
[2]Department of Orthopaedic Surgery, Kyung-Hee University Hospital at Gangdong, Seoul;
[3]Department of Orthopaedic Surgery, Yonsei University College of Medicine, Seoul, Korea.

**Purpose:** To determine the bone bridge effect (BBE) and compare treatment outcomes of different osteoporosis medications in patients with lumbar osteoporotic vertebral compression fractures (OVCF).

**Materials and Methods:** This study followed 264 patients with lumbar OVCFs undergoing conservative treatment for more than 12 months. Patients were divided into four groups based on medication: denosumab monotherapy (group D), teriparatide and denosumab combination (group TDco), sequential romosozumab followed by denosumab (group RDse), and bisphosphonate monotherapy (group B). Changes in bone mineral density (BMD), radiological parameters including BBE, and visual analog scale (VAS) scores were compared from injury to 1 year post-injury.

**Results:** The 1-year BBE incidence was highest in groups treated with anabolic agents: group RDse (56.3%) and group TDco (51.8%). These rates were significantly higher than in group D (28.6%) and group B (21.1%). The annual BMD increase was significantly greater in group TDco (1.04) compared to the other groups (RDse: 0.63; D: 0.55; B: 0.35). VAS scores decreased significantly by the 3-month mark in anabolic agent groups and in patients with confirmed BBE, indicating rapid pain relief. Multivariate logistic regression analysis confirmed that anabolic agent groups (TDco and RDse) were significant independent predictors of BBE formation (odds ratio 2.717 and 3.472, respectively), even after adjusting for confounding variables such as initial BMD.

**Conclusion:** Anabolic agents appeared to be associated with more BBE formation, greater BMD gains, and faster pain reduction compared to anti-resorptive agents. Therefore, treatment strategies using anabolic agents, such as those in groups TDco and RDse, may be important considerations for treating patients with OVCFs.

**Key Words:** Osteoporosis, osteoporotic vertebral compression fractures, treatment strategy, anabolic agents, bone bridge effect

## INTRODUCTION

Osteoporotic fracture is a common complication of osteoporosis, occurring in one in two women and one in five men throughout their lifetime.[1] Among the types of osteoporotic fractures, osteoporotic vertebral compression fractures (OVCFs) have emerged as the most common type of fracture in patients with osteoporosis.[2] The presence of OVCFs doubles the risk of future fragility fractures and quadruples the risk of future vertebral fractures.[3] Therefore, aggressive treatment and prevention are crucial for OVCFs.

Most patients with OVCFs are treated conservatively; however, some patients in whom conservative treatment fails may be treated using surgery or other procedures.[3,4] In addition, appropriate osteoporosis drugs are essential for fracture healing and preventing further vertebral fractures. Recently, anabolic agents, such as teriparatide (TPTD) and romosozumab

**Received:** August 29, 2025 **Revised:** January 14, 2026
**Accepted:** January 27, 2026 **Published online:** April 21, 2026
**Corresponding author:** Byung Ho Lee, MD, PhD, Department of Orthopaedic Surgery, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea.
E-mail: bhlee96@yuhs.ac

•The authors have no potential conflicts of interest to disclose.

(RM), have become increasingly valuable for the prevention of fractures, along with anti-resorptive agents that have been widely used in the past. Moreover, according to the Endocrine Society Clinical Practice Guidelines, patients with osteoporosis at high to very high risk of fracture are recommended to receive anabolic agent treatment.[5]

In the follow-up of patients newly diagnosed with OVCFs, we observed the bone bridge effect (BBE) in patients treated with osteoporosis medications without surgery and other procedures. BBE involves the fusion of adjacent vertebrae via bone formation at the anterior margin of the fractured vertebrae. This retrospective study hypothesized that anabolic agents are more likely to cause BBE than anti-resorptive agents and compared BBE and other outcomes across treatment groups.

## MATERIALS AND METHODS

### Patient selection

The study protocol was approved by the Institutional Review Board (IRB) of Severance Hospital, Yonsei University College of Medicine (IRB No.: 4-2022-0003). Patients with OVCFs were evaluated at the orthopaedic outpatient clinic or emergency room of the same institution between May 2018 and December 2020. All patients were newly diagnosed with OVCFs following low-energy trauma. One or more vertebral compression fractures were found on computed tomography images and confirmed by low-intensity signal changes on T1-weighted images and high-intensity changes on T2-weighted images with fat suppression on MRI.[6]

The bone mineral density (BMD) was measured by T-score using dual-energy X-ray absorptiometry (Horizon, Hologic Inc., Bedford, MA, USA). If a patient had undergone a BMD test within 1 year, the value from that test was used, and the history of osteoporosis medication use was also examined in all patients.

The inclusion criteria of the study were as follows: 1) patients aged over 60 years, male patients or postmenopausal women with a diagnosis of osteoporosis (T-score ≤-2.5); 2) patients taking osteoporosis drugs after being diagnosed with OVCF (anabolic or anti-resorptive agents); 3) patients who were followed up with imaging for more than 1 year and compared with a BMD test performed 1 year later; and 4) naïve patients who had not been taking osteoporosis medications before being newly diagnosed with OVCF.

The exclusion criteria were as follows: 1) patients who had undergone fusion surgery or procedures, such as vertebroplasty (VP) or kyphoplasty (KP), at the fractured or adjacent level; 2) patients with a follow-up period of less than 1 year; 3) patients diagnosed with fractures due to infection or malignancy; and 4) patients diagnosed with secondary osteoporosis (including long-term steroid use, endocrine disorders, marrow-related disorders, renal disease, and cancer).

### Drug treatments

According to the Endocrine Society Clinical Practice Guidelines, patients with osteoporosis at high- to very-high-risk are recommended for anabolic agent treatment— i.e., TPTD or abaloparatide for 2 years or RM for 1 year.[5] However, anabolic agents are difficult to use for a sufficient period of time due to the inconvenience of once-a-month visits or daily self-administration for patients and poor cost-effectiveness. Therefore, we included patients who used anabolic agents for at least 6 months in this study.

The reasons for setting the anabolic treatment period to 6 months were as follows: 1) At least 3 months of cyclic TPTD use is reported to be helpful in treating osteoporosis and OVCF; therefore, two cycles are more helpful in treating fractures.[7] 2) In addition, for both TPTD and RM, up to 6 months is the period showing the maximum anabolic window.[8,9] 3) Finally, the period to reach the formation phase in the bone remodeling cycle is approximately 4 months.[10]

Since many studies have reported that combination therapy with TPTD and denosumab (DMAB) is more effective than TPTD monotherapy, this study adopted a combination strategy for TPTD with DMAB.[11-13]

Following its approval in May 2019, RM was introduced as an effective bone-forming agent for the treatment of osteoporosis. A sequential therapy, in which the BMD gains from an initial course of RM are maintained and enhanced by subsequent treatment with DMAB, is now a widely used strategy in clinical practice.[14] In this study, sequential therapy was chosen over combination therapy, as the concurrent administration of RM and DMAB is considered to have no additional pharmacological benefit due to the overlapping anti-resorptive effects.

If a patient did not consent to the use of anabolic agent, DMAB was given as the first-line medication. Bisphosphonate (BP) was prescribed only when the patient preferred to take BP. These patients were informed of the side effects of long-term BP use and the need for a drug holiday.

Based on the preceding information, all patients were divided into four groups according to medication: 1) DMAB only (Prolia; Amgen Ltd, Thousand Oaks, CA, USA), group D; 2) DMAB and TPTD simultaneously for the first 6 months, followed by DMAB monotherapy for maintenance (group TDco); TPTD was injected subcutaneously once a day (Forsteo; Eli Lilly and Company Ltd, Indianapolis, IN, USA or Terrosa; Richter-Helm Biologics Ltd, Hamburg, Germany) according to the patient's preference; 3) RM (Evenity; Amgen Ltd) for the first 6 months in all cases, then only DMAB, group RDse; and 4) BP agents alendronate (Fosamax; Merck Sharp & Dohme, Rahway, NJ, USA) once a week and ibandronate (Bonfild inj.; Hanlim Pharm, Seoul, Korea) every 3 months, group B. Importantly, RM was not prescribed if a patient had cardiovascular risk factors (e.g., myocardial infarction, stroke, or history of stents) (Fig. 1).[15]

Following standard orthopedic principles, initial conservative treatment resulted in pain reduction for all patients.[2] Therefore, percutaneous cement augmentation techniques, such as

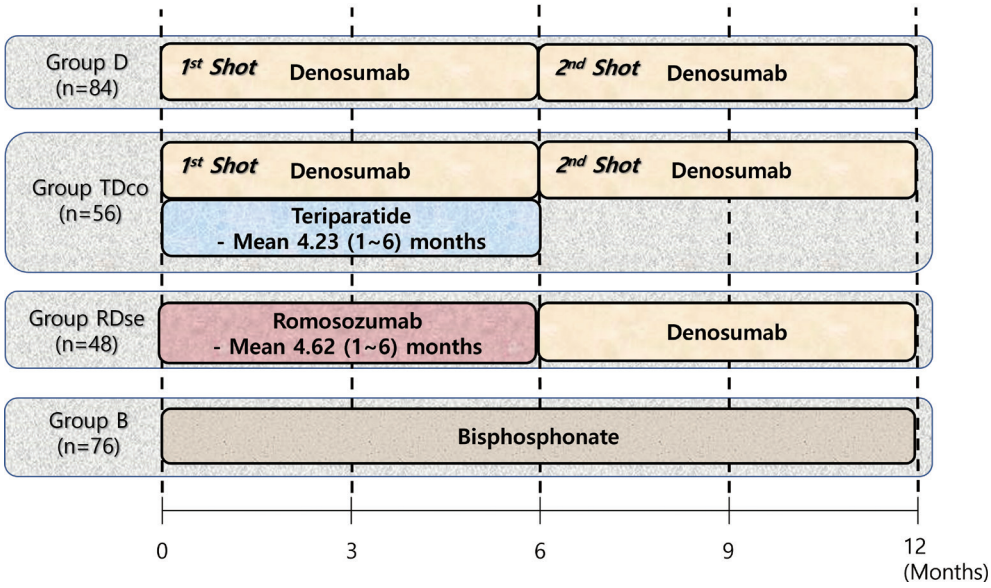


**Fig. 1.** Drug treatment schedule for each group. Group D, denosumab monotherapy; Group TDco, teriparatide and denosumab combination therapy; Group RDse, sequential denosumab after romosozumab; Group B, bisphosphonate monotherapy.

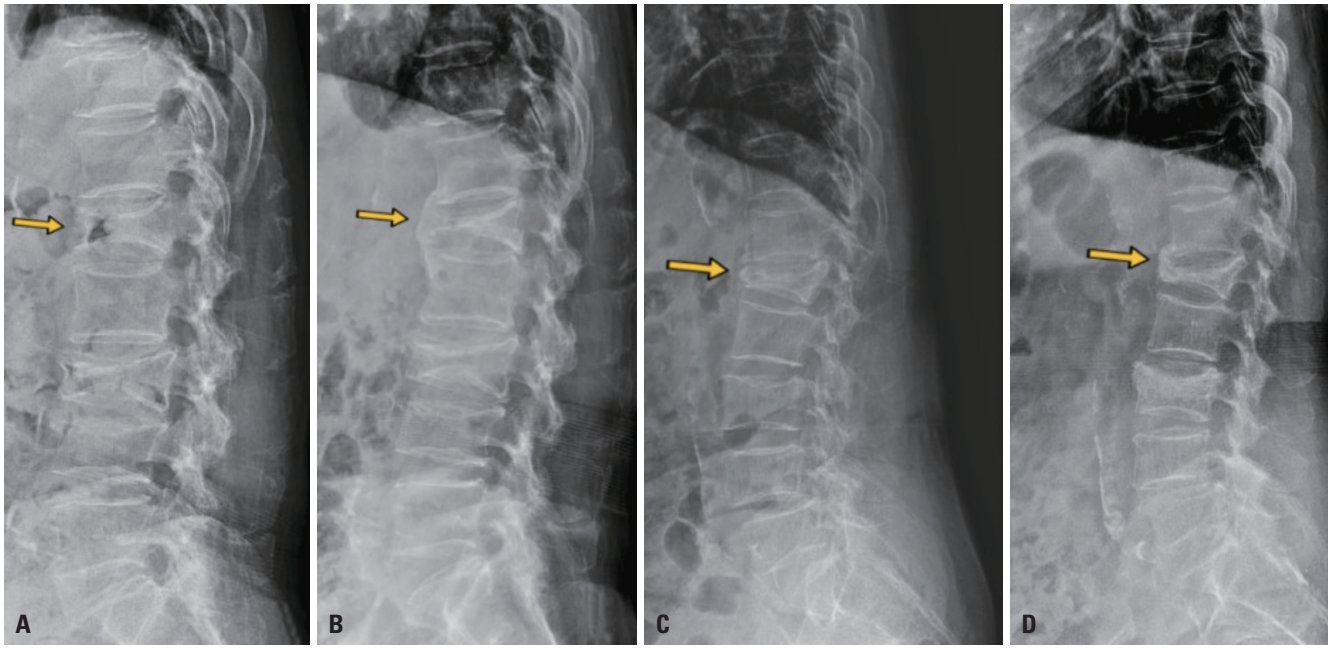


**Fig. 2.** BBE on X-ray. (A) Initial X-ray of a 76-year-old woman with L1 osteoporotic fracture. (B) BBE was formed between T12 and L2 after 12 months of combined treatment with teriparatide and denosumab. (C) An 83-year-old woman with L1 osteoporotic fracture. (D) BBE between T12 and L2 was observed after 12 months of sequential romosozumab therapy (yellow arrow indicates fracture site). BBE, bone bridge effect.

VP or KP, were not performed. All patients were supplemented with vitamin D at 1000 IU/day by oral administration according to the recommended dose.[5]

### Assessment and statistical analysis

Outpatient follow-up was conducted for 1, 3, 6, 9, and 12 months. Visual analog scale (VAS) was assessed for the clinical results, and the degree of collapse and occurrence of BBE were observed by X-ray at each visit (Fig. 2). In addition, at the 12th month, the BMD level using DXA was re-measured. The BMD values were investigated using the T-score of the spine except for fractured vertebrae. Radiological assessments were performed at the beginning of diagnosis and at the last follow-up session, and, if BBE had occurred, at the time of BBE. The local Cobb angle (CA) and CA were measured using lateral plain radiographs.[16] In addition, the vertebral height (VH) was measured by obtaining the average of the anterior and posterior heights of the fractured vertebra (Fig. 3). In the case of multilevel


https://doi.org/10.3349/ymj.2025.0325

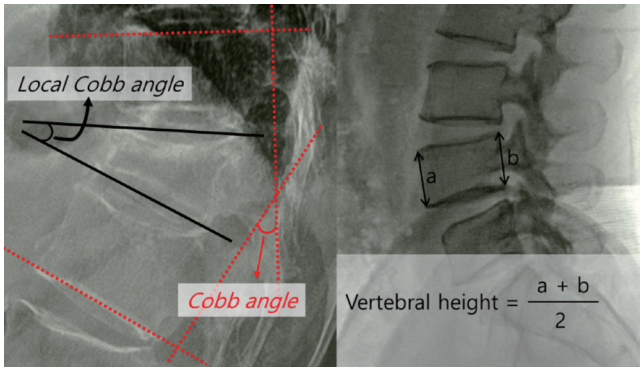


**Fig. 3.** Methods used to assess the local CA, CA, and vertebral height on X-ray. CA, Cobb angle.

fractures, measurements were made focusing on one vertebral body that had collapsed the most. For the purpose of this study, BBE was defined as the presence of continuous, mature bone formation connecting the anterior cortex of the fractured vertebral body to the anterior cortex of the adjacent superior or inferior vertebra, as observed on sequential lateral plain radiographs.

All radiological assessments, including the determination of BBE and the measurements of CA, local CA, and VH, were performed independently by two orthopedic spine surgeons (J.Y. Yoon, with more than 5 years of clinical experience; and B.H. Lee, with more than 10 years of clinical experience), who were blinded to each other's measurements and the patient groups. Any discrepancies were resolved by consensus. To assess the inter-rater reliability, 40 cases (approximately 15% of the cohort) were randomly selected and evaluated by both surgeons. The intraclass correlation coefficient (ICC) was calculated for all key measurements.

For continuous variables that can be analyzed in multiple ways, analysis of variance was performed. For nominal variables, Pearson's chi-squared test was performed to compare two groups among the four groups. Furthermore, to specifically analyze the 1-year change in BMD while adjusting for baseline differences, an analysis of covariance (ANCOVA) was performed, with the initial baseline BMD T-score serving as the covariate. To identify the independent risk factors for BBE formation and to adjust for baseline confounding variables, a multivariate logistic regression analysis was performed. The occurrence of BBE (presence or absence) was set as the dependent variable. Independent variables included the drug treatment group (groups D, TDco, RDse, and B), patient characteristics [age, sex, body mass index (BMI), and initial BMD], and radiological parameters (initial CA, CA change, initial local CA, local CA change, initial VH, and VH change). SPSS 23.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. All variables were expressed as number, percentages, means± standard deviation, or medians. Statistical significance was set at a $p$-value <0.05.

## RESULTS

### Baseline characteristics

The total number of patients included in the final analysis was 264, comprising 84 in group D, 56 in group TDco, 48 in group RDse, and 76 in group B (Fig. 1).

The initial demographic and radiologic values were compared across the four treatment groups (Table 1). No statistically significant differences were found in age, BMI, or the proportion of multiple fractures. However, there was a significant difference in sex distribution ($p$=0.039), primarily because group RDse consisted entirely of female patients due to treatment allocation criteria. Initial BMD was also significantly different among groups ($p$<0.001), with group B having the highest mean T-score (-1.91) and group RDse having the lowest (-3.06). Significant differences were also observed in the initial CA ($p$=0.007), whereas the initial local CA and VH did not differ significantly.

### Reliability of radiological measurements

The inter-rater reliability for the radiological measurements was found to be excellent. The ICC value for the determination of BBE (presence vs. absence) was 0.95 [95% confidence interval (CI): 0.91–0.98], that for the CA measurement was 0.96 (95% CI: 0.93–0.98), and that for the VH measurement was 0.94 (95% CI: 0.90–0.97), indicating almost perfect agreement.

### Incidence and timing of BBE

Regarding the incidence of BBE according to drug regimen, the anabolic agent groups showed the highest rates: group RDse at 56.3% and group TDco at 51.8%. These were significantly higher than group D (28.6%) and group B (21.1%) (overall $p$<0.001). There was no significant difference in BBE incidence between the two anabolic groups (TDco vs. RDse, post-hoc $p$=0.910), nor between the two anti-resorptive groups (D vs. B, post-hoc $p$>0.999) (Table 1).

BBE was confirmed significantly earlier in the anabolic groups (overall $p$<0.001). The mean formation period was fastest in group RDse (4.56±2.15 months), followed by group TDco (7.17±4.15 months), group D (9.17±4.07 months), and group B (10.50±3.46 months). Post-hoc analysis revealed significant differences between group RDse and all other groups, and between group TDco and group B (Table 1).

### Changes in BMD and radiological parameters

The 1-year changes in BMD and radiological parameters also varied by group (Table 1). The mean increase in BMD T-score was greatest in group TDco (1.04 ± 0.96), which was significantly higher than all other groups (group D: 0.55±0.61; group RDse: 0.63±0.58; group B: 0.35±0.53; overall $p$<0.001). This finding was validated by an ANCOVA, which confirmed that the superior BMD gain in group TDco remained highly significant even after adjusting for differences in baseline BMD (overall $p$=0.001).

Furthermore, the change in local CA was significantly greater

**Table 1.** Baseline Characteristics and Outcomes by Osteoporosis Medication Group

| Characteristic | Group D (n=84) | Group TDco (n=56) | Group RDse (n=48) | Group B (n=76) | Overall *p* |
|---|---|---|---|---|---|
| Basic demographics in the initial period | | | | | |
| Sex (male/female) | 7/77 | 9/47 | 0/48 | 8/68 | 0.039* |
| Age (yr) | 76.10±8.46[a] | 78.48±8.73[a] | 75.38±6.95[a] | 77.63±9.13[a] | 0.187 |
| BMI (kg/m$^2$) | 24.42±2.84[a] | 24.23±3.82[a] | 22.95±2.71[b] | 24.30±2.31[ab] | 0.033* |
| Fracture level (single/multiple) | 64/20 | 39/17 | 12/36 | 60/16 | 0.671 |
| BMD (T-score) | -2.55±1.07[ab] | -2.47±1.49[ab] | -3.06±0.98[b] | -1.91±1.64[a] | <0.001* |
| Initial CA (°) | 19.66±11.33[ab] | 21.74±14.73[ab] | 24.95±13.40[a] | 16.78±13.54[b] | 0.007* |
| Local CA (°) | 15.16±8.23[a] | 17.50±9.68[a] | 16.78±9.43[a] | 16.71±8.10[a] | 0.435 |
| VH (mm) | 22.04±4.94[a] | 20.79±3.57[a] | 22.08±3.81[a] | 21.72±3.81[a] | 0.305 |
| Difference between initial and last follow-up | | | | | |
| BMD (T-score) | 0.55±0.61[a] | 1.04±0.96[b] | 0.63±0.58[a] | 0.35±0.53[a] | <0.001* |
| CA (°) | 1.34±6.09[a] | 0.86±4.91[a] | 0.88±8.69[a] | 2.44±4.30[a] | 0.381 |
| Local CA (°) | 1.04±5.96[a] | 0.58±4.58[a] | 0.74±7.72[a] | 3.11±4.64[b] | 0.034* |
| VH (mm) | -1.65±2.71[a] | -1.06±2.02[ab] | -1.93±1.84[a] | -0.81±1.16[b] | 0.008* |
| Bone bridge effect | | | | | |
| (+) | 24 (28.6)[a] | 29 (51.8)[b] | 27 (56.2)[b] | 16 (21.1)[a] | <0.001* |
| Formation period (months) | 9.17±4.07[a] | 7.17±4.15[b] | 4.56±2.15[c] | 10.50±3.46[a] | <0.001* |

BMI, body mass index; BMD, bone mineral density; CA, Cobb angle; VH, vertebral height.
Values are presented as mean±standard deviation or n (%). Overall *p*-values were calculated using analysis of variance (for continuous variables) or chi-squared test (for categorical variables). Values in the same row not sharing a common superscript letter (a, b, c) are significantly different from each other ($p<0.05$) based on Tukey's HSD post-hoc test.
*$p<0.05$.

in group B (3.11±4.64) compared to group D and group TDco ($p=0.034$). The change in VH was significantly less in group B (-0.81±1.16) compared to group D and group RDse ($p=0.008$). There was no significant difference in the 1-year change for the main CA ($p=0.381$).

### Independent predictors of BBE formation

A multivariate logistic regression analysis was performed to identify independent predictors of BBE formation (Table 2). After adjusting for all patient and radiologic variables, the drug regimen was a significant independent predictor. Compared to the reference group D, both group TDco [odds ratio (OR)=2.717, $p=0.010$, 95% CI: 1.268–5.823] and group RDse (OR=3.472, $p=0.004$, 95% CI: 1.488–8.103) showed a significantly higher likelihood of BBE formation. Both anabolic groups were also significantly superior to group B (TDco vs. B: $p=0.002$; RDse vs. B: $p<0.001$). There was no significant difference between the two anabolic groups (RDse vs. TDco, $p=0.579$).

Among the radiologic factors, CA change (1-year change) was also identified as a significant independent predictor of BBE formation (OR=1.074, $p=0.009$, 95% CI: 1.018–1.134). In this multivariate model, other variables such as initial BMD ($p=0.698$), initial CA ($p=0.104$), and BMI ($p=0.772$) were not found to be significant independent predictors.

### Pain outcomes (VAS scores)

The mean VAS scores for pain were similar across all groups at the initial diagnosis (Fig. 4A). However, at 1 month, the anabolic agent groups (TDco and RDse) reported lower mean VAS scores (4-point range) compared to the anti-resorptive groups (D and B, 5-point range). This difference became more pronounced at 3 months, with anabolic groups in the 2-point range and anti-resorptive groups in the 3-point range or higher. From 6 months onward, mean VAS scores were similarly low (plateaued) across all groups.

Statistical analysis of the decrease in VAS from baseline confirmed significantly greater pain reduction in the anabolic groups compared to group D and group B at both 1 month and 3 months (Fig. 4C). There was no significant difference between the two anabolic groups (TDco vs. RDse) at these early time points ($p=0.325$ at 1 month, $p=0.542$ at 3 months). At 6 months, while a numerically greater reduction was observed in the anabolic groups, the difference was no longer statistically significant among the four groups.

When comparing patients based on BBE formation, the group with confirmed BBE (+) showed a significantly greater reduction in VAS scores at the 3-month mark compared to the group without BBE (-) ($p=0.016$) (Fig. 4B and D). No significant differences in VAS reduction were observed between the BBE (+) and BBE (-) groups at 1 month or 6 months. Additionally, no new vertebral or non-vertebral fractures were observed in any of the four treatment groups during the 12-month follow-up period.

## DISCUSSION

In OVCFs, the primary therapy is conservative treatment.[2,17] As previously described, cement augmentation procedures for


https://doi.org/10.3349/ymj.2025.0325

**Table 2.** Multivariate Logistic Regression Analysis of Risk Factors for BBE Formation (n=263)

| Variable | OR (95% CI) | *p* |
|---|---|---|
| Drug regimen (pairwise comparisons) | | |
| Group TDco vs. Group D | 2.717 (1.268–5.823) | 0.010* |
| Group RDse vs. Group D | 3.472 (1.488–8.103) | 0.004* |
| Group B vs. Group D | 0.581 (0.257–1.311) | 0.191 |
| Group RDse vs. Group TDco | 1.278 (0.539–3.033) | 0.579 |
| Group B vs. Group TDco | 0.214 (0.082–0.560) | 0.002* |
| Group B vs. Group RDse | 0.167 (0.061–0.457) | <0.001* |
| Patient and radiologic factors | | |
| Sex, male (vs. female) | 0.885 (0.287–2.728) | 0.832 |
| Age | 1.027 (0.990–1.065) | 0.150 |
| BMI | 0.984 (0.886–1.094) | 0.772 |
| Initial BMD (T-score) | 0.951 (0.739–1.224) | 0.698 |
| Initial CA (°) | 1.022 (0.996–1.048) | 0.104 |
| CA change (°) | 1.074 (1.018–1.134) | 0.009* |
| Initial local CA (°) | 1.020 (0.974–1.069) | 0.399 |
| Local CA change (°) | 1.019 (0.962–1.078) | 0.523 |
| Initial VH (mm) | 0.967 (0.879–1.065) | 0.498 |
| VH change (mm) | 1.063 (0.912–1.238) | 0.434 |

OR, odds ratio; CI, confidence interval; Group D, denosumab monotherapy; Group TDco, teriparatide and denosumab combination therapy; Group RDse, sequential denosumab after romosozumab; Group B, bisphosphonate monotherapy; BMI, body mass index; BMD, bone mineral density; CA, Cobb angle; VH, vertebral height.
Statistical notes: the OR indicates the likelihood of bone bridge effect formation; an OR >1 suggests an increased likelihood, while an OR <1 suggests a decreased likelihood compared to the reference group. For pairwise drug regimen comparisons, the second-named group in each pair (e.g., Group D in "Group TDco vs. Group D") serves as the reference group. For categorical variables, the reference category is "female" for sex. The 95% CI is the range in which the true OR is likely to fall; if the interval does not include 1.0, the finding is considered statistically significant. "Change" variables (e.g., CA change) represent the 1-year difference calculated as (Last follow-up value - Initial value).
*$p<0.05$.

OVCFs are commonly performed when conservative treatment fails during the early period after fracture, and favorable outcomes have been reported.[18-20] However, cement leakage during the procedure or adjacent segmental fractures after the procedure are commonly reported complications.[21,22] Therefore, we focused on conservative treatment and avoided this procedure when possible. Accordingly, cement augmentation was not performed, except in patients with Kummel disease (who were not included in the present study), as patients generally responded well to conservative treatment.

In this study, we analyzed and compared the outcomes of different osteoporosis medications in the treatment of patients with OVCF. Among the drugs, TPTD and RM are used as anabolic agents. TPTD is a recombinant human parathyroid hormone primarily involved in remodeling-based bone formation.[7,8,21,23,24] RM, another anabolic agent, is a humanized immunoglobulin G2 monoclonal antibody that binds to sclerostin and inhibits its interaction with the Wnt signaling co-receptor.[25,26] Unlike the action mechanism of TPTD, RM has a dual action of promoting bone formation and reducing bone resorption. Several studies have reported the use of these anabolic agents in combination, sequential therapy, or monotherapy.[27,28] Among these, the combination of TPTD and DMAB significantly increased BMD; notably, in short-term studies of less than 1 year, a greater increase in BMD was observed compared with anabolic agent monotherapy.[28-30] Therefore, this combination is widely used as it is considered beneficial for fracture healing. In addition, DMAB inhibits bone resorption more than BP and preserves modeling-based bone formation, while BP inhibits both bone resorption and modeling-based bone formation.[28,31,32] Thus, when combination therapy with TPTD and DMAB is used, PTH-stimulated bone modeling can occur in the relative absence of remodeling, thereby maximizing the anabolic window.[33] Therefore, we chose DMAB as the drug used in combination therapy in this study. As another anabolic therapy, RM has been shown to significantly increase BMD of the spine and hip and to reduce the risk of vertebral fracture when used as sequential therapy or monotherapy.[25,34] In another report demonstrating that RM significantly increased spinal BMD, treatment-naïve patients achieved significantly higher BMD than patients with a history of prior osteoporosis treatment.[35] Based on these findings, we included only treatment-naïve patients in this study to more clearly evaluate the effects of RM.

Unlike previous studies reporting that RM showed more gains in BMD than TPTD,[36,37] group TDco demonstrated the most significant BMD gains compared with the other groups in our study. Additionally, group RDse demonstrated a higher BMD increase than group D and group B, but was only significantly higher than group B. The reason for this is likely that previous studies compared TPTD and RM monotherapy, whereas our study compared combination and sequential therapy. Our findings showed that the combination of TPTD and DMAB increased BMD more than sequential therapy using RM over a short period of 1 year.

The Endocrine Society Clinical Practice Guidelines recommend 12 months of RM therapy for very-high-risk patients.[5] In addition, a study of bone turnover markers during RM treatment reported that the anabolic window was greatest for up to 6 months, after which the anti-resorptive effect predominated.[38] In this study, because RM was administered for a maximum of 6 months, mid- to long-term results (longer than 6 months) were not assessed. The difficulty in continuing RM (or combination therapy with TPTD) for longer than 6 months is largely due to the economic burden imposed on patients under Korean insurance standards. Therefore, additional studies are needed to determine whether the anabolic effect of RM can be clinically sustained for a longer period after 6 months, which could then be compared with our data on DMAB sequential treatment.

In this study, we focused more on the BBE phenomenon rather than the drug-related increase in BMD. BBE occurs when a

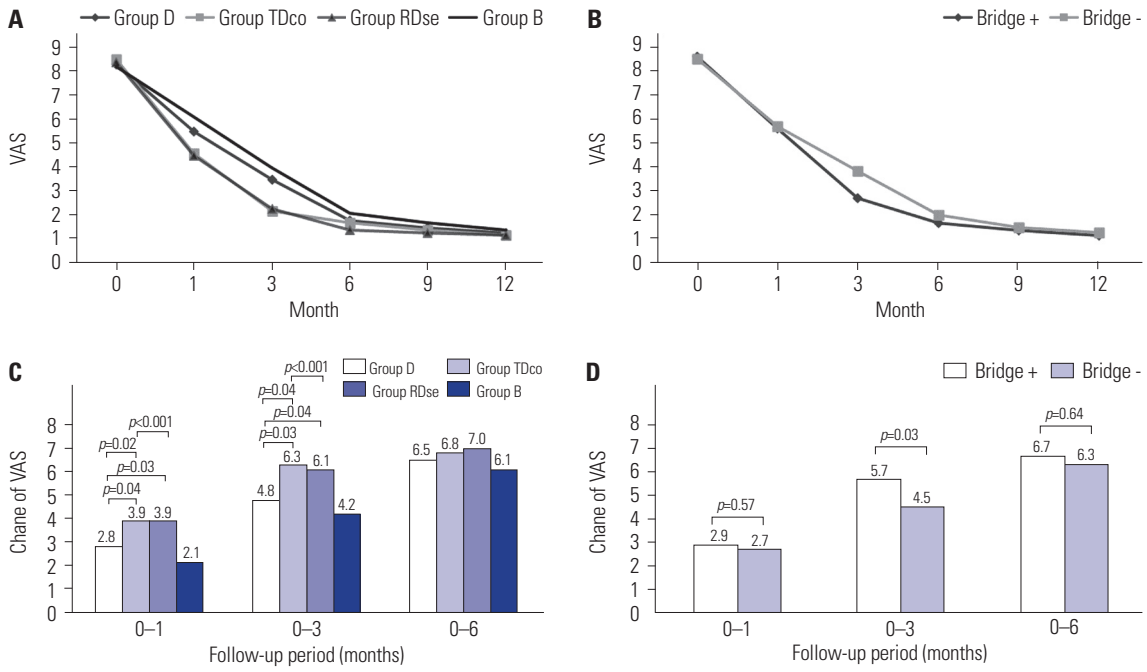


**Fig. 4.** Changes in the VAS according to treatment agent and the presence or absence of the BBE. (A and B) Differences in mean VAS by treatment strategy and with or without BBE from initial diagnosis to 1, 3, 6, 9, and 12 months. (C and D) VAS decrease at 1, 3, and 6 months from initial diagnosis according to treatment strategy and the presence or absence of BBE. (C) If there is statistical significance, each group is marked with a connecting line, and the *p*-value is indicated. (D) All *p*-values between groups are displayed above the connecting lines. Group D, denosumab monotherapy; Group TDco, teriparatide and denosumab combination therapy; Group RDse, sequential denosumab after romosozumab; Group B, bisphosphonate monotherapy. Data were presented as medians, and comparisons were performed using Pearson's chi-squared test. VAS, visual analog scale. BBE, bone bridge effect.

fractured vertebra fuses with an adjacent vertebra via bone formation at the anterior margin of the vertebral body (Fig. 2). This fusion is considered to be helpful in fracture healing by stabilizing the vertebrae.

Our results suggest that treatment with group RDse and group TDco is associated with a stronger bone formation effect compared with anti-resorptive monotherapy, and the initiation of bone bridge formation appeared faster in group RDse than in group TDco (Table 1). A greater impact on new fracture-related bone turnover and enhanced healing, potentially contributing to greater spine BMD gains, has been reported in patients treated with RM.[35,39] Furthermore, a recent experimental study demonstrated that RM significantly enhances neobone formation and stability even in compromised osteoporotic conditions, supporting its potent biological stimulus for BBE formation.[40] Therefore, the authors recommend that patients actively consider starting RM to further increase BMD when a new fracture occurs.[35]

A key concern in this retrospective study was that the significant baseline imbalances, particularly in group RDse, could have introduced confounding variables. Our multivariate logistic regression analysis (Table 2) was performed to address this potential bias.

The analysis yielded two critical findings. First, even after adjusting for all patient and radiologic confounders (including age, sex, BMI, and initial BMD), the anabolic agent groups (TDco and RDse) remained powerful independent predictors of BBE formation compared with anti-resorptive groups (D and B). This strongly suggests that the observed increase in BBE is a true pharmacological effect associated with anabolic agents, not simply an artifact of selection bias.

Second, our multivariate logistic regression analysis (Table 2) provided critical insights by separating true independent predictors from confounding factors. Notably, initial BMD was not found to be a significant independent predictor of BBE formation ($p$=0.698). This finding suggests that the higher BBE incidence observed in the anabolic groups (particularly group RDse) is not simply an artifact of their lower baseline bone density.

Instead, the analysis revealed two significant and independent predictors of BBE formation: the drug regimen and radiological change. Even after adjusting for all other variables, anabolic treatment (e.g., group RDse vs. D, OR=3.472, $p$=0.004) remained the most potent predictor. Independently of this drug effect, the CA change (representing progressive collapse over 1 year) was also identified as a significant predictor (OR=1.074, $p$=0.009).

This suggests that BBE formation may be influenced by two distinct conditions: a "biological stimulus" (provided by the anabolic agent, which actively promotes bone formation, as studies on RM have reported enhanced bone turnover and healing at recent fracture sites[35]) and a "geometric opportunity" (creat-


https://doi.org/10.3349/ymj.2025.0325

ed when progressive collapse narrows the anterior gap between vertebrae). Therefore, the superior BBE rate in the anabolic groups cannot be dismissed as a simple result-oriented consequence of collapse; rather, it appears to be a robust pharmacological effect that is further facilitated by the fracture's geometric changes.

We additionally investigated VAS scores at each follow-up period to evaluate clinical outcomes. It was observed that both group RDse and group TDco showed greater pain improvement than the anti-resorptive groups up to 3 months, corresponding to the early stage of fracture healing. Previous studies have demonstrated improvement in VAS scores when TPTD was administered to patients with fractures[7,41] In addition, pain relief was also achieved when TPTD was combined with DMAB in our study. However, no studies have directly compared TPTD monotherapy with combination therapy; therefore, further research is warranted.

In addition, it was observed that the group in which BBE was formed had a significant decrease in VAS at 3 months from the initial diagnosis and quickly reached a plateau with VAS scores of less than 2 points. Considering that the overall mean time to BBE confirmation was 7.4 months, and that faster confirmation was observed in group RDse (mean 4.5 months), which also showed early pain relief, this observation raises the possibility that the BBE formation process itself might be associated with pain reduction. Furthermore, it is important to consider the clinical significance of this pain reduction. While the Minimal Clinically Important Difference (MCID) for spine-related VAS pain scores can vary, it is frequently cited in the literature to be approximately 1.5 to 2.0 points.[42] Our findings, which showed a significantly greater VAS reduction at 3 months in both the anabolic agent groups and the BBE (+) group (Fig. 4), exceeded this MCID threshold. This suggests that the observed early pain relief was not only statistically significant but also clinically meaningful for the patients. However, more detailed research is needed to determine whether other factors influence pain outcomes and how these effects differ across additional clinical criteria.

This study is the first to describe BBE, and we believe these findings are significant in terms of the utilization of potent anabolic agents or combination therapies.

However, our study also had several limitations. First and most importantly, this study has a retrospective, non-randomized design, which carries an inherent risk of selection bias and confounding variables. As mentioned, treatment allocation was based on factors such as differences in drug-related cost burden and the contraindication of RM in patients with a history of cardiovascular disease. This led to significant baseline imbalances, notably in group RDse, which consisted entirely of female patients and had significantly lower baseline BMD. Although we performed a multivariate regression analysis (Table 2) to adjust for these factors, this limitation must be considered when interpreting the results. Furthermore, as a single-center study with treatment allocation influenced by national insurance policies and patient preferences, the generalizability of our findings to other clinical settings or populations may be limited. Second, the follow-up duration of 12 months is relatively short. This timeframe may not be sufficient to fully capture the long-term evolution of the BBE or to definitively assess sustained clinical outcomes, such as long-term pain relief and prevention of subsequent fractures. Third, our clinical assessment was limited to VAS scores for pain. Due to the retrospective nature of the study, more comprehensive functional outcome measures, such as the Oswestry Disability Index or quality-of-life scores (e.g., EuroQol 5-dimension), were not available for analysis. Therefore, future prospective studies incorporating these functional and quality-of-life measures are essential to more comprehensively evaluate the clinical significance and long-term benefits of the BBE. Fourth, the 6-month duration of active anabolic agent administration (both TPTD and RM), which was based on national insurance reimbursement policies, warrants discussion. While standard protocols often extend to 12 or 24 months, we believe this timeframe was appropriate for the study's specific endpoints. The 6-month active treatment period aligns well with the typical window for acute osteoporotic fracture healing—which is commonly assessed radiologically at 3 and 6 months[43]—making it a sufficient duration to assess the primary endpoint of BBE formation. Furthermore, the total 12-month follow-up period was adequate to observe the subsequent maturity of the BBE and to monitor for our key clinical outcome: the incidence of new subsequent fractures. Fifth, data on bone turnover markers were incomplete, a limitation stemming from both the retrospective design and the economic burden on patients undergoing these tests. Sixth, this study only included naïve patients, so it was difficult to observe the effect of previous osteoporosis drugs on current treatment. In future studies, it will be necessary to analyze patients who were previously treated. Seventh, patients in this study did not undergo procedures such as VP or KP because none had uncontrolled pain or neurological deficits. However, as these procedures are still commonly used in the treatment of OVCFs, it would be necessary to compare the results of osteoporosis medication treatments in patients who underwent cement augmentation procedures. Finally, to determine whether segments with BBE have greater stability, biomechanical studies are needed.

In summary, group TDco appeared to be associated with greater short-term BMD gain compared to group RDse. Although BBE occurred most rapidly with group RDse, the occurrence of BBE between group RDse and group TDco was not significantly different. In addition, anabolic treatments were associated with superior BBE formation and earlier VAS reduction compared with anti-resorptive agents. Therefore, non-surgical treatment of OVCFs likely benefits from aggressive administration of osteoporosis medication, and a treatment strategy involving combination or sequential administration of anabolic

agents may be more effective than conventional anti-resorptive monotherapy.

## AUTHOR CONTRIBUTIONS

Conceptualization: Ja-Yeong Yoon, Seong-Hwan Moon, Hak-Sun Kim, Kyung-Soo Suk, Si-Young Park, Ji-Won Kwon, and Byung Ho Lee. Data curation: Ja-Yeong Yoon and Byung Ho Lee. Formal analysis: Ja-Yeong Yoon and Byung Ho Lee. Investigation: Ja-Yeong Yoon, Sung-Min Kim, and Byung Ho Lee. Methodology: Ja-Yeong Yoon, Sung-Min Kim, Ji-Won Kwon, and Byung Ho Lee. Project administration: Ja-Yeong Yoon and Byung Ho Lee. Resources: all authors. Software: Ja-Yeong Yoon and Byung Ho Lee. Supervision: Seong-Hwan Moon, Hak-Sun Kim, Kyung-Soo Suk, Si-Young Park, Ji-Won Kwon, and Byung Ho Lee. Validation: Ja-Yeong Yoon, Sung-Min Kim, and Byung Ho Lee. Visualization: Seong-Hwan Moon, Hak-Sun Kim, Kyung-Soo Suk, Si-Young Park, Ji-Won Kwon, and Byung Ho Lee. Writing—original draft: Ja-Yeong Yoon and Byung Ho Lee. Writing—review & editing: Ja-Yeong Yoon, Seong-Hwan Moon, Hak-Sun Kim, Kyung-Soo Suk, Si-Young Park, Ji-Won Kwon, and Byung Ho Lee. Approval of final manuscript: all authors.

## ORCID iDs

Ja-Yeong Yoon https://orcid.org/0000-0003-2696-4302
Sung-Min Kim https://orcid.org/0000-0003-4935-9412
Seong-Hwan Moon https://orcid.org/0000-0002-5165-1159
Hak-Sun Kim https://orcid.org/0000-0002-8330-4688
Kyung-Soo Suk https://orcid.org/0000-0003-0633-2658
Si-Young Park https://orcid.org/0000-0002-1216-901X
Ji-Won Kwon https://orcid.org/0000-0003-4880-5310
Byung Ho Lee https://orcid.org/0000-0001-7235-4981

## REFERENCES

1. Lippuner K, Johansson H, Kanis JA, Rizzoli R. Remaining lifetime and absolute 10-year probabilities of osteoporotic fracture in Swiss men and women. Osteoporos Int 2009;20:1131-40.
2. Jang HD, Kim EH, Lee JC, Choi SW, Kim K, Shin BJ. Current concepts in the management of osteoporotic vertebral fractures: a narrative review. Asian Spine J 2020;14:898-909.
3. Klotzbuecher CM, Ross PD, Landsman PB, Abbott TA 3rd, Berger M. Patients with prior fractures have an increased risk of future fractures: a summary of the literature and statistical synthesis. J Bone Miner Res 2000;15:721-39.
4. Evans AJ, Jensen ME, Kip KE, DeNardo AJ, Lawler GJ, Negin GA, et al. Vertebral compression fractures: pain reduction and improvement in functional mobility after percutaneous polymethylmethacrylate vertebroplasty—retrospective report of 245 cases. Radiology 2003;226:366-72.
5. Shoback D, Rosen CJ, Black DM, Cheung AM, Murad MH, Eastell R. Pharmacological management of osteoporosis in postmenopausal women: an Endocrine Society guideline update. J Clin Endocrinol Metab 2020;105:587-94.
6. Kanchiku T, Taguchi T, Kawai S. Magnetic resonance imaging diagnosis and new classification of the osteoporotic vertebral fracture. J Orthop Sci 2003;8:463-6.
7. Suk KS, Lee HM, Moon SH, Kim HJ, Kim HS, Park JO, et al. At least one cyclic teriparatide administration can be helpful to delay initial onset of a new osteoporotic vertebral compression fracture. Yonsei Med J 2014;55:1576-83.
8. Tabacco G, Bilezikian JP. Osteoanabolic and dual action drugs. Br J Clin Pharmacol 2019;85:1084-94.
9. Moon NH, Shin WC, Jang JH. [Romosozumab: a novel agent in the management of osteoporosis]. J Korean Fract Soc 2021;34:148-53. Korean
10. Kenkre JS, Bassett J. The bone remodelling cycle. Ann Clin Biochem 2018;55:308-27.
11. Leder BZ, Tsai JN, Uihlein AV, Wallace PM, Lee H, Neer RM, et al. Denosumab and teriparatide transitions in postmenopausal osteoporosis (the DATA-Switch study): extension of a randomised controlled trial. Lancet 2015;386:1147-55.
12. Saag KG, Petersen J, Brandi ML, Karaplis AC, Lorentzon M, Thomas T, et al. Romosozumab or alendronate for fracture prevention in women with osteoporosis. N Engl J Med 2017;377:1417-27.
13. McClung MR. Using osteoporosis therapies in combination. Curr Osteoporos Rep 2017;15:343-52.
14. Lewiecki EM, Dinavahi RV, Lazaretti-Castro M, Ebeling PR, Adachi JD, Miyauchi A, et al. One year of romosozumab followed by two years of denosumab maintains fracture risk reductions: results of the FRAME extension study. J Bone Miner Res 2019;34:419-28.
15. Elliott W, Chan J. Romosozumab-aqqg injection (Evenity) [Internet] [accessed on 2026 April 8]. Available at: https://www.clinician.com/articles/144394-romosozumab-aqqg-injection-evenity.
16. Jiang SD, Wu QZ, Lan SH, Dai LY. Reliability of the measurement of thoracolumbar burst fracture kyphosis with Cobb angle, Gardner angle, and sagittal index. Arch Orthop Trauma Surg 2012;132:221-5.
17. Park YS, Kim HS. Prevention and treatment of multiple osteoporotic compression fracture. Asian Spine J 2014;8:382-90.
18. McGraw JK, Cardella J, Barr JD, Mathis JM, Sanchez O, Schwartzberg MS, et al. Society of Interventional Radiology quality improvement guidelines for percutaneous vertebroplasty. J Vasc Interv Radiol 2003;14(9 Pt 2):S311-5.
19. Kallmes DF, Comstock BA, Heagerty PJ, Turner JA, Wilson DJ, Diamond TH, et al. A randomized trial of vertebroplasty for osteoporotic spinal fractures. N Engl J Med 2009;361:569-79.
20. Mills ES, Ton AT, Bouz G, Alluri RK, Hah RJ. Acute operative management of osteoporotic vertebral compression fractures is associated with decreased morbidity. Asian Spine J 2022;16:634-42.
21. Berlemann U, Ferguson SJ, Nolte LP, Heini PF. Adjacent vertebral failure after vertebroplasty. A biomechanical investigation. J Bone Joint Surg Br 2002;84:748-52.
22. Park JH, Kim HS, Kim SW. Cement leakage into adjacent vertebral body following percutaneous vertebroplasty. Korean J Spine 2016;13:74-6.
23. Lindsay R, Cosman F, Zhou H, Bostrom MP, Shen VW, Cruz JD, et al. A novel tetracycline labeling schedule for longitudinal evaluation of the short-term effects of anabolic therapy with a single iliac crest bone biopsy: early actions of teriparatide. J Bone Miner Res 2006;21:366-73.
24. Eriksen EF, Chapurlat R, Boyce RW, Shi Y, Brown JP, Horlait S, et al. Modeling-based bone formation after 2 months of romosozumab treatment: results from the FRAME clinical trial. J Bone Miner Res 2022;37:36-40.
25. Boyce RW, Niu QT, Ominsky MS. Kinetic reconstruction reveals time-dependent effects of romosozumab on bone formation and osteoblast function in vertebral cancellous and cortical bone in cynomolgus monkeys. Bone 2017;101:77-87.
26. Kim SW, Lu Y, Williams EA, Lai F, Lee JY, Enishi T, et al. Sclerostin antibody administration converts bone lining cells into active osteoblasts. J Bone Miner Res 2017;32:892-901.
27. Cosman F. Combination therapy for osteoporosis: a reappraisal. Bonekey Rep 2014;3:518.
28. Langdahl B, Ferrari S, Dempster DW. Bone modeling and remod-


https://doi.org/10.3349/ymj.2025.0325

eling: potential as therapeutic targets for the treatment of osteoporosis. Ther Adv Musculoskelet Dis 2016;8:225-35.
29. Tsai JN, Uihlein AV, Lee H, Kumbhani R, Siwila-Sackman E, McKay EA, et al. Teriparatide and denosumab, alone or combined, in women with postmenopausal osteoporosis: the DATA study randomised trial. Lancet 2013;382:50-6.
30. Leder BZ, Tsai JN, Uihlein AV, Burnett-Bowie SA, Zhu Y, Foley K, et al. Two years of denosumab and teriparatide administration in postmenopausal women with osteoporosis (the DATA extension study): a randomized controlled trial. J Clin Endocrinol Metab 2014;99:1694-700.
31. Brown JP, Prince RL, Deal C, Recker RR, Kiel DP, de Gregorio LH, et al. Comparison of the effect of denosumab and alendronate on BMD and biochemical markers of bone turnover in postmenopausal women with low bone mass: a randomized, blinded, phase 3 trial. J Bone Miner Res 2009;24:153-61.
32. Miller PD, Pannacciulli N, Malouf-Sierra J, Singer A, Czerwiński E, Bone HG, et al. Efficacy and safety of denosumab vs. bisphosphonates in postmenopausal women previously treated with oral bisphosphonates. Osteoporos Int 2020;31:181-91.
33. Ominsky MS, Libanati C, Niu QT, Boyce RW, Kostenuik PJ, Wagman RB, et al. Sustained modeling-based bone formation during adulthood in cynomolgus monkeys may contribute to continuous BMD gains with denosumab. J Bone Miner Res 2015;30:1280-9.
34. Cosman F, Crittenden DB, Adachi JD, Binkley N, Czerwinski E, Ferrari S, et al. Romosozumab treatment in postmenopausal women with osteoporosis. N Engl J Med 2016;375:1532-43.
35. Tominaga A, Wada K, Okazaki K, Nishi H, Terayama Y, Kato Y. Early clinical effects, safety, and predictors of the effects of romosozumab treatment in osteoporosis patients: one-year study. Osteoporos Int 2021;32:1999-2009.
36. McClung MR, Grauer A, Boonen S, Bolognese MA, Brown JP, Diez-Perez A, et al. Romosozumab in postmenopausal women with low bone mineral density. N Engl J Med 2014;370:412-20.
37. Langdahl BL, Libanati C, Crittenden DB, Bolognese MA, Brown JP, Daizadeh NS, et al. Romosozumab (sclerostin monoclonal antibody) versus teriparatide in postmenopausal women with osteoporosis transitioning from oral bisphosphonate therapy: a randomised, open-label, phase 3 trial. Lancet 2017;390:1585-94.
38. Papapoulos SE. New bone-forming treatments for osteoporosis. Nat Rev Endocrinol 2015;11:69-70.
39. Veitch SW, Findlay SC, Hamer AJ, Blumsohn A, Eastell R, Ingle BM. Changes in bone mass and bone turnover following tibial shaft fracture. Osteoporos Int 2006;17:364-72.
40. Kwon JW, Moon SH, Suk KS, Park SY, Kim HS, Park SR, et al. Romosozumab enhances implant stability in glucocorticoid-induced osteoporotic bone: a rabbit model study. Neurospine 2025;22:880-90.
41. Yu D, Kim S, Jeon I. Therapeutic effect of teriparatide for osteoporotic thoracolumbar burst fracture in elderly female patients. J Korean Neurosurg Soc 2020;63:794-805.
42. Hägg O, Fritzell P, Nordwall A. The clinical importance of changes in outcome scores after treatment for chronic low back pain. Eur Spine J 2003;12:12-20.
43. Kim HS, Kim SW, Lee MH, Park KS, Shin DA. Cement augmentation for traumatic burst fracture of the thoracolumbar spine: comparison between kyphoplasty and short-segment posterior fixation with vertebroplasty. J Korean Neurosurg Soc 2013;54:341-6.