CLINICAL ARTICLE

Vertebral Collapse Prevented Following Teriparatide Treatment in Postmenopausal Kümmell’s Disease Patients with Severe Osteoporosis

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Objective: To compare the preventive effects of teriparatide and alendronate on the progression of vertebral body collapse in postmenopausal single-level Kümmell’s disease (KD).

Methods: From March 2013 to December 2020, the medical records for 53 postmenopausal single-level KD patients who received conservative treatment with teriparatide (25 patients, teriparatide group) or alendronate (28 patients, alendronate group) were retrospectively reviewed. Midsagittal computed tomography (CT) images were analyzed by ImageJ to assess the intravertebral bone formation (mineralized bone) by calculating the ratio of area of intravertebral mineralized bone (AIMB) to the area of fractured vertebral body (AFVB). The changes in radiological parameters of the fractured vertebral body including kyphosis angle (KA), anterior and posterior border heights (ABH and PBH) and spinal canal diameter (SCD), bone turnover biomarkers (BTMs), and bone mineral density (BMD) were analyzed to evaluate the therapeutic effect.

Results: At month 12, the ratio of AIMB to AFVB was significantly greater in teriparatide group (54.28% ± 15.30%) than in alendronate group (35.57% ± 17.61%) (P < 0.001). Sagittal CT substantiated the formation of bone bridge in 16 patients in teriparatide group. No bone bridge was detected in alendronate group. The KA was significantly smaller and the ABH, PBH, and SCD was greater in teriparatide group than in alendronate group (all P < 0.001). The KA increments were significantly smaller in teriparatide group (3.98° ± 1.30°) than in alendronate group (11.43° ± 3.73°) (P < 0.001). The ABH and PBH decrement were significantly lower in teriparatide group (11.96% ± 1.93% and 2.80% ± 2.52%) than in alendronate group (37.04% ± 8.00% and 19.50% ± 8.22%) (both P < 0.001). The BTMs and BMD were significantly greater in the teriparatide group than in the alendronate group. In teriparatide group, KA increment was negatively correlated with the change in PINP (r = −0.781, P < 0.001) and the ratio of AIMB to AFVB (r = −0.592, P = 0.002) from baseline to month 12. The ABH decrement was negatively correlated with the change in PINP (r = −0.612, P = 0.001) and the ratio of AIMB to AFVB (r = −0.806, P < 0.001) from baseline to month 12.

Conclusions: In postmenopausal single-level KD patients, conservative treatment with teriparatide was better than alendronate at preventing the progressive vertebral collapse.

Key words: Alendronate; Conservative treatment; Kyphosis; Osteoporotic fractures; Teriparatide

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**Introduction**

Kummell’s disease (KD) is a clinical entity from the non-union of osteoporosis vertebral compression fracture (OVCF). The fractured vertebral body developed vertebral kyphosis as the result of a delayed vertebral collapse\(^1\) – \(^2\). Currently, avascular osteonecrosis is the prevailing hypothesis for the interpretation of the delayed vertebral collapse\(^3\). It frequently occurs in postmenopausal OVCF patients with severe osteoporosis. There are reports that the incidence of KD varies between 7% and 37% among the OVCF\(^4\) – \(^6\). With a consequent increase in the elderly population of OVCF with severe osteoporosis, KD is not uncommon and remains a clinical problem with great challenges. As a result of such progressive vertebral collapse and kyphosis, severe cases suffered from intractable back pain and/or neurologic complications either from the local kyphosis or the retropulsed bone fragment from the fractured posterior cortical wall in the collapsed vertebral body\(^7\).

The intravertebral vacuum cleft (IVC) sign, a positive imaging finding detected on computed tomography (CT) image or magnetic resonance (MR) image within the fractured vertebral body, is highly indicative of KD\(^8\). Gas collection in the cleft is detectable by CT scan. Fluid collection is detectable as a hyperintensity lesion in T2-weighted and fat-suppressed sequence MR images. The thoracolumbar junction is the most frequently involved vertebral segment. According to Laredo, OVCF complicated by impaired healing and secondary osteonecrosis may be the main reason for IVC\(^9\).

Goldstein et al. thought that the IVC sign was significantly related to the vertebral collapse\(^10\). In their research on conservative treatment for OVCF during a minimum 3-month follow up, IVC was significantly correlated to the vertebral collapse of more than 50%. Ito et al.\(^7\) examined whether the radiographic findings of IVC can be used for an early prediction of delayed vertebral collapse with neurological deficit. The IVC appeared approximate 3 weeks following OVCF and enlarged over time. This process led to the postero-superior wall collapse of the affected vertebra, resulting in delayed vertebral collapse and subsequent development of neurological deficits. Besides, a thoracolumbar fracture with the involvement of the vertebral posterior wall is also a relative risk factor for progressive collapse.

Surgical treatment is widely accepted for the treatment of KD. This clinical entity was commonly refractory to such conservative treatment as bed rest, narcotic analgesics, or the brace. For open internal fixation, various surgical procedures were reported for the prevention of the fractured vertebra from kyphotic formation and further collapse. However, associated medical problems in elderly populations and the loosening of pedicle screws within the severe osteoporotic vertebra have caused surgical treatments to result in significant morbidity and poor outcomes\(^11\).

In recent years, vertebra augmentation procedure (VAP), a minimally invasive alternative, seems to be a promising method to maintain the vertebral height to prevent progressive vertebral collapse in KD. In the past decades, VAP was widely applied and recommended by the Cardiovascular and Interventional Radiological Society of Europe (CIRSE) for the treatment of KD to achieve height restoration and correct kyphotic deformity\(^1\) – \(^2\), \(^7\). However, the complications related to VAP such as cement leakage, post-operation dislocation of cement, re-collapse of the augmented vertebral and secondary adjacent level fractures were not rare\(^14\) – \(^16\). Since the process of vertebral collapse may be aggravated following the VAP, therefore, the indication of a VAP should be taken with caution\(^14\).

Teriparatide, an anabolic agent, has been used increasingly for the treatment of OVCF in patients with severe osteoporosis. There has been evidence that intermittent systemic administration of teriparatide directly increased osteoblast activity to boost bone formation for improving bone mass and bone mineral density (BMD) in the lumbar spine, and subsequent improvement of the strength of the vertebral body\(^17\). Retrospectively, clinical trials have shown the preventive effects of conservative treatment with teriparatide on the progressive vertebral collapse following OVCF by improving vertebral strength and quality\(^18\), \(^19\). In theory, teriparatide treatment could prevent progressive vertebral collapse and kyphosis in KD patients.

However, there are few reports concerning the conservative treatment of patients with KD. Besides, there are few safer and effective treatments for the prevention of progressive vertebral collapse and kyphosis. Considering our previous research on the preventative role of teriparatide treatment on aggravation of spinal cord compromise in OVCF patients with surgical contraindications\(^20\), and the weakness for surgical treatment and traditionally conservative management for KD, finding an effective conservative treatment may be more suitable for elderly patients with KD. Based on the previous research on the criterion for progressive vertebral collapse, we defined the progression of kyphotic angle of more than 10° and height loss of more than 15% compared to initial values as vertebral collapse\(^21\).

We hypothesized that conservative treatment with teriparatide could boost the formation of new bone within the fractured vertebral body to rapidly improve bone strength related to BMD and to prevent progressive vertebral collapse in postmenopausal KD patients with severe osteoporosis.

Therefore, the objective of the current study was to: (i) analyse the radiographic changes following teriparatide treatment in KD patients with severe osteoporosis; (ii) evaluate whether a correlation exists between the vertebral collapse and the changes in intravertebral bone formation and bone turnover biomarkers (BTMs); (iii) raise awareness of the progressive vertebral collapse and attach importance to the earlier treatment following the KD diagnosis; (iv) provide the clinician with practical experiences of teriparatide therapy for KD.

**Materials and Methods**

**Inclusion Criteria**

The inclusion criteria were as follows: (i) postmenopausal female patients aged 60–90 years; (ii) single-level KD patients; (iii) severe osteoporosis; (iv) underwent...
conservative treatment with teriparatide or alendronate for a minimum of 3 months.

**Exclusion Criteria**
The exclusion criteria were as follows: (i) a history of spinal surgery; (ii) diseases affecting bone metabolism other than osteoporosis; (iii) period of follow-up less than 6 months; (iv) receiving anti-osteoporosis therapy before OVCF.

**Patients**
From March 2013 to December 2020, the medical records for KD patients with severe postmenopausal osteoporosis in Tianjin Medical University General Hospital were retrospectively reviewed. The IVC was a widely accepted radiological sign for the KD diagnosis\(^22, 23\), in which fluid collection was detectable as a hyperintensity on T2-weighted and fat-suppressed sequence MR images, or gas collection was detectable on computed tomography (CT) images (Fig. 1). After applying the inclusion and exclusion criteria, a total of 53 patients were chosen to be analyzed in this study, including 25 patients in teriparatide group with a mean age 73.72 years (64–84 years) and 28 in alendronate group with a mean age 72.50 years (66–87 years). The precipitating events leading to KD were fall in 18 patients (72%) and lift of a heavy object in seven patients (28%) in teriparatide group, and fall in 21 patients (75%) and lift of a heavy object in seven patients (25%) in alendronate group. The fractured thoracic and lumbar vertebrae were 23 and 2 in teriparatide group, 25 and 3 in alendronate group, respectively (Table 1).

**Treatment**
Patients in teriparatide group received daily teriparatide 20 μg given by subcutaneous injection in the morning\(^24\), with average treatment duration of 10.76 months (7–13 months). Patients in alendronate group refused teriparatide treatment and were orally administered with alendronate 70 mg once a week with average treatment duration of 10.64 months (7–13 months). All patients received daily supplements of calcium (1200 mg) and vitamin D (400–800 IU) immediately after KD diagnosis. The mean period of follow-up was 14.04 months (12–16 months) in teriparatide group and 14.36 months (12–16 months) in alendronate group (Table 1).

The study was approved by the responsible institutional review boards in Tianjin Medical University General Hospital. All participants provided written informed consent.

**Outcome Measures**

**Intravertebral Mineralized Bone Formation Evaluation**
CT images were the principal radiology method for assessing the formation of intravertebral mineralized bone in the fractured vertebral body. A helical 64-channel CT scanner was used on all subjects with the parameters including a slice thickness of 0.6 mm with a 0.52 mm interval, a tube voltage of 120 kVp, a tube current of 300 mA and 0.8 s for exposure time per rotation. Bone windows were used to view the CT images series for all fractured vertebral bodies. Sagittal CT image was analyzed by ImageJ (Wayne Rasb and National Institutes of Health, USA, Java 1.8.0_112 [64-bit], https://imagej.nih.gov/ij/) by placing a single click-and-drag region of interest (ROI) on the outline of the fractured vertebrae, as shown in Figs 2–4. Within the ROI, the ratio of the area of intravertebral mineralized bone (AIMB) with 300–1000 Hounsfield units (HU) to the area of fractured vertebral body (AFVB) was calculated on midsagittal CT images for each patient. The changes in the ratio of AIMB to AFVB was used to assess the intravertebral bone formation from baseline to month 12 following treatment. The formation of bone bridge was also observed on sagittal CT images, which crossed the IVC and connected the upper and lower endplates.

**Vertebral Collapse Assessment**
The progressive vertebral collapse was defined as the increment of kyphosis angle (KA) \(\geq 10^\circ\) or the loss rate of vertebral height \(\geq 15\%\)\(^21\). The KA referred to the angle between the superior and inferior endplate line of the fractured vertebral body. The KA, anterior border heights (ABH), and posterior border heights (PBH) of the fractured vertebral body were measured on a lateral radiograph. The spinal canal was narrowed.

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**Fig. 1** Illustrating the KD diagnosis. The hyperintensity detected on sagittal T2-weighted MR images (A) and fat-suppressed sequence (B) within T12 for an 84-year-old patient or the gas-containing cleft detected on the CT scan (C) with T10 for a 69-year-old patient demonstrates the formation of intravertebral vacuum cleft (arrows), indicating KD. **KD** Kümmell’s disease.
The sagittal CT images, analyzed by ImageJ. The sagittal CT image at baseline (A) and month 12 (B) for a 69-year-old patient with T12 KD in the teriparatide group (upper panels). The ratio of AIMB (red color area) to AFVB (yellow line area) increased from 39% at baseline (C) to 63% at month 12 (D), indicating increased bone formation. The bone bridge (arrow) is also detected at month 12. The sagittal CT image at baseline (E) and month 12 (F) for a 76-year-old patient with T12 KD in the alendronate group (lower panels). The ratio of AIMB to AFVB increased from 41% at baseline (G) to 47% at month 12 (H). AIMB area of intravertebral mineralized bone, AFVB area of fractured vertebral body.

Fig. 2

The sagittal CT images, analyzed by ImageJ. The sagittal CT image at baseline (A) and month 12 (B) for a 80-year-old patient with T11 KD in teriparatide group (upper panels). The ratio of AIMB (red color area) to AFVB (yellow line area) increased from 35% at baseline (C) to 81% at month 12 (D), indicating increased bone formation. The bone bridge (arrow) is also detected at month 12. The sagittal CT image at baseline (E) and month 12 (F) for a 73-year-old patient with L1 KD in the alendronate group (lower panels). The ratio of AIMB to AFVB increased from 26% at baseline (G) to 42% at month 12 (H). AIMB area of intravertebral mineralized bone, AFVB area of fractured vertebral body.

Fig. 3

TABLE 1 Demographic data

|                               | Teriparatide group (n = 25) | Alendronate group (n = 28) | P value |
|-------------------------------|----------------------------|-----------------------------|---------|
| Age (years)                   | 73.72 ± 6.35               | 72.50 ± 5.82                | 0.469   |
| <75/≥75                       | 10/14                      | 14/15                       | —       |
| BMI (kg/m²)                   | 23.12 ± 2.17               | 22.43 ± 1.67                | 0.196   |
| <24/≥24                       | 16/9                       | 20/8                        | —       |
| Alcohol                       | 4                          | 4                           | 0.865   |
| Diabetes                      | 2                          | 5                           | 0.299   |
| Steroid use                   | 3                          | 4                           | 0.811   |
| Precipitating events (fall/lift of a heavy object) | 18/7 | 21/7 | 0.809 |
| Fractured site (thoracic/lumbar) | 23/2 | 25/3 | 0.908 |
| Average period from fracture to initial treatment (months) | 9.16 ± 3.90 | 9.39 ± 3.76 | 0.826 |
| Treatment period (months)     | 10.76 ± 1.64               | 10.64 ± 1.77                | 0.804   |
| Follow-up period (months)     | 14.04 ± 1.21               | 14.36 ± 1.28                | 0.360   |

AIMB area of intravertebral mineralized bone, AFVB area of fractured vertebral body.
diameter (SCD) of the fractured vertebra was measured on axial MR images. The loss rate of ABH or PBH (%) was calculated with the following formula:

\[
\text{Height loss rate} = \frac{\text{Height at baseline} - \text{Height at month 12}}{\text{(Lower vertebral height} + \text{Upper vertebral height})/2} \times 100\%
\]

All the collected radiological data of the fractured vertebrae, including KA, ABH, PBH, and SCD, were measured and analyzed to evaluate the therapeutic effect. The radiological parameters were assessed at baseline and month 12 after the intervention.

### BTMs Assessment

The serum concentrations of BTMs, including N-terminal propeptide of type I collagen (PINP) and \(\beta\)-C-telopeptide of type I collagen (\(\beta\)-CTx), were measured as biomarkers of bone formation and bone resorption, respectively. Serum concentrations of BTMs were measured using electrochemiluminescence measurement techniques with a fully automated system (Cobas® e 411 immunoanalyzer, Roche Diagnostics Corp., Indianapolis, IN, USA) and were reviewed at baseline, month 6 and 12 following treatment.

### BMD Assessment

BMD is considered a major determinant of bone strength. The BMD at L3–L4 was measured using dual energy X-ray absorptiometry (DXA) scan (SONOST-3000; OsteoSys Co., Ltd., Seoul, Korea) at baseline, month 6 and 12 following treatment.

The outcome measures were assessed at baseline and month 12. All data collection and analysis were performed by two experienced orthopaedic surgeons to guarantee data reliability and minimize deviations as much as possible.

### Power Calculation

Based on our pilot experiment, we assumed normal distribution and the height loss of ABH SD of 0.15. With a two-sided \(\alpha = 0.05\), a minimum of sample size of 21 patients in each group gave a power of 0.8 to detect a mean difference of 0.15 in the loss of ABH.

### Statistical Analysis

We reported the results in terms of mean ± standard deviation (mean ± SD). For the differences of quantitative variables between the two groups, an independent samples \(t\)-test was performed for the normality parameters and a Mann–Whitney \(U\) test for non-normality parameters. For the intragroup differences of quantitative variables, a paired \(t\) test was performed for the normality parameters and a Wilcoxon sign rank test for non-normality parameters. A subgroup analysis was performed using Cochran–Mantel–Haenszel analysis to identify whether age, BMI and fractured vertebrae as potentially confounding factors affect the therapeutic effect. In addition, Pearson’s correlation analysis was performed for the normality parameters and Spearman’s correlation analysis for non-normality parameters to evaluate associations between changes in KA and vertebral height and changes in BTMs and BMD. The collected data were computed by IBM SPSS Statistics for Windows, Version 21 (SPSS Inc., Chicago, IL, USA). \(P < 0.05\) was accepted for statistical significance.

### Results

#### Demographic Data

No statistically significant differences in demographic data were found between the two groups (all \(P > 0.05\) (Table 1).
Intravertebral Mineralized Bone Formation

The ratio of AIMG to AFVB was similar between the teriparatide group (29.80% ± 10.91%) and the alendronate group (28.14% ± 12.81%) at baseline (P = 0.682). At month 12, the ratio was significantly greater in the teriparatide group (54.28% ± 15.30%) than in the alendronate group (35.57% ± 17.61%) (P < 0.001). The increment in the ratio from baseline to month 12 was (24.48% ± 20.46%) in the teriparatide group and (7.43% ± 7.42%) in the alendronate group (P < 0.001) (Table 2). By the end of follow-up, sagittal CT substantiated the formation of bone bridge in 16 patients in the teriparatide group, however, no bone bridge was detected in the alendronate group. Typical cases were shown in Figs 2–4.

Vertebral Collapse

KA

The KA was similar between the teriparatide group (11.98° ± 3.38°) and the alendronate group (11.07° ± 4.04°) at baseline (P = 0.380), but was significantly smaller in the teriparatide group (15.97° ± 3.59°) than in the alendronate group (22.50° ± 3.80°) at month 12 (P < 0.001). Although there was increased KA in both groups (P < 0.001 for both), the KA increment was 3.98° ± 1.30° in the teriparatide group and 11.43° ± 3.73° in the alendronate group, respectively (P < 0.001 for both) (Table 3 and Fig. 5).

ABH and PBH

The ABH in the teriparatide group (1.49 ± 0.34 cm) and the alendronate group (1.57 ± 0.30 cm) did not differ significantly at baseline (P = 0.336), but was significantly greater in the teriparatide group (1.21 ± 0.32 cm) than in the alendronate group (0.70 ± 0.22 cm) at month 12 (P < 0.001). Although significantly decreased in ABH in both groups from baseline to month 12 (both P < 0.001), the ABH decrement was 11.96% ± 1.93% in the teriparatide group and 37.04% ± 8.00% in the alendronate group, respectively (P < 0.001) (Table 3 and Fig. 5).

The PBH in the teriparatide group (2.30 ± 0.26 cm) and the alendronate group (2.32 ± 0.27 cm) did not differ significantly at baseline (P = 0.765). At month 12, significant differences in PBH were found in the teriparatide group (2.23 ± 0.25 cm) and in the alendronate group (1.86 ± 0.20 cm), respectively (P < 0.001). Although there was a significant decrease in PBH in both groups from baseline to month 12 (both P < 0.001), the PBH decrement was 2.80% ± 2.52% in the teriparatide group and 19.50% ± 8.22% in the alendronate group, respectively (P < 0.001) (Table 3 and Fig. 5).

SCD

The SCD was similar between the teriparatide group (13.64 ± 2.11 mm) and the alendronate group (14.59 ± 1.50 mm) at baseline (P = 0.142). Significant differences in SCD were found between the teriparatide group (13.61 ± 2.10 mm) and the alendronate group (9.04 ± 2.10 mm) at month 12 (P < 0.001). The SCD in the alendronate group significantly decreased from baseline to month 12 (P < 0.001), however, no significant differences were found in SCD in the teriparatide group from baseline to month 12 (P = 0.06). The SCD decrement was 0.04 ± 0.07 mm in the teriparatide group and 5.55 ± 2.54 mm in the alendronate group (P < 0.001) (Table 3).

Bone Turnover Biomarkers

The PINP was similar between the teriparatide group (47.40 ± 5.05 µg/L) and the alendronate group (46.89 ± 5.35 µg/L) at baseline (P = 0.80). However, the PINP was significantly higher in the teriparatide group (146.08 ± 9.39 µg/L) than in the alendronate group (15.64 ± 2.21 µg/L) at month 6 (P < 0.001), and significantly higher in the teriparatide group (107.76 ± 7.01 µg/L) than in the alendronate group (18.04 ± 2.89 µg/L) at month 12 (P < 0.001). The β-CTx was similar between the teriparatide group (0.45 ± 0.02 ng/mL) and the alendronate group (0.46 ± 0.02 ng/mL) at baseline (P = 0.38). However, the β-CTx was significantly higher in the teriparatide group (0.75 ± 0.03 ng/mL) than in the alendronate group (0.10 ± 0.02 ng/mL) at month 6 (P < 0.001), and significantly higher in the teriparatide group (0.63 ± 0.03 ng/mL) than in the alendronate group (0.12 ± 0.01 ng/mL) at month 12 (P < 0.001) (Table 4).

In the teriparatide group, PINP increased significantly from baseline (47.40 ± 5.05 µg/L) to month 6 (146.08 ± 9.39 µg/L) (P < 0.001) and decreased significantly from month 6 to month 12 (107.76 ± 7.01 µg/L) (P < 0.001). The changes in PINP from baseline to month 12 was 128.48% ± 14.31%. β-CTx increased significantly from baseline (0.45 ± 0.02 ng/mL) to month 6 (0.75 ± 0.03 ng/mL) (P < 0.001) and decreased significantly from month 6 to

| Table 2 The Comparisons of the Changes in Intravertebral Mineralized Bone Formation Between Groups (mean ± SD) |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| AIMG/AFVB (%) | Baseline | Month 12 | Increment (%) |
|----------------|-----------|-----------|---------------|
| Teriparatide group | 29.80 ± 10.91 | 54.28 ± 15.30 | 24.48 ± 20.46 |
| Alendronate group | 28.14 ± 12.81 | 35.57 ± 17.61 | 7.43 ± 7.42 |
| P value | P = 0.682 | P < 0.001 | P < 0.001 |

AIMB, the area of intravertebral mineralized bone, AFVB, the area of fractured vertebral body.
The changes in β-CTX from baseline to month 12 was 38.40% /C6 4.11%.

In the alendronate group, PINP decreased significantly from baseline (46.89 /C6 5.35 μg/L) to month 6 (15.64 /C6 2.21 μg/L) (P < 0.001) and increased significantly from month 6 to month 12 (18.04 /C6 2.89 μg/L) (P < 0.001). The changes in PINP from baseline to month 12 was −61.64% /C6 3.31%.

β-CTX decreased significantly from baseline (0.46 /C6 0.02 ng/mL) to month 6 (0.10 /C6 0.02 ng/mL) (P < 0.001) and increased significantly from month 6 to month 12 (0.12 /C6 0.01 ng/mL) (P < 0.001). The changes in β-CTX from baseline to month 12 was −73.18% /C6 2.74%.

**BMD**

The BMD was similar between the teriparatide group (0.65 /C6 0.02 g/cm²) and the alendronate group (0.65 /C6 0.02 g/cm²).
g/cm²) at baseline (P = 0.16) but was significantly higher in the teriparatide group (0.72 ± 0.01 g/cm²) than in the alendronate group (0.69 ± 0.02 g/cm²) at month 12 (P < 0.001). The mean values of BMD increased significantly from baseline (0.65 ± 0.02 g/cm²) to month 12 (0.72 ± 0.01 g/cm²) in the teriparatide group (P < 0.001), and increased significantly from baseline (0.65 ± 0.02 g/cm²) to month 12 (0.69 ± 0.02 g/cm²) in the alendronate group (P < 0.001) (Table 4).

**Subgroup Analysis for the Assessment of Efficacy**

Subgroup analysis performed using Cochran–Mantel–Haenszel analysis demonstrated that the efficacy on the prevention of vertebral collapse was not affected by such potential confounding factors as age (χ² = 44.11, P < 0.001), BMI (χ² = 47.17, P < 0.001), or fracture site (χ² = 46.97, P < 0.001) at the end of follow-up.

**Correlations Between Changes in KA and Changes in BTMs and Intravertebral Bone Formation**

**KA Increment and the Changes in BTMs**

From baseline to month 12, significant negative correlations between the KA increment (3.98° ± 1.30°) and the changes in PINP (128.48% ± 14.31%) from baseline to month 12 (r = −0.781, P < 0.001) were observed in the teriparatide group. However, no significant correlations were observed between the KA increment and the changes in β-CTx (38.40% ± 4.11%) in the teriparatide group (both P > 0.05).

In the alendronate group, however, no significant correlations were observed between the KA increment (11.43° ± 3.73°) and changes in the ratio of AIMB to AFVB (7.43 % ± 7.42%) from baseline to month 12 (P = 0.092).

**Correlations Between Changes in ABH and PBH and Changes in BTMs and Intravertebral Bone Formation**

**ABH and PBH Increment and the Changes in BTMs**

In teriparatide group, significant negative correlations between ABH decrement (11.96% ± 1.93%) and the changes in PINP (128.48% ± 14.31%) from baseline to month 12 (r = −0.612, P = 0.001) were observed. There were no significant correlations between ABH decrement and the changes in β-CTx (38.40% ± 4.11%) from baseline to month 12 (P = 0.175) were observed. There were no significant correlations between PBH decrement (0.06% ± 0.06%) and the changes in PINP or β-CTx from baseline to month 12 in the teriparatide group (both P > 0.05).

In the alendronate group, no significant correlations between the decrement of ABH (37.04% ± 8.00%) and PBH (19.50% ± 8.22%) and the changes in PINP (−61.64% ± 3.31%) or β-CTx (−73.18% ± 2.74%) from baseline to month 12 (all P > 0.05).

**ABH and PBH Increment and the Changes in Intravertebral Bone Formation**

In the teriparatide group, significant negative correlations between the ABH decrement (11.96% ± 1.93%) and the changes in the ratio of AIMB to AFVB (24.48% ± 20.46%) were observed from baseline to month 12 (r = −0.806, P < 0.001) (Fig. 6). However, no significant correlations were found between PBH decrement (2.80% ± 2.52%) and the changes in the ratio of AIMB to AFVB from baseline to month 12 (P = 0.294).

There were no significant correlations between the decrement of ABH (37.04% ± 8.00%) and PBH (19.50% ± 8.22%) and the changes in the ratio of AIMB to AFVB (7.43 % ± 7.42%) in the alendronate group from baseline to month 12.

**TABLE 4 Comparisons of Changes in BTMs and BMD (mean ± SD)**

|                      | Teriparatide group | Alendronate group |
|----------------------|--------------------|-------------------|
|                      | Baseline | Month 6 | Month 12 | Baseline | Month 6 | Month 12 |
| PINP (μg/L)          | 47.40 ± 5.05 | 146.08 ± 9.39*  | 107.76 ± 7.01* | 46.89 ± 5.35 | 15.64 ± 2.21 | 18.04 ± 2.89 |
| β-CTx (ng/mL)        | 0.45 ± 0.02 | 0.75 ± 0.03*  | 0.63 ± 0.03*  | 0.46 ± 0.02 | 0.10 ± 0.02  | 0.12 ± 0.01  |
| BMD (g/cm²)          | 0.65 ± 0.02 | —       | 0.72 ± 0.01* | 0.65 ± 0.02 | —       | 0.69 ± 0.02  |

BMD, bone mineral density, PINP, N-terminal propeptide of type I collagen, β-CTx, β-C-telopeptide of type I collagen. * Means difference between groups was significant (P < 0.001).
Discussion

In this study, the ratio of AIMB to AFVB and the changes in radiological parameters, BTMs and BMD of the fractured vertebra were examined following treatment. The ratio of AIMB to AFVB substantiating the bone formation was higher in the teriparatide group than in the alendronate group. The KA was significantly smaller in the teriparatide group than in the alendronate group. The radiological parameters with respect to ABH, PBH, and SCD were better in the teriparatide group than in the alendronate group. By the end of follow-up, sagittal CT substantiated the formation of bone bridge in 16 patients in the teriparatide group; however, no bone bridge was detected in the alendronate group. The BTMs, including PINP and β-CTX, and BMD were significantly higher in the teriparatide group than in the alendronate group. Although there was an increase in KA and a loss of ABH and PBH in both groups, the increment of KA was 3.98° ± 1.30° in the teriparatide group and 11.43° ± 3.73° in the alendronate group, and the decrement in ABH and PBH was 11.96% ± 1.93% and 2.80% ± 2.52% in the teriparatide group and 37.04% ± 8.00% and 19.50% ± 8.22% in the alendronate group. Besides, we found strong negative correlations between the changes in PINP and the ratio of AIMB to AFVB and the changes in KA and ABH in the teriparatide group, but not in the alendronate group. All the results support that conservative treatment with teriparatide could enhance vertebral strength by boosting the intravertebral bone formation to effectively prevent progressive vertebral collapse in KD patients.

Challenging for Traditional Treatment

Because of the rarity of this condition and the paucity of literature, specific treatment protocols are limited. Traditional nonoperative treatment including pain management with analgesic drugs, bed rest, and bracing may lead to progressive collapse. More recent surgical intervention is favored to correct the kyphotic deformity and restore spinal alignment. However, open surgery such as either anterior or posterior decompression and fusion can have severe consequences in elderly patients with comorbidities. VAP seems to be a promising method to maintain the vertebral height to prevent progressive vertebral collapse. However, controversies on its benefits for KD remain for lacking high- to moderate-quality randomized controlled trials (RCTs).

Advantage of Teriparatide for Mineralized Bone Formation

In our study, intravertebral mineralized bone formation was assessed by the ratio of AIMB to AFVB. The higher ratio indicates the more formation of new bone within the fractured vertebral body, indicating the increased compressive strength. The significantly increased ratio in the teriparatide group was related to more formation of mineralized bone than in the alendronate group. In addition, the bone bridge was detected on sagittal CT images in most patients in the teriparatide group. All the changes indicated teriparatide treatment effectively boosted the intravertebral bone formation.

BTMs are a non-invasive and reliable way to monitor bone turnover during anti-osteoporosis treatment. A 30%--
70% reduction in bone resorption markers is related to antiresorptive therapy, and 30%–50% increase in bone formation markers to anabolic therapy\(^{31}\). The changes in BTMs indicating teriparatide was more effective in improving bone turnover during anti-osteoporosis treatment than alendronate therapy in our study.

**Prevention of Progressive Vertebral Collapse**
The improved cancellous bone structure following teriparatide treatment was related to the preventive effect on progressive vertebral collapse in OVCF\(^{19, 32}\). Until recently, there have been few safe and effective conservative treatments regarding the prevention of progressive vertebral collapse in KD. Fabbriciani et al.\(^{33}\) had reported one case of KD treated with teriparatide. The bone anabolic agent may be considered a valid treatment to boost bone formation and enhance vertebral strength to prevent vertebral collapse. In our study, both the intravertebral mineralized bone formation evaluated by CT images, the BTMs, and improved BMD indicated the improved cancellous bone structure following teriparatide treatment. Ha et al.\(^{21}\) defined the vertebral collapse as KA increment $\geq 10^\circ$ or loss of vertebral height decrement $\geq 15\%$. Although there was decreased ABH and PBH and increased KA detected in both groups in this study, these parameters were significantly better in the teriparatide group than in the alendronate group. By the end of the follow-up, the ABH and PBH decrement (11.96% and 2.80%) was less than 15%, and the mean KA increment $\geq 10^\circ$ was less than 10$^\circ$ following teriparatide treatment. All the results mentioned above indicated that vertebral collapse was effectively prevented following teriparatide treatment, even after the subgroup analysis performed to control the potential confounders such as age, BMI, and fractured vertebrae.

When the posterior wall of the vertebral body is broken due to progressive collapse, the retropulsed bone fragment from the fractured posterior wall may lead to secondary spinal stenosis\(^{34, 35}\). Our previous trial has confirmed the effect of teriparatide on preventing the aggravation of spinal cord dysfunction by restoring the vertebral strength and stability in patients with unstable OVCF\(^{20}\). In our study, the SCD was significantly greater in teriparatide group than in alendronate group by the end of follow-up. The secondary spinal stenosis was effectively prevented following teriparatide treatment by preventing the vertebral collapse to keep the posterior wall intact.

**Correlation of Increased Bone Formation and Vertebral Collapse**
The increased PINP and ratio of AIMB to AFVB are consistent with vertebral strength following teriparatide treatment in postmenopausal osteoporosis patients\(^{17, 18, 35}\). The increased ratio of AIMB to AFVB following teriparatide administration was better than alendronate treatment in our study. Compared with alendronate treatment, the increased ratio of AIMB to AFVB gives an indication for greater strength of the fractured vertebrae following teriparatide treatment. Besides, significant negative correlations between the changes in PINP and ratio of AIMB to AFVB and changes in KA and ABH were observed in teriparatide group. The improved vertebral strength related to the improved ratio of AIMB to AFVB following teriparatide therapy could exert the effects in preventing aggravation of vertebral collapse.

**Limitations**
Some limitations should be addressed in our retrospective investigation. First, the authors confirmed the preventive effects of teriparatide on the progressive vertebral collapse in KD patients with severe osteoporosis. However, the loss of vertebral height and increase of kyphotic angle could not entirely prevent this collapse. Studies on influence factors are necessary for analysis. Second, subjective clinical symptoms were not analyzed in this study. Such objective data as imaging and laboratory tests were analyzed to decrease the weakness of our investigation. Thirdly, this study focused on postmenopausal KD patients. Further studies need to be performed to evaluate the efficacy in male patients. Lastly, long-term follow-up with a large number of patients is needed to validate the positive effects of teriparatide in conservative treatments of KD patients.

**Conclusions**
In postmenopausal single-level Kümmell’s disease patients, conservative treatment with teriparatide could effectively prevent the progressive vertebral collapse by boosting the intravertebral bone formation to enhance the vertebral strength.

**Authors’ Contributions**
Yuan Xue and Feng Chang conceived and designed the study and helped to draft the manuscript. Lin-hui Ren, Xiao-yun Wang, Yu-feng Mu, and Yun-guo Wang performed the experiments. Peng-guo Gou, Zhi-hui Zhao, and Jia-ming Zhou performed the data analyses and wrote the manuscript. All authors read and approved the final manuscript.

**Disclosure Statement**

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**Conflicts of Interest**
All the authors declare that they have no conflict of interest.

**Ethics Approval**
All procedures performed in studies involving human participants were in accordance with the ethical standards of the responsible institutional review boards and with the ethical standards of the Declaration of Helsinki.
Consent to Participate

Informed consent was obtained from all individual participants included in the study.

Consent for Publication

The authors declare the consent for publication.