



# Effects of Teriparatide on Treatment Outcomes in Osteoporotic Hip and Pelvic Bone Fractures: Meta-analysis and Systematic Review of Randomized Controlled Trials

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The primary objective of this study was to evaluate randomized controlled trials (RCTs) that have reported the effects of teriparatide on bone-healing in osteoporotic hip and pelvic bone fractures to determine the efficacy of teriparatide in lowering the rate of treatment failure. A total of 2,809 studies were identified using a comprehensive literature search (MEDLINE [n=1,061], Embase [n=1,395], and Cochrane Library n=353). Five RCTs were included in the final analysis. Treatment failure rates at the last follow-up of osteoporotic hip and pelvic bone fractures between the teriparatide and control groups was the primary outcome. Treatment failure was defined as non-union, varus collapse of the proximal fragment, perforation of the lag screw, and any revision in cases due to mechanical failure of the implant during the follow-up period. The number of treatment failures in the teriparatide and placebo groups were 11.0% (n=20 out of 181) and 17.6% (n=36 out of 205), respectively. Although the rate of treatment failure in the teriparatide group was lower than that in the control group, this difference was not significant (odds ratio, 0.81 [95% confidence interval, 0.42-1.53]; P=0.16; F=42%). This meta-analysis did not identify any significant differences in the rate of treatment failure between the teriparatide and control groups at final follow-up. Based on these results, we believe that there is a lack of evidence to confirm efficacy of teriparatide in reducing treatment failures in osteoporotic hip and pelvic bone fractures.

**Key Words:** Teriparatide, Parathyroid hormone, Hip fractures, Pelvic bone fracture, Osteoporosis

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## INTRODUCTION

With an increase in the incidence of osteoporotic fractures owing to the growing elderly population, teriparatide (a form of human parathyroid hormone) is being widely prescribed by many orthopedic surgeons for the treatment of osteoporosis<sup>1,2)</sup>. The intermittent administration of human parathyroid hormone, including teriparatide, promotes bone formation, owing to the anabolic window created by the difference in the levels of bone formation and bone resorption markers, which can improve mineral content, density, and bone strength<sup>3-6)</sup>. Teriparatide was the only United States Food and Drug Administration (FDA)-approved anabolic therapeutic option indicated in the management of osteoporosis until the recent availability of the FDA-approved romosozumab<sup>7-9)</sup>. The theoretical advantages of teriparatide in bone formation led many orthopedic surgeons to expect that it might have a positive effect on bone healing after fracture or fracture surgery.

Bone healing is accelerated upon treatment with the parathyroid hormone in animal models<sup>10-12)</sup>. Some studies also report the bone-healing potential of teriparatide, when used in human subjects who have vertebral or lower limb fractures<sup>13-17)</sup>. However, recently published results from randomized controlled trials (RCTs) have questioned the efficacy of teriparatide on bone healing, contrary to the available data<sup>18-20)</sup>. Furthermore, there are debates over the appropriateness of using teriparatide to promote bone healing after fractures, owing to a lack of evidence confirming its ability to improve fracture healing<sup>13,21,22)</sup>.

Osteoporotic hip and pelvic bone fractures are common in the elderly and are responsible for high mortality rates owing to post-fracture immobilization<sup>23,24)</sup>. Although substantial evidence indicating that teriparatide efficaciously improves bone healing is required to determine the most appropriate treatment strategy for reducing post-fracture mortality by improving bone healing and early mobilization, relatively few meta-analyses have addressed this topic. We hypothesized that teriparatide would lower the treatment failure rate in osteoporotic hip and pelvic bone fractures. Therefore, the primary objective of this study was to analyze the results of RCTs that have reported the bone-healing effect of teriparatide in osteoporotic hip and pelvic bone fractures to determine the efficacy of teriparatide in reducing treatment failure rates.

## MATERIALS AND METHODS

### 1. Search Strategy

This study was conducted based on the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and the Cochrane review method. To identify studies evaluating the effects of teriparatide on treatment outcomes in osteoporotic hip and pelvic bone fractures, all records until March 2020 in the PubMed, Embase, and Cochrane Library databases were searched by an independent medical librarian. There were no restrictions regarding language, publication year, nationality, or race in the search process. Search terms used in the subject headings, text words, and keywords fields included the following: “teriparatide” [MeSH] OR “human parathyroid hormone” [MeSH] OR “hPTH” [MeSH] OR “Forteo” [MeSH] AND (“hip fracture” [MeSH] OR “femoral neck fracture” [MeSH] OR “intertrochanteric fracture” [TW] OR “subtrochanteric fracture” [TW]). After the initial database screening, two researchers manually searched additional relevant studies. In this meta-analysis, only RCTs were included; non-randomized comparative experimental trials, comparative observational studies, case series, and case reports were excluded. When multiple studies were published by the same author or group of authors on the same subject, only the most recent article was included in this study. Enrolled studies in our meta-analysis were required to comprise at least two treatment arms: a teriparatide group and a placebo injection or no injection group (Fig. 1).

### 2. Inclusion Criteria

Eligibility was determined based on the PICOS criteria (population, intervention, comparator, outcomes, and study design). Population: patients who had an osteoporotic fracture of the hip or pelvis; intervention: patients who used teriparatide injection; comparator: patients who received no injection or a placebo injection (control group); outcomes: radiological assessments for non-union, revision, and implant failure, in which, at least one of the mentioned radiological measurements was employed; study design: two reviewers independently reviewed the titles and abstracts of RCTs and chose relevant studies for a full-text review. The articles to be included in the study were based on reviewers' consensus; there was no disagreement over literature selection between the reviewers.

### 3. Data Extraction and Assessment of Methodological Quality

Using a predefined data extraction form, two reviewers independently extracted the following data from the selected studies: first author, year of publication, study design, sample size, mean age of the patients, mean follow-up duration, diagnoses of hip fractures, fixation instruments used for surgery, treatment failure, and clinical outcome assessments. Two reviewers independently evaluated the methodological quality of each study using the Cochrane risk-of-bias tool for RCTs, documenting their potential for bias in selection, performance, detection, attrition, and reporting. Decisions were based on the reviewers' consensus. Disagreements were resolved by a third reviewer. Publication bias was visually and quantitatively assessed using funnel plots and Egger's regression test, respectively. Publication bias was considered to be absent if the funnel plot was symmetrical and the  $P$ -value was  $>0.05$ .

### 4. Statistical Analysis

Treatment failure at the last follow-up of osteoporotic hip and pelvic bone fractures between the teriparatide and control groups was the primary outcome. Treatment failure included non-union, varus collapse of the proximal fragment, perforation of the lag screw, and any revision owing to mechanical failure of the implant during the follow-up period. The odds ratio (OR) and 95% confidence intervals (CI) were com-

puted for these categorical variables. Heterogeneity was assessed using the  $I^2$  statistic, in which  $I^2=25\%$  was considered low heterogeneity, 50% was considered moderate, and 75% was considered high. When there was no statistical evidence of heterogeneity ( $I^2<50\%$ ,  $P>0.1$ ), a fixed-effects model was adopted; otherwise, a random-effects model was chosen. Forest plots were used to illustrate the results of each study, the pooled estimate of effect, and the overall summary effect. Significance was set at  $P<0.05$ . All statistical analyses were conducted using R software version 3.6.3 (2020; The R Foundation for Statistical Computing, Vienna, Austria).

## RESULTS

### 1. Search Summary and Study-selection Process

The outline of the study-selection process is presented in Fig. 1. A total of 2,809 studies were identified through literature searches of MEDLINE ( $n=1,061$ ), Embase ( $n=1,395$ ), and the Cochrane Library ( $n=353$ ). No additional studies were identified via a manual search and 906 duplicate studies were excluded. After screening the titles and abstracts, 1,880 studies were excluded. After conducting a full-text review of the remaining 23 studies, five studies were included in the final analysis<sup>18-20,25-27</sup>.

The five studies included 181 cases in the teriparatide group and 205 cases in the placebo group (Table 1). The mean follow-up duration ranged from 3-19.5 months. Treatment out-

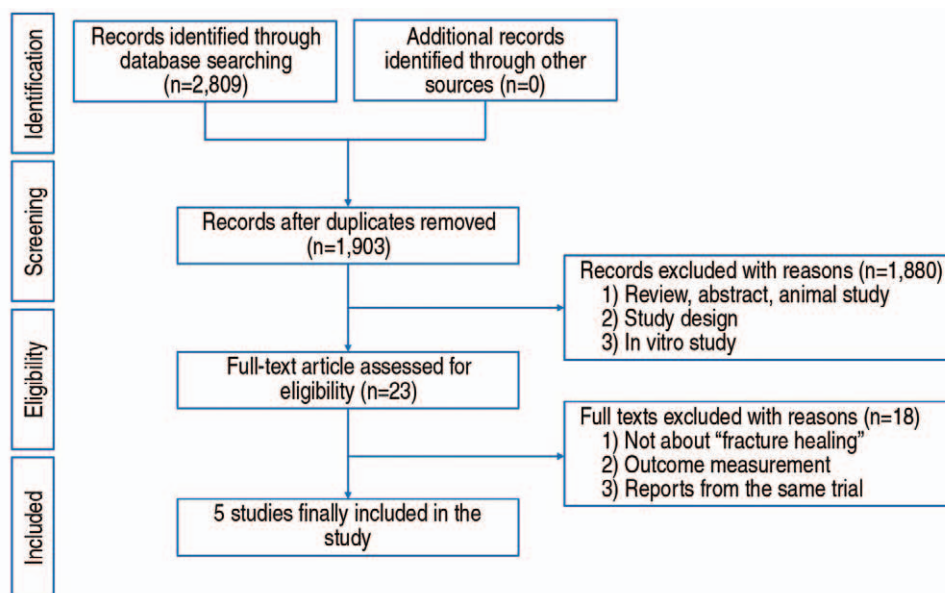


Fig. 1. PRISMA flow diagram.

**Table 1.** Study Characteristics Enrolled in the Present Study

Study (year)	Study design	Country	TP protocol	Follow-up	Age at the surgery (yr)	Cases in TP group (n)	Cases in control group (n)	Type of fracture (n)	Type of fixation (n)	Outcomes assessments
Bhandari et al. <sup>(18)</sup> (2016)	Randomized control study	Canada	Once-daily subcutaneous injection of 20 µg TP and supplemental calcium and vitamin for 6 months	12 months	TP: 70 (50-90), control: 70 (50-94)*	81	78	Femoral neck: 8	Cancellous screw: 143, sliding hip screw 16	Revision surgery at 6 and 12 months
Kanakaris et al. <sup>(21)</sup> (2015)	Randomized control study	United Kingdom	Once-daily subcutaneous injection of 20 µg TP and supplemental calcium and vitamin	6 months	TP: 75±8.98, control: 75±8.85 <sup>+</sup>	09	10	Intracapsular: 8, intertrochanteric: 3, subtrochanteric: 8	DHS: 14, intramedullary nail: 5	JHRQ at 6 weeks and 3 months, non-union at 6 months
Chesser et al. <sup>(20)</sup> (2016)	Randomized control study	United Kingdom	Once-daily subcutaneous injection of 20 µg TP and supplemental calcium and vitamin for 42 days	6 months	TP: 80.6±8.8, control: 78.6±9.3 <sup>+</sup>	12	10	Trochanteric hip fracture: 12	Sliding hip screw: 15, cephalomedullary nail: 4	EQ-5D, SPPD, VAS, and union at 3 months
Aspenberg et al. <sup>(19)</sup> (2016)	Randomized control study	Multi-national	Once-daily subcutaneous injection of 20 µg TP and supplemental calcium and vitamin for 26 weeks	78 weeks	TP: 81±8, control (BP): 82±10 <sup>+</sup>	62	63	Low-trauma pertrochanteric hip fracture (AO/OTA31-A1 or 31-A2): 125	An intra-medullary nail or a sliding compression hip screw	Radiologic healing at 6, 12, and 26 weeks, TUG test, hip pain, and SF-36

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Table 1. Continued

Study (year)	Study design	Country	TP protocol	Follow-up	Age at the surgery (yr)	Cases in TP group (n)	Cases in control group (n)	Type of fracture (n)	Type of fixation (n)	Outcomes assessments
Peichl et al. <sup>26)</sup> (2011)	Randomized control study	Austria	Once-daily subcutaneous treatment with 100 mg of PTH 1-84 and supplemental calcium and vitamin	Minimum follow up of 12 weeks	TP: 82.7±4.6, control (BP): 82.4±3.8 <sup>+</sup>	21	44	Osteoporotic pubic bone fracture: 65	Conservative treatment	Fracture healing, VAS score, TUG test at week 12

TP: teriparatide, PTH: parathyroid hormone, BP: bisphosphonate, DHS: dynamic hip screw, JHRQ: Johanson Hip Rating Questionnaire, EQ-5D: EuroQol 5D, SPPB: Short Physical Performance Battery, VAS: visual analogue score, TUG: Timed Up and Go, SF: short form.  
 \* Values are presented as median (range). † Values are presented as mean ± standard deviation.

comes in these five studies included union rate, revision rate, mechanical failures, clinical scores, and complications. However, as radiological measurements and follow-up time points after surgery were different in each study, we assessed the rate of treatment failure at the last follow-up as the primary outcome.

## 2. Pooled Estimate of the Effect of Postoperative Teriparatide

A comparison of treatment failure rates in patients with osteoporotic hip and pelvic bone fracture between the teriparatide and placebo groups is presented in Table 2. For the analysis of treatment failures at the last follow-up, five studies comprising a total of 386 patients were assessed (teriparatide group n=181; placebo group n=205). Among the five included studies, four showed no significant difference in the rate of treatment failure between the teriparatide and control group; only Peichl et al.<sup>26)</sup> demonstrated a lower rate of treatment failure in the teriparatide group compared with the control group. The total number of treatment failures included 20 out of 181 cases in the teriparatide group (11.0%) and 36 out of 205 cases in the placebo group (17.6%). Although the rate of treatment failure in the teriparatide group was numerically lower than that in the control group, this difference was not significant (OR, 0.81 [95% CI, 0.42-1.53]; *P*=0.16; *I*<sup>2</sup>=42%) (Fig. 2).

## 3. Risk-of-bias Assessment and Publication Bias

Table 3 and Fig. 3 summarize the results of the risk-of-bias assessment of our meta-analysis. Asymmetry of funnel plots was suspected on visual assessment (Fig. 4). However, funnel plot asymmetry is generally considered as significant when more than 10 studies are included in a meta-analysis<sup>28,29)</sup>. As only five studies were included in our meta-analysis, the number of studies was too small to be subjected to the Egger's regression test to conduct statistical analysis for asymmetry.

## DISCUSSION

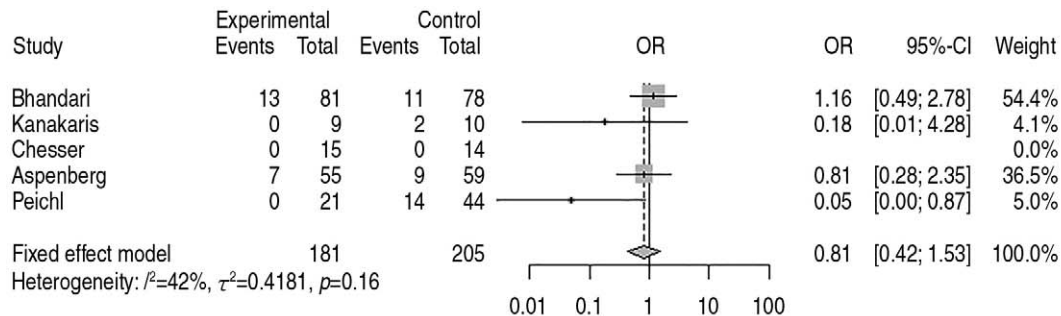
We conducted this meta-analysis of five RCTs, which included 386 patients, to assess the effect of teriparatide on osteoporotic hip and pelvic bone fractures. Our revealed that there was no significant difference in the rates of treatment failure at the final follow-up between the teriparatide and control groups. This result suggested that there is a lack of



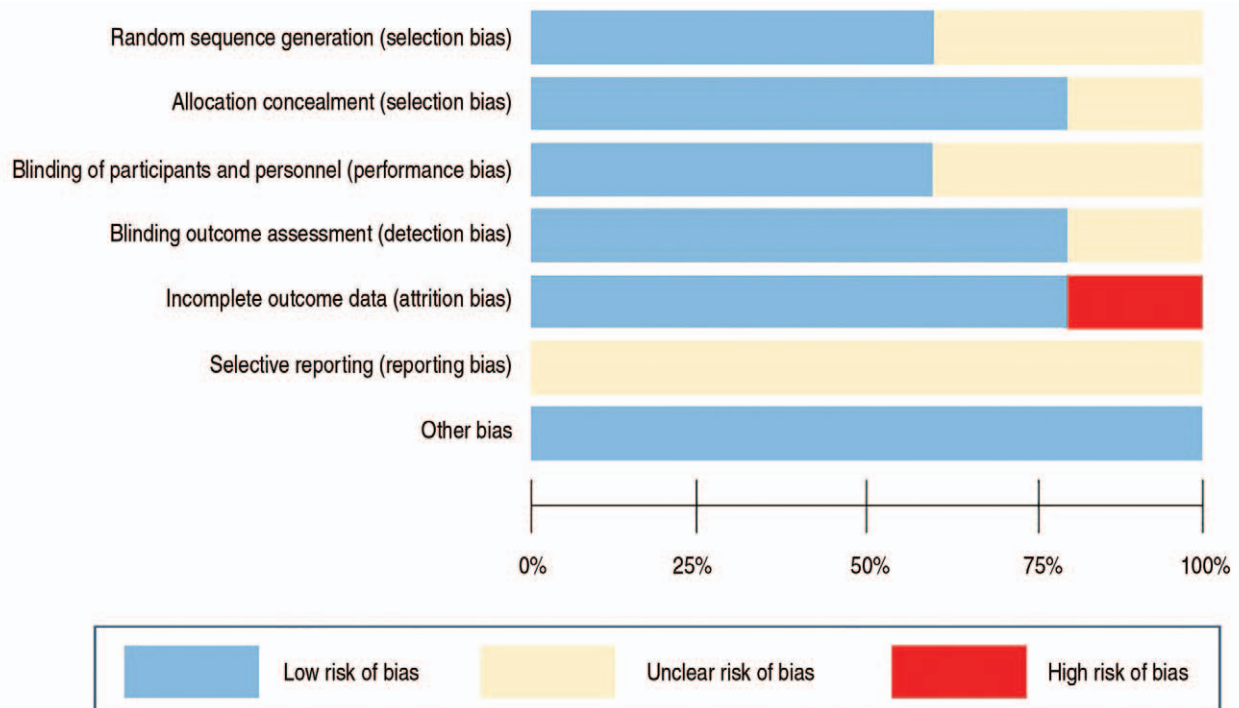
**Table 2.** Comparison of the Treatment Failure in Patients with Osteoporotic Hip and Pubic Bone Fracture between the Teriparatide and Placebo Group

Study (year)	Teriparatide	Placebo	P-value
Bhandari et al. <sup>18)</sup> (2016)	13/81 (16.0)	11/78 (14.1)	0.589
Kanakaris et al. <sup>27)</sup> (2015)	0/9 (0)	2/10 (20.0)	0.314
Chesser et al. <sup>20)</sup> (2016)	0/15 (0)	0/14 (0)	-
Aspenberg et al. <sup>19)</sup> (2016)	7/55 (12.7)	9/59 (15.3)	0.791
Peichl et al. <sup>26)</sup> (2011)	0/21 (0)	14/44 (31.8)	0.004

values are presented as number of treatment failure/total number in the group (%).



**Fig. 2.** Forest plot of the treatment outcomes.  
OR: odds ratio, CI: confidence interval.



**Fig. 3.** Summary of risk of bias in the selected studies.

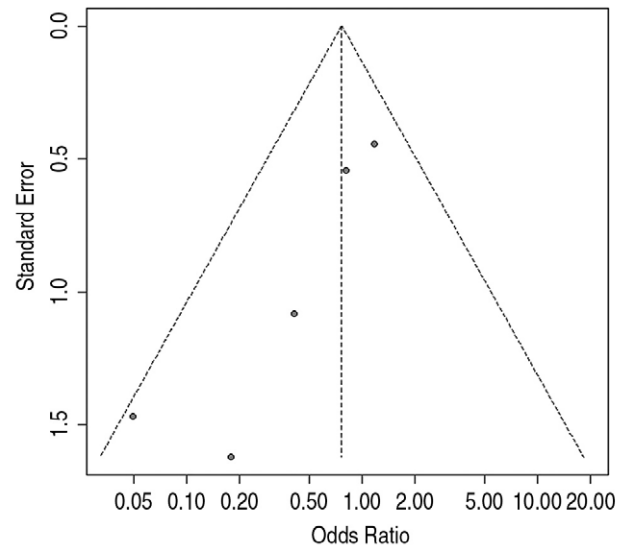
evidence demonstrating efficacy of teriparatide in treating osteoporotic hip and pelvic bone fractures, which was contrary to our hypothesis suggesting the clinical advantage

of teriparatide.

Our study had several strengths. Firstly, our meta-analysis was compliant with the PRISMA guidelines and the recom-

**Table 3.** Results of Risk of Bias for the Selected Studies according to the Recommendations of the Cochrane Collaboration

Study (year)	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Bhandari et al. <sup>18)</sup> (2016)	Unclear	Low	Low	Low	Low	Unclear	Low
Kanakaris et al. <sup>27)</sup> (2015)	Low	Unclear	Low	Low	High	Unclear	Low
Chesser et al. <sup>20)</sup> (2016)	Low	Low	Unclear	Unclear	Low	Unclear	Low
Aspenberg et al. <sup>19)</sup> (2016)	Low	Low	Unclear	Low	Low	Unclear	Low
Peichtl et al. <sup>26)</sup> (2011)	Unclear	Low	Low	Low	Low	Unclear	Low

**Fig. 4.** Funnel plot for the treatment outcomes.

recommendations of the Cochrane Collaboration. Secondly, the heterogeneity of enrolled studies was moderate ( $I^2=0.420$ ). Previously published meta-analyses evaluating the effects of teriparatide on bone healing have included different bones including the humerus, radius, femur, spine, and pelvis, which resulted in a higher heterogeneity than reported here<sup>13,22,30,31</sup>. As the process of bone healing and the effect of teriparatide can vary depending on mechanical stimulation including load-bearing, fracture healing can manifest differently in the upper and lower limbs and give rise to a higher heterogeneity<sup>32,33</sup>. All previous studies indicated this factor as one of the major limitations of their respective studies, and consequently, the conclusions derived are inconsistent among studies. However, our meta-analysis included studies that focused exclusively on osteoporotic hip and pelvic bone fractures which, we believe, resulted in moderate heterogeneity. Thirdly, the hip and pelvic bones in elderly patients are most suitable to evaluate the effects of teriparatide on fracture healing. Osteoporotic hip and pelvic fractures are known to increase mortality owing to immobilization and subsequent medical complications (e.g., aspiration pneumonia, pressure sores, venous thromboembolism)<sup>2,23,24</sup>. Thus, if the efficacy of teriparatide on treatment outcomes was established, this study could have supported the use of teriparatide in the treatment of osteoporotic hip and pelvic bone fractures. Unfortunately, our study did not demonstrate that teriparatide effectively improved treatment outcomes in these fractures. Therefore, this lack of evidence precludes the use of teriparatide to improve treatment outcomes in osteoporotic hip and pelvic bone fractures.

There were a few limitations of this meta-analysis. Firstly, only five RCTs were included, which constitutes a relatively small sample size. Secondly, although we included RCTs involving osteoporotic hip and pelvic bone fractures, these studies also included various other fractures (e.g., femoral neck, intertrochanteric, subtrochanteric, pelvic bone), and their sub-classification could affect reported treatment outcomes. In particular, the study by Peichl et al.<sup>26)</sup> exclusively included patients with pubic bone fractures, thus making it difficult to conclude that the results of the present study are representativeness of osteoporotic pelvic bone fractures. However, there have been no RCTs to date investigating insufficiency fractures of the pelvic bone related to osteoporosis, and we believe that osteoporotic pubic bone fracture is representative of insufficiency fractures of pelvic bone. Furthermore, various fracture-treatment protocols were identified including intramedullary nailing, fixation using a dynamic hip screw or cannulated screw, and conservative treatment, and there could have been additional factors that might have affected treatment outcomes including: treatment-related factors (e.g., surgical techniques, postoperative reduction), and patient-related factors (e.g., bone mineral density, body mass index, extent of preoperative mobility, rehabilitation compliance). Thirdly, each study had different treatment periods for teriparatide therapy and follow-ups. Although teriparatide is known to induce early callus formation after fractures, the long-term bone-healing effect can vary depending on the treatment period, as teriparatide can not only affect the early bone-formation phase, but also the remodeling phase<sup>14,29,32)</sup>. Additionally, some studies have demonstrated that functional improvement depends on the period of teriparatide treatment. Thus, it is important to consider studies with identical treatment periods when comparing clinical outcomes.

Next, this study could not assess other key clinical outcomes. The five studies included in our meta-analysis evaluated varying clinical outcomes that were not consistent across studies (e.g., Harris hip score, short form 12, short form 36, Timed Up and Go test, Johanson Hip Rating Questionnaire), thus making it difficult to comprehensively assess the clinical effect of teriparatide<sup>18,20,25-27,34)</sup>. Mortality after fracture is an important clinical outcome in the elderly with hip and pelvic bone fractures, however, none of the studies included in this meta-analysis evaluated mortality after fractures. In addition, this study did not include any data comparing the safety of teriparatide versus placebo groups. As the number of complications reported in the enrolled studies was not adequate to conduct statistical analysis, and

considering that the side effects related directly to teriparatide were low, it was difficult to include safety data on teriparatide.

Lastly, the radiological outcomes of fracture healing evaluated in this study were limited. As the five studies selected for this meta-analysis included various radiological measurements at different time points and stages of follow-up, it was difficult to conduct a meta-analysis for the fracture-healing effect of teriparatide in the early stages of bone healing, including those after a 6- or 12-week follow-up. This was a major limitation of this study given that teriparatide increases callus formation at an early stage of bone healing. In particular, as the acceleration of bone healing in the early stage of osteoporotic hip and pelvic bone fractures can improve rehabilitation and lower long-term mortality rates, simply because there is no significant difference in treatment outcomes at the last follow-up does not mean that there are no positive effect of teriparatide on osteoporotic hip and pelvic bone fractures. Thus, further studies on the bone-healing effect of teriparatide in the early stages of healing are warranted.

## CONCLUSION

This meta-analysis did not identify any significant differences in treatment failure rates at final follow-up between the teriparatide and control groups. Based on these results, we believe that there is a lack of evidence to suggest that teriparatide improves treatment failure rates in osteoporotic hip and pelvic fractures. However, further studies are needed to determine the efficacy of teriparatide on fracture healing and in improving other clinical outcomes.

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## CONFLICT OF INTEREST

The authors declare that there is no potential conflict of interest relevant to this article.

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