

# GENERAL ORTHOPAEDICS

# Teriparatide in postmenopausal osteoporosis: uncovering novel insights into efficacy and safety compared to other treatments – a systematic review and meta-analysis

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- *Objective:* The aim of the study was to evaluate the efficacy and safety of teriparatide compared to other treatments for postmenopausal osteoporosis.
- Methods: A review of studies from 2000 to January 2023 analyzed randomized controlled trials on postmenopausal women treated with teriparatide (PTH 1–34), comparing it to placebo or other osteoporosis treatments. The analysis focused on bone mineral density (BMD), bone turnover markers, and clinical outcomes, employing Review Manager 5.4.1 and the RoB 2 tool for bias assessment.
- *Results:* Our analysis of 23 randomized controlled trials (RCTs) found that PTH (134) treatment significantly increased lumbar spine BMD (mean difference (MD) = 0.02, 95% CI: 0.01–0.03) and femoral neck BMD (MD = 0.01, 95% CI: 0.00–0.01). However, there were no significant changes in total hip and radial bone BMD among the 3536 and 2046 participants, respectively. We also found that PTH (1–34) increased P1NP in a larger cohort (*n* = 1415) when compared to osteocalcin (*n* = 206). Although the risk of adverse events increased (relative risk (RR) = 1.65, 95% CI: 1.32–2.07), the incidence of fractures decreased significantly (RR = 0.57, 95% CI: 0.45–0.072), with no significant difference observed in mortality rates between treatment and control groups.
- Conclusion: Teriparatide improves lumbar spine and femoral neck BMD in postmenopausal women. Particularly
  notable is the novel finding regarding its effect on radius BMD, an area less explored in previous research.
  Despite an uptick in adverse events, the marked decrease in fracture incidence confirms its clinical utility for
  high-risk osteoporosis patients, highlighting the necessity for ongoing investigations into its full skeletal effects.

Keywords: fractures; parathyroid hormone; postmenopausal osteoporosis; systematic review; teriparatide



# Introduction

Osteoporosis is a critical global health issue, disproportionately affecting postmenopausal women by leading to diminished bone mass, compromised bone strength, and an elevated risk of fractures. The World Health Organization underscores this, noting that approximately 30% of women post menopause have osteoporosis, which underscores the urgent need for efficacious management strategies (1, 2). Postmenopausal Osteoporosis (PMO) primarily results from estrogen deficiency, leading to structural deterioration of bone tissue and an increased susceptibility to fractures. These fractures not only cause pain and deformities but also severe health complications and, in extreme cases, premature mortality (3).

Despite considerable advancements in therapeutic options, fractures remain alarmingly prevalent among those with PMO, particularly in areas rich in trabecular bone like the lumbar spine and femoral neck. Fractures at critical sites, such as the hip, carry significant morbidity and mortality risks (4, 5, 6, 7, 8). The therapeutic landscape for PMO, traditionally divided into antiresorptive and osteoanabolic drugs, has been notably enhanced by teriparatide, a synthetic parathyroid hormone analog recognized for its bone anabolic properties since its approval in 2003 (9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19).

Research has broadly documented teriparatide's impacts on bone mineral density (BMD) and fracture healing across various skeletal sites (3, 6, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48). Nonetheless, the specific effects of teriparatide, particularly on radial BMD, have yet to be thoroughly explored. Although some studies have highlighted teriparatide's potential in enhancing bone density and reducing fracture risks, the concrete evidence, especially from the limited two RCTs focusing on these effects, does not show statistically significant differences between treatment groups. This critical understanding gap emphasizes the need for more targeted research (25, 26, 27, 28, 29, 30, 31, 32, 33, 34).

The systematic review by Metcalf *et al.* investigated the effects of various PTH peptides (1–34 and 1–84) across multiple skeletal sites but was limited by heterogeneity, obscuring the distinct impacts of each peptide form (35). Our study aims to bridge this gap by focusing exclusively on applying PTH 1–34, particularly its effects on the radial bone, hip, and lumbar regions in postmenopausal women. Through this specialized approach, we strive to provide novel insights into PTH 1–34's specific impact on radial BMD, setting our research apart from broader analyses and illuminating the peptide's distinct advantages and challenges.

In pursuing this aim, our study employs a rigorous methodology, systematically reviewing and meta-

analyzing high-quality RCTs. This approach is designed to elucidate the nuanced role of teriparatide in the clinical management of PMO, potentially reshaping therapeutic strategies.

Addressing the complex landscape of PMO management and teriparatide's nuanced applications, this study poses a critical question: How does teriparatide's efficacy and safety in enhancing bone mineral density and reducing fracture incidence, compare with other standard postmenopausal osteoporosis treatments, given its unique anabolic properties?

To address the identified research gap, our study considered several objectives: first, to evaluate teriparatide's impact on BMD at the lumbar spine, femoral neck, and notably, the radial bone, identify site-specific effects, and assess its broader therapeutic potential; secondly, to critically compare teriparatide's efficacy in reducing fracture incidence with that of placebo and other established osteoporosis medications, defining its clinical value for individuals at heightened risk of fractures; and finally, to thoroughly explore teriparatide's safety profile, emphasizing on adverse events, thereby providing a balanced perspective on its therapeutic application.

By addressing these objectives, our study seeks to provide deep insights into teriparatide's efficacy and safety, advance therapeutic strategies for managing postmenopausal osteoporosis, and enrich the knowledge available to the scientific and clinical communities.

## Materials and methods

This systematic review and meta-analysis followed the 2020 PRISMA guidelines (see Supplemental Materials, see section on supplementary materials given at the end of this article) (49). The protocol can be accessed through PROSPERO (see Supplemental Materials).

## Study Design

Quantifying the impact of the parathyroid hormone (PTH 1–34) on postmenopausal osteoporosis is the purpose of this meta-analysis, which includes publications published between 2000 and January 2023. The research plan consisted of the following sections: i) establishing the goals of the study and the criteria for selecting relevant materials; ii) using the stated search terms and search algorithms to search the most pertinent databases for the topic of interest and the pertinent literature; iii) identifying relevant studies by comparing them to predetermined inclusion/exclusion criteria; iv) carefully collecting the necessary information using the data extraction form; v) data input and analysis using Review Manager version, version 2 of Cochrane Collaboration risk-of-bias assessment tool for randomized trials and

Stata 15.0; and finally, vi) developing conclusions and interpretations from the data.

### Search strategy

#### **Inclusion criteria**

Our study adopted a structured approach defining the inclusion criteria, utilizing the PICO framework to ensure a comprehensive and targeted analysis as follows: i) Population: Our focus was on postmenopausal women diagnosed with osteoporosis, aiming to understand the therapeutic impact of teriparatide across this specific demographic. ii) Intervention: The intervention of interest was the administration of single daily injections of teriparatide (PTH 1-34) to the treatment groups. iii) Comparator: Participants in comparator groups received various anti-osteoporosis medications or placebo, including risedronate, zoledronic acid, alendronate, salmon calcitonin, elcatonin, general antiresorptive drugs, placebo, denosumab, abaloparatide, and romosozumab. These comparators were selected to offer a broad perspective on teriparatide's efficacy and safety relative to the standard treatments for postmenopausal osteoporosis. iv) Outcome: The primary outcomes assessed were the incidence of vertebral fractures and changes in BMD at critical anatomical sites (total hip, lumbar spine, radius, and femoral neck). Secondary outcomes included bone turnover markers (P1NP, CTx, and osteocalcin), adverse events, and mortality. v) Study type: Only randomized controlled trials (RCTs) involving postmenopausal women with osteoporosis treated with PTH 1–34, with outcomes as specified above.

## **Exclusion criteria**

The criteria of exclusion were as follows: i) repeated publications; ii) literature unrelated to the study topic; iii) conference summary, reviews, and patents with no detailed data; iv) animal experiments; v) study subjects with non-osteoporotic fractures; or nonvertebral fractures; vi) study subjects with secondary osteoporosis, such as (GIOP, malignant tumor associated bone diseases, bone metastases); vii) study subjects participants with underlying diseases such as autoimmune diseases, inflammatory bowel diseases, malignant tumors, and hypogonadism; viii) non-therapeutic literature or group design; ix) only the abstract but no full-text report; x) literature with inappropriate clinical study design (retrospective clinical trials, non-randomized controlled studies, observational studies, etc.); xi) studies that have participants with less than 6 months of teriparatide treatment; and xii) literature with incomplete data.

## Search strategy

We conducted a comprehensive search for studies about treating postmenopausal osteoporosis with PTH 1–34 using a detailed plan suggested by the Cochrane Collaboration. We looked for articles using specific search terms like 'Parathyroid Hormone', 'Osteoporosis, Postmenopausal', 'Teriparatide', and 'Randomised Controlled Trial' from 2000 to January 2023. The search included databases such as Web of Science, Cochrane Library, Scopus, Embase, and several Chinese databases without limiting language. We carefully checked the full texts and references of the studies we found to gather information on using PTH 1–34 for postmenopausal osteoporosis.

## **Literature selection**

Two separate reviewers checked titles and abstracts to find relevant papers. Subsequently, the full-text articles meeting the inclusion criteria, including adverse events, patient demographics, medications, treatment protocols, duration of follow-up, BMD outcome measures, and adverse event incidence, were accessed for data extraction. When many studies reported the same data, the most thorough data were obtained, and the studies were credited under one research name. A third reviewer was consulted to reach a consensus if the two disagreed. Cochrane standards were used to evaluate included studies to examine selection, detection, attrition, performance, and reporting biases, categorized as low, uncertain, or high risk of bias for quality evaluation.

## **Data extraction**

The studies included have been considered for the extraction of data. This included general data such as the first author of the literature, time, sample size, basic population information fracture site, post-fracture treatment method, and characteristics such as drug intervention method, treatment initiation time, treatment duration, and outcome measures of the test group and control group. Results included fracture rate, BMD change, bone turnover, death, and incidence of adverse events.

## Quality evaluation of study quality

Two authors independently utilized the Cochrane Collaboration risk-of-bias assessment tool for randomized trials, specifically version 2 (RoB 2), to assess the quality of the study. Based on the criteria mentioned above, the studies included in this analysis were categorized as either 'low risk', 'high risk', or 'some concerns'. The potential for bias in the included studies was visually depicted using Review Manager (v5.4.1) and Stata 15.0. Disputes about the adequacy of the studies were resolved via deliberation among the review's authors until a consensus was achieved.

## **Statistical analysis**

Statistical analyses were performed using specialized software designed for systematic reviews, namely Review Manager 5.4.1 (RevMan 5.4) and Stata 15.0. To

analyze count data, like the incidence of adverse events or the fracture rate, we employed odds ratios (ORs) or risk differences (RDs). In the case of continuous data, such as BMD score or bone turnover, the mean difference (MD) was employed. The  $I^2$  index was utilized to quantify the level of heterogeneity, representing the proportion of variation in effect estimates attributed to heterogeneity rather than random chance. An  $I^2$  value exceeding 50% indicated significant heterogeneity. The Peto method for combining effect sizes was used when  $I^2$  was  $\leq$  50%, while the random-effects model DerSimonian–Laird calculation method was used when  $I^2$  was  $\geq$  50%. The publication bias assessment was conducted by utilizing the Egger test. A two-sided *P* value less than 0.05 is considered statistical significance.

## Results

## Identification and selection of studies

In total, 2220 published articles were found through the search, but 1062 duplicate articles were removed. Of the 1158 remaining articles, 1071 were ineligible based on predetermined criteria. Of the remaining 87 full articles, 65 were excluded. In the end, the study evaluated 23 RCTs. No additional studies that met the established inclusion criteria were found by systematically examining the reference lists of the incorporated studies. The PRISMA statement's flowchart (Fig. 1) illustrates the study's screening and selection process. Supplementary Table 1 outlines the key features of these studies (See supplementary material). All studies involved patients randomly assigned to receive at least one daily dose of Teriparatide for at least 6 months.

#### Heterogeneity and publication bias

We used Rob 2 2 (Fig. 2A and B) and the RevMan funnel plot to evaluate publication bias (See supplementary material). The results did not show any clear evidence of publication bias. We also performed Egger's test to assess publication bias. Our analysis showed significant heterogeneity among the studies for continuous variable data. The *I*<sup>2</sup> value was 71.1%, and the estimate of between-study variance was Tau-squared = 0.3042. The OR = 1 test showed a significant difference in ORs across studies. Egger's test revealed a non-statistically significant bias coefficient, indicating that the variations are not due to chance (See supplementary material).

Regarding binary variable data, our findings revealed significant heterogeneity among the studies, with an  $I^2$  value of 99.0%. This suggests that factors other than chance may affect the results, and the estimate of between-study variance was Tau-squared = 7.6244. However, we found no significant difference in effect sizes across studies, indicating that the variations are not due to chance. Egger's test exhibited no clear indication of publication bias.

In conclusion, while no publication bias was found for binary and continuous variable data, significant heterogeneity was present for binary variable data.



#### Figure 1

Literature screening flowchart.

Therefore, it is necessary to exercise caution while interpreting the results of this meta-analysis.

#### **Primary Outcome**

#### Efficacy of teriparatide

**Incidence of vertebral fracture**: An analysis of 11 studies involving 2756 patients was conducted to compare the incidence of fractures in the teriparatide-treated and the control groups. The studies had minimal heterogeneity ( $I^2 = 31\%$ , P = 0.16), indicating a consistent pattern of results, allowing for using a fixed-effects model to synthesize the data.

The synthesized outcomes showed a significant reduction in fracture risk in the teriparatide group compared to the control group, with a –relative risk (RR) of 0.57 and a 95% CI ranging from 0.45 to 0.72. These results were statistically significant (P=0.00001), as shown in Fig. 3. These data confirm that teriparatide, also known as PTH 1–34, effectively reduces the likelihood of fracture events compared to a placebo, emphasizing its efficacy in fracture risk management in orthopedic patient care.

#### BMD

**Total hip BMD result**: After reviewing data from 12 studies with 3536 participants, we investigated the effect of teriparatide (PTH 1–34) injections on total hip BMD compared to a control group without treatment. Due to the high variability in study results ( $I^2 = 100\%$ , P < 0.00001), a random-effects model was used for analysis.

The results did not indicate a significant improvement in total hip BMD at 6, 12, and 24 months post treatment



Studies with intention-to-treat	Experimental	Comparator	tion process		mterventio	outcome data	nt of the outcome	reported result	Overall		
A. D. Anastasilakis 2008	Teriparatide	Risedronate	+		t	+	•	•	•	•	Low risk
David L Kendler 2018	Teriparatide	Risedronate	•		+	+	+	+	•	?	Some concerns
Jean-Jacques Body 2002	Teriparatide	Alendronate	•		+	+	•	+	•	•	High risk
Felicia Cosman 2011	Teriparatide	Zoledronic acid	•		•	+	•	+	•		
Jing Deng 2017	Teriparatide	Alendronate	•		+	+	+	•	•		
Joel S. Finkelstein 2010	Teriparatide	Alendronate	?		?	•	+	?	?		
Ko Chiba 2022	Teriparatide	Alendronate	•		+	+	•	•	•		
Li Mei 2022	Teriparatide	S Calcitonin	+		?	•	•	?	?		
Li ying 2013	Teriparatide	Elcatonin	?		•	+	•	•	?		
Michael R. McClung 2005	Teriparatide	Alendronate	•		+	•	•	•	+		
ROBERT M. NEER 2001	Teriparatide	Placebo	•		+	+	+	•	+		
S. Gonnelli 2006	Teriparatide	Antiresorptive	•		+	•	•	•	•		
Tony M Keaveny 2006	Teriparatide	Alendronate	•		•	•	•	•	?		
Wu Yingchun 2017	Teriparatide	Zoledronic acid	•		+	+	•	+	+		
Yang Yan 2014	Teriparatide	Elcatonin	•		+	+	•	•	•		
Yutao Tang 2019	Teriparatide	Alendronate	•		+	+	•	+	+		
ZHANG Xiu-zhen 2009	Teriparatide	Elcatonin	•		÷	•	•	•	$\bullet$		
Tsai, 2013	Teriparatide	Denosumab	•		÷	•	•	•	•		
Leder, 2015	Teriparatide	Denosumab	•		÷	•	•	•	•		
Z. Leder,2015	Teriparatide	Abaloparatide	•		+	•	+	•	•		
Genant 2017	Teriparatide	Romosozumab	•		+	+	•	•	•		
Keaveny 2017	Teriparatide	Romosozumab	+	1	+	+	+	•	•		
Langdahl 2017	Teriparatide	Romosozumab	•		·	•	+	•	+		

(A) A proportional risk of bias graph is presented, showcasing the percentage of biased items from all the studies included in the analysis (20, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71). This visual representation allows for a clear judgment of the level of bias present in the studies and provides insight into the overall reliability of the results. (B) Diagram Illustrating Risk of Bias: Evaluating Bias in Various Aspects Across Included Studies (20, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71).

	Teripara	tide	Contr	ol		Odds Ratio	Odds Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I	M-H, Fixed, 95% Cl		
ROBERT M. NEER,2001	79	1093	136	544		Not estimable				
Felicia Cosman, 2011	4	237	13	137	8.7%	0.16 [0.05, 0.51]				
Jing Deng,2017	0	43	1	22	1.0%	0.16 [0.01, 4.22]				
JEAN-JACQUES BODY,2002	3	73	10	73	5.1%	0.27 [0.07, 1.03]				
Wu Yingchun,2017	2	50	4	50	2.1%	0.48 [0.08, 2.74]				
David L Kendler,2018	68	516	121	533	55.5%	0.52 [0.37, 0.72]				
Li ying,2013	11	341	6	112	4.7%	0.59 [0.21, 1.63]				
Ko Chiba,2022	40	91	21	40	8.8%	0.71 [0.34, 1.50]				
Yang Yan,2014	5	40	2	13	1.4%	0.79 [0.13, 4.63]				
Michael R. McClung,2005	9	102	8	101	3.9%	1.13 [0.42, 3.04]				
Li Mei,2022	39	121	18	61	8.7%	1.14 [0.58, 2.22]		+		
Total (95% CI)		1614		1142	100.0%	0.57 [0.45, 0.72]		•		
Total events	181		204							
Heterogeneity: Chi <sup>2</sup> = 13.07, df =	= 9 (P = 0.1	16); l² =	31%				1000			
Test for overall effect: Z = 4.69 (	P < 0.0000	)1)					0.001	Control Teriparatide	1000	

Forest plot comparing the incidence of fractures between teriparatide and control groups (20, 51, 52, 53, 54, 55, 57, 60, 61, 62, 64).

with teriparatide. The outcomes were as follows: at 6 months, the mean difference was slight (MD = -0.14, with 95% CI between -0.16 and -0.13); at 12 months, the improvement was minimal (MD = -0.02, with 95% CI between -0.03 and -0.01); and at 24 months, there was almost no change (MD = 0.02, with 95% CI between -0.00 and 0.03). The overall analysis, incorporating all time points, showed an overall mean difference of -0.06 (with 95% CI between -0.07 and -0.05), indicating that teriparatide did not have a significant impact on total hip BMD compared to controls, as depicted in Fig. 4.

In conclusion, this synthesis suggests that teriparatide may not have a marked effect on hip BMD, prompting clinicians to consider other factors or treatments in managing patients' bone health.

**Lumbar BMD result**: The study analyzed data from 20 articles involving 6356 patients to examine the effects of teriparatide (PTH) on lumbar BMD over time, comparing it to control groups. Due to diverse study outcomes ( $I^2 = 100\%$ , P < 0.00001), a random-effects model was employed.

Initially, at 3 and 6 months, there was no significant change in lumbar BMD between the teriparatide and control groups, with MDs of 0.01 (95% CI: -0.02–0.04, P=0.44) and 0.00 (95% CI: -0.01–0.01, P=0.37) respectively. However, at 12 months, there was a significant decrease in BMD in the teriparatide group (MD=-0.07, 95% CI: -0.10 to -0.05, P < 0.00001), which shifted to significant increases at 18 months (MD=0.05, 95% CI: 0.01–0.09, P=0.01) and 24 months (MD=0.05, 95% CI: 0.04–0.07, P < 0.00001).

Considering all time points, there was no significant long-term difference in lumbar spine BMD changes between the teriparatide treatment and control groups (MD = -0.00, 95% CI: -0.01-0.01, P = 0.98), as shown in

Fig. 5, indicating that teriparatide's benefits on lumbar BMD emerge over time, especially at 18 and 24 months, suggesting the importance of long-term treatment for bone density improvements.

**Femoral neck BMD result**: We analyzed 15 studies with 5742 patients, focusing on the change in BMD at the femoral neck. Given the extensive variability in results across these studies ( $I^2 = 100\%$ , P < 0.00001), a random-effects model was employed to synthesize the data accurately.

The analysis showed no significant differences in femoral neck BMD changes at 6 months (MD = -0.00, 95% CI = (-0.00, 0.00), P = 0.93), 12 months (MD = -0.01, 95% CI = (-0.02, -0.00), P = 0.01), and 18 months (MD = 0.00, 95% CI = (-0.02, 0.02), P = 0.97). However, significant changes were observed at 3 months (MD = 0.00, 95% CI = (0.00, 0.00), P < 0.0001) and particularly at 24 months (MD = 0.03, 95% CI = (0.03, 0.03),  $I^2 = 0\%$ , P < 0.00001), indicating a notable improvement in the femoral neck BMD for the PTH 1–34 group compared to controls.

The overall data revealed a statistically significant improvement in femoral neck BMD (MD = 0.00, 95% CI = (0.00, 0.01),  $I^2$  = 100%, P = 0.004). This underscores the significant positive effect of prolonged teriparatide treatment on femoral neck BMD, as depicted in Fig. 6. The results highlight the benefits of extended teriparatide administration for enhancing femoral neck BMD compared to control groups, indicating its efficacy in this specific aspect of patient care.

**Radius BMD result**: Data from two studies involving 2046 patients were analyzed to assess the impact of teriparatide (PTH 1–34) on radial BMD over time, compared to a control group. Due to the high degree of variability in results across these studies ( $I^2 = 100\%$ , P <

	Ter	iparatide		Control				Mean Difference		Mean Difference				
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI		IV, Random, 95% Cl				
1.5.2 6 months														
Jing Deng,2017	0.005	0.0005	43	-0.019	0.002	22	9.6%	0.02 [0.02, 0.02]						
Ko Chiba,2022	0.01	0.002	91	0.012	0.001	40	9.6%	-0.00 [-0.00, -0.00]						
Langdahl 2017	-0.8	0.4	209	2.3	0.39	206	1.7%	-3.10 [-3.18, -3.02]	•					
Leder, 2015	0.005	0.039	45	0.014	0.026	43	8.3%	-0.01 [-0.02, 0.00]		+				
S. Gonnelli,2006	-0.014	0.0958	27	0.011	0.0943	28	3.1%	-0.03 [-0.08, 0.03]						
Yutao Tang,2019	0.007	0.0007	28	0.009	0.0009	26	9.6%	-0.00 [-0.00, -0.00]						
Subtotal (95% CI)			443			365	41.9%	-0.14 [-0.16, -0.13]	•					
Heterogeneity: $Tau^2 = 0.00$ ; $Chi^2 = 9526.42$ , df = 5 (P < 0.00001); I <sup>2</sup> = 100%														
Test for overall effect: Z = 15.29 (P < 0.00001)														
1.5.3 12 moonths														
Genant 2017	0.8	1.09	19	3.9	1.52	9	0.0%	-3.10 [-4.21, -1.99]	•					
JEAN-JACQUES BODY,2002	0.035	0.006	73	0.0177	0.0025	73	9.6%	0.02 [0.02, 0.02]						
Jing Deng,2017	-0.0002	0.00001	43	-0.013	0.001	22	9.6%	0.01 [0.01, 0.01]						
Keaveny 2017	-0.7	2.2	19	3.6	3.2	9	0.0%	-4.30 [-6.61, -1.99]	•					
Langdahl 2017	-0.5	0.4	209	0.9	0.51	206	1.3%	-1.40 [-1.49, -1.31]	•					
Li Mei,2022	0	0.09	32	0	0.11	59	3.9%	0.00 [-0.04, 0.04]						
S. Gonnelli,2006	-0.005	0.0981	27	-0.021	0.12	28	2.6%	0.02 [-0.04, 0.07]		<u> </u>				
Yutao Tang,2019	0.009	0.0008	28	0.0099	0.00099	26	9.6%	-0.00 [-0.00, -0.00]						
Subtotal (95% CI)			450			432	36.6%	-0.02 [-0.03, -0.01]		$\bullet$				
Heterogeneity: Tau <sup>2</sup> = 0.00; Ch	i² = 2968.8	2, df = 7 (	P < 0.0	0001); l²	= 100%									
Test for overall effect: Z = 2.75	(P = 0.006)	)												
1.5.5 24 months														
Leder, 2015	0.756	0.072	27	0.759	0.102	27	3.4%	-0.00 [-0.05, 0.04]						
Li Mei,2022	0	0.09	32	0	0.11	59	3.9%	0.00 [-0.04, 0.04]		<u>†</u>				
ROBERT M. NEER,2001	0.0215	0.004	1093	-0.007	0.0012	544	9.6%	0.03 [0.03, 0.03]		-				
Tsai, 2013	0.643	0.061	31	0.641	0.086	33	4.6%	0.00 [-0.03, 0.04]						
Subtotal (95% CI)			1183			663	21.5%	0.02 [-0.00, 0.03]						
Heterogeneity: Tau <sup>2</sup> = 0.00; Ch	i² = 5.53, d	f = 3 (P =	0.14); I	² = 46%										
Test for overall effect: Z = 1.52	(P = 0.13)													
Total (95% CI)			2076			1460	100.0%	-0.06 [-0.07, -0.05]		▼				
Heterogeneity: Tau <sup>2</sup> = 0.00; Ch	i² = 32852.	54, df = 1	7 (P < 0	).00001);	l <sup>2</sup> = 100%	, )			-0 -	1 -0.05 0 0.05 0	1			
Test for overall effect: Z = 11.59	9 (P < 0.00		-0.	Control Teriparatide										
Test for subaroup differences: (	Chi <sup>2</sup> = 165.	17, df = 2	(P < 0.	00001). I	<sup>2</sup> = 98.8%					Control Foliparatido				

This forest plot diagram illustrates changes in bone mineral density between teriparatide and placebo treatments at the hip (52, 54, 55, 59, 61, 65, 67, 69, 70, 71, 72).

0.00001), a random-effects model was applied for analysis to accommodate the observed statistical heterogeneity.

The analysis revealed that at 6, 18, and 24 months, there were no statistically significant changes in radial BMD between the Teriparatide and the control groups. Specifically, at 6 months, the mean difference (MD) was -0.01 (95% CI: -0.02-0.01,  $I^2$ =93%, P=0.28), at 18 months, MD was -0.01 (95% CI: -0.06-0.03,  $I^2$ =100%, P=0.63), and at 24 months, MD was -0.01 (95% CI: -0.08-0.05,  $I^2$ =100%, P=0.72), indicating no significant change in radial BMD due to teriparatide treatment over these periods. The aggregated data from these time points showed an overall MD of -0.01 (95% CI: -0.02-0.01,  $I^2$ =100%, P=0.23).

These findings, as illustrated in Fig. 7, suggest that long-term teriparatide treatment does not significantly affect radial BMD compared to controls. This outcome highlights the nuanced effectiveness of teriparatide, indicating that while it may have significant effects on other bone regions, its impact on radial BMD over the studied durations is minimal.

#### Secondary outcome

#### **Bone turnover markers**

**Osteocalcin result**: Data from two key studies involving 206 participants were analyzed to examine the impact of teriparatide (PTH 1–34) on osteocalcin levels, a marker of bone formation. The studies exhibited a high degree of variability in their results ( $I^2 = 100\%$ , P < 0.00001), necessitating using a random-effects model for synthesis.

At the 6-month evaluation, the difference in osteocalcin levels between the teriparatide group and the control group was not statistically significant, with a mean difference (MD) of 60.64 and a 95% CI ranging from –38.35 to 159.63 ( $I^2 = 100\%$ , P = 0.23). However, a significant increase in osteocalcin levels was observed at 12 months in the Teriparatide group, with an MD of 100.82 and a 95% CI of 93.20–108.44 ( $I^2 = 0\%$ , P < 0.00001).

When considering the combined results across time points, the overall analysis indicated a significant enhancement in osteocalcin levels with an MD

	Ter	iparatide		(	Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	I IV, Random, 95% Cl
1.4.1 3 months									
A. D. Anastasilakis,2008	-0.5	4.474	22	-0.1	4.74	22	0.0%	-0.40 [-3.12, 2.32]	
JEAN-JACQUES BODY,2002	0.04	0.005	100	0.015	0.002	101	4.1%	0.03 [0.02, 0.03]	· · · · · · · · · · · · · · · · · · ·
Michael R. McClung,2005	0.05	0.03	28	2.322	0.002	26	0.0%		
Subtotal (95% CI)	0.021	0.001	225	0.027	0.002	222	8.2%	0.01 [-0.02, 0.04]	-
Heterogeneity: $Tau^2 = 0.00$ : Chi	<sup>2</sup> = 1676.	41. df = 3	(P < 0	.00001)	: l² = 100	)%			
Test for overall effect: Z = 0.77 (	(P = 0.44	)		,	,				
1.4.2 6 months									
A. D. Anastasilakis,2008	0.1	4.941	22	0.1	4.941	22	0.0%	0.00 [-2.92, 2.92]	,
JEAN-JACQUES BODY,2002	0.07	0.0004	73	0.04	0.006	73	4.1%	0.03 [0.03, 0.03]	
Jing Deng,2017	0.009	0.0008	43	0.006	0.0004	22	4.1%		
Ko Chiba 2022	-0.001	0.0002	20 91	0.027	0.004	29 40	4.1%		-
Langdahl 2017	0.072	0.0059	206	0.036	0.005	209	4.1%	0.04 [0.03, 0.04]	
Li ying,2013	0.033	0.004	341	0.015	0.002	112	4.1%	0.02 [0.02, 0.02]	•
Michael R. McClung,2005	10.37	6.298	102	2.322	5.96	101	0.0%	8.05 [6.36, 9.73]	•
S. Gonnelli,2006	0.043	0.114	27	0.01	0.115	28	1.4%	0.03 [-0.03, 0.09]	
Tony M Keaveny,2006	0.015	0.0003	25	0.025	0.0005	28	4.1%	-0.01 [-0.01, -0.01]	•
Wu Yingchun,2017	0.031	0.13	50	0.064	0.139	50	1.6%	-0.03 [-0.09, 0.02]	
Yang Yan,2014	0.63	0.0951	40	0.856	0.102	13	1.3%	-0.23 [-0.29, -0.16]	•
Yutao Tang,2019	0.033	0.003	28	0.031	0.002	26	4.1%	0.00 [0.00, 0.00]	· · ·
Subtotal (95% CI)	0.04	0.006	1168	0.01	0.001	858	4.1%		•
Heterogeneity: $Tau^2 = 0.00$ ; Chi	<sup>2</sup> = 22287	7.37 df =	13 (P <	< 0.000	$(1) \cdot l^2 = 1$	00%	41.170	0.00[-0.01, 0.01]	Ť
Test for overall effect: $Z = 0.91$	(P = 0.37)	)	10 (1	- 0.0000	,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	0070			
		,							
1.4.3 12 months									
A. D. Anastasilakis,2008	-27.39	4.64	22	0.025	0.0895	22	0.0%	-27.41 [-29.35, -25.48]	
Genant 2017	6.9	1.38	30	12.3	1.55	24	0.0%	-5.40 [-6.19, -4.61]	•
JEAN-JACQUES BODY,2002	0.0112	0.001	73	0.046	0.007	73	4.1%	-0.03 [-0.04, -0.03]	· .
Jing Deng,2017	0.0265	0.002	43	0.023	0.001	22	4.1%	0.00 [0.00, 0.00]	
Joel S. Finkeistein,2010	19.5	0.008	20	0.035	0.005	29	4.1%		•
Landahl 2017	5.4	0.82	209	9.8	0.69	206	0.0%	-0.00 [-11.11, -0.49]	•
Li Mei.2022	0.102	0.152	121	0.02	0.08	32	2.2%	0.08 [0.04, 0.12]	
Li ying,2013	0.052	0.0007	341	0.021	0.002	112	4.1%	0.03 [0.03, 0.03]	
S. Gonnelli,2006	0.05	0.12	27	0.012	0.115	28	1.3%	0.04 [-0.02, 0.10]	
Wu Yingchun,2017	0.064	0.139	50	0.059	0.132	50	1.6%	0.01 [-0.05, 0.06]	
Yang Yan,2014	0.07	0.097	40	0.025	0.095	13	1.4%	0.05 [-0.01, 0.10]	
Yutao Tang,2019	0.049	0.004	28	0.037	0.003	26	4.1%	0.01 [0.01, 0.01]	
Subtotal (95% CI)	2 - 1/10/	IGE df -	103Z	- 0 0000	1). 12 - 1	0001	21.3%	-0.07 [-0.10, -0.05]	•
Test for overall effect: $7 = 6.73$	P < 0.00	1.05, ui – 001)	12 (F \$	- 0.0000	), i= − i	00 %			
	(1 - 0.00	001)							
1.4.5 18 months									
Joel S. Finkelstein,2010	0.114	0.014	20	0.044	0.006	29	4.0%	0.07 [0.06, 0.08]	
Ko Chiba,2022	0.074	0.018	91	0.05	0.009	40	4.0%	0.02 [0.02, 0.03]	
Yang Yan,2014	0.092	0.095	40	0.03	0.095	13	1.4%	0.06 [0.00, 0.12]	
Subtotal (95% CI)	2 - 407 0	4 -15 - 0 /	151	0004	12 - 000/	82	9.4%	0.05 [0.01, 0.09]	
Test for overall offect: 7 = 2.47	- = 127.8	n, at = 2 (	ר < 0.(	,0001);	ı- = 98%				
Test for overall effect. $Z = 2.47$	(F = 0.01	)							
1.4.6 24 months									
Joel S. Finkelstein,2010	0.137	0.001	20	0.056	0.008	29	4.1%	0.08 [0.08, 0.08]	
Leder, 2015	0.815	0.119	27	0.863	0.096	27	1.4%	-0.05 [-0.11, 0.01]	
Li Mei,2022	0	0.09	121	0.03	0.08	32	2.6%	-0.03 [-0.06, 0.00]	
ROBERT M. NEER,2001	0.095	0.025	1093	0.009	0.001	544	4.1%	0.09 [0.08, 0.09]	
Tsai, 2013 Subtatal (05%, CI)	0.823	0.111	31	0.866	0.088	33	1.7%	-0.04 [-0.09, 0.01]	<b>▲</b>
Subtotal (95% CI)	2 - 104 4	2 df − //	1292	00041	12 - 069/	065	14.0%	0.05 [0.04, 0.07]	
Test for overall offoct: 7 - 7 21	- 104.4	∠, uī = 4 ( 001)	r < 0.(	JUUU1);	1. – 90%				
103110100001011011001. Z = 1.311	(1 ~ 0.00	001)							
Total (95% CI)			3868			2488	100.0%	-0.00 [-0.01, 0.01]	<b></b>
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi	² = 69988	3.93, df =	38 (P <	< 0.0000	01); l² = 1	00%			
Test for overall effect: Z = 0.03 (	(P = 0.98	)							-U.1 -U.U5 U U.U5 U.1 Control Terinaratide
Test for subgroup differences: C	Chi² = 98.	67, df = 4	(P < 0	.00001)	, l² = 95.9	9%			Control Temparatide

This forest plot diagram illustrates changes in bone mineral density between teriparatide and placebo treatments at the lumbar spine (50, 51, 52, 53, 54, 54, 56, 57, 59, 60, 61, 62, 63, 64, 65, 66, 68, 69, 70, 71).

Study croup         Mean         SD. Total         Mean         SD. Total <th></th> <th>Ter</th> <th>iparatide</th> <th></th> <th>0</th> <th>Control</th> <th></th> <th></th> <th>Mean Difference</th> <th>Mean Difference</th>		Ter	iparatide		0	Control			Mean Difference	Mean Difference
1.6.1.3 Months         2HAN3 Xux-then.2009       0.005       0.0062       28       0.004       0.001       126       5.1%       0.00       0.00       0.00       0.00         2HAN3 Xux-then.2009       0.002       0.000       105       5.1%       0.00	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	I IV, Random, 95% CI
Viteo Tang 2019         0.006         0.0006         228         0.004         0.001         0.001         0.000         0.000           Stubbel (9% C)         0.00         1.00         0.000 <th0.000< th=""> <th0.000< th="">         0.000</th0.000<></th0.000<>	1.6.1 3 Months									
2HANG X0:=zhen.2009         0.002         0.0004         100         0.0007         0.0001         105         5.1%         0.000         0.000         0.000           Heberogeneity: Tatif = 0.00. Chill = 56.08, df = 1 (P < 0.00001); P = 98%.	Yutao Tang.2019	0.006	0.00062	28	0.0044	0.0004	26	5.1%	0.00 [0.00. 0.00]	•
Subter (9%, C) 128 (0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0	ZHANG Xiu-zhen.2009	0.002	0.0004	100	-0.0007	0.0001	105	5.1%	0.00 [0.00, 0.00]	•
Heterogeneiry: Tail* 0 00: Chil* 6 68. df = 1 (P < 0.00001); P = 86%. Test for overall effect: Z = 3.92 (P < 0.0001) 100 5: Finkelstein: 2010 100 005 0.0000 0 0001 43 -0.000 0.0001 22 5:1% 0.01 [0.01, 0.01] 100 5: Finkelstein: 2010 0.0007 0.00000 9 100 0: 0.000 0.001 12 5:1% 0.01 [0.01, 0.01] 100 0: 0.000 0.001 12 5:1% 0.01 [0.01, 0.01] 100 0: 0.000 112 5:1% 0.00 [0.00 0.02] 100 0: 0.000 112 5:1% 0.00 [0.00 0.02] 100 0: 0.000 112 5:1% 0.00 [0.00 0.00] 100 0: 0.000 112 5:1% 0.00 [0.00 0.00] 100 0: 0.000 125 5:1% 0.00 [0.00 0.00] 100 0: 0.000 28 0: 0.02 0: 0.02 0: 0.02 210 0: 5: 1% 0.00 [0.00 0.00] 214NAS Nu:zhen.2009 0.004 0.001 100 0.0000 22 5:1% 0.00 [0.00 0.00] 100 0: 0.000 20 0: 0.00 22 0: 0.000 22 0: 0.000 22 0: 0.000 0: 0.00 0: 0.000 0: 0	Subtotal (95% CI)			128			131	10.3%	0.00 [0.00, 0.00]	•
Test for overall effect: Z = 3.92 (P < 0.0001)	Heterogeneity: $Tau^2 = 0.00$ ; Chi	<sup>2</sup> = 56.08 c	f = 1 (P < 1	00001	). 12 = 989	%				
10a. Lotonal violation       L2 6 Norths         Jing Deng 2017       0.008       0.0007       43       -0.006       0.0001       22       5.1%       .0.01 [0.01.0.01]         10.6 S. Finkelstein       20       0.0007       0.0009       0.001       28       5.1%       .0.01 [0.01.0.01]         10.6 S. Finkelstein       2011       0.044       45       0.027       0.004       43       2.00       .0.01 [0.01.0.01]         1. Ungdant       2017       0.011       0.006       0.0001       122       5.1%       .0.01 [0.03.000]       .0.01         S. Gonnelli2006       -0.006       0.0881       28       0.0%       .0.01 [0.03.000]       .0.001         Yinab Tang 2019       0.007       0.006       286       1.5       .0.00 [0.00.000]       .0.001         ZHANG Skuzhen.2009       0.004       0.0011       100       0.0000       .0001       73       0.008       .0.001       <	Test for overall effect: $7 = 3.92$	/P < 0 000/	1) I (I I I I I)		), 1 00	/0				
1.6.2 δ Months         Jack 5 Finkelisticn, 2010       0.0007       0.00070       0.00009       20       0.01       0.001       29       51%       0.01 [0.01, 0.01]         Langdaha 2017       0.015       0.003       341       0.002       426       0.004       43       0.009       200       0.01       40       51%       -0.01 [0.05, 0.001       -0.01       45       -0.02       -0.		(1 < 0.0001	')							
Imp Derg 2017         0.088         0.0007         43         0.008         0.0001         22         5.1%         0.01	1626 Months									
Jing Leng,2017       0.008       0.0007       43       0.008       0.0001       22       5.1%       0.001 [0.01, 0.01]         Ko Chiba,2022       0.005       0.003       91       0.099       0.001       40       5.1%       0.01 [0.01, 0.01]         Langdarl 2017       0.011       0.046       45       0.027       0.004       43       2.0%       0.021 [0.00, 0.00]         Langdarl 2017       0.011       0.046       45       0.027       0.004       43       2.0%       0.021 [0.00, 0.00]         Light 2017       0.010       0.000       314       0.000       0.0000       112       5.1%       0.001 [0.00, 0.00]         S. Gonnell,2006       -0.006       0.006       1.05       5.1%       0.001 [0.00, 0.00]         ZhANG Xiu-zhen 2009       0.004       0.001       100       0.008       0.001       105       5.1%       0.001 [0.00, 0.00]         ZhANG Xiu-zhen 2009       0.004       0.014       0.002       29       5.1%       0.001 [0.00, 0.00]         ZhANG Xiu-zhen 2009       0.004       0.001       1.03       0.006       0.001       15       5.1%       0.001 [0.00, 0.01]         Light 2017       0.012       0.014       0.002       <	line Deep 2017	0.000	0 0007	40	0.000	0 0000	22	E 40/	0.04 [0.04, 0.04]	
Jole S. Finkelstein, 2010 Langdath 2017 4.005 4	Jing Deng,2017	0.008	0.0007	43	-0.006	0.0008	22	5.1%	0.01[0.01, 0.01]	-
No Chi06.2022 0.000 0.003 91 0.009 0.001 40 0.1% -0.00 [200.000] -1 Lader.2015 0.011 0.044 45 0.027 0.004 43 2.0% -0.02 [-0.05.00] -1 Liying.2013 0.001 0.0003 341 0.002 0.0003 112 5.1% -0.00 [-0.0.0.00] -1 Liying.2013 0.001 0.0003 241 0.002 0.0003 113 0.1% -0.02 [-0.0.0.00] -1 Vitato Tang.2019 0.007 0.0077 28 0.005 0.006 288 0.0% -0.01 [-0.0.0.00] -1 Vitato Tang.2019 0.007 0.0077 28 0.005 0.006 5.1% 0.00 [0.0.0.00] -1 Vitato Tang.2019 0.007 0.0077 73 0.008 0.001 105 5.1% 0.00 [0.0.0.00] -1 Heterogeneity. Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 9649.98, df = 10 (P < 0.0001); P = 100% Test for overall effect: Z = 0.09 (P = 0.3) 1.6.3 12 Months JEAN-JACCUES BODY.2002 0.032 0.007 73 0.008 0.001 73 50% 0.02 [0.02, 0.03] -1 Jean Status - 1 Jean Status - 2 Jean Status - 1 Jean Status - 2 Jean Status - 2	Joel S. Finkeistein,2010	0.00007	0.000009	20	0.01	0.001	29	5.1%	-0.01 [-0.01, -0.01]	-
Langean 2017 4.0.11 0.006 209 0.021 6 208 0.07 4.0 20% 0.02 [-0.03.0.00] Lying 2013 0.001 0.0003 341 0.002 0.0003 112 5.1% 0.00 [-0.00.0.00] Wu Ying Yang Yang Yang Yang Yang Yang Yang Ya	Ko Chiba,2022	0.005	0.003	91	0.009	0.001	40	5.1%	-0.00 [-0.00, -0.00]	_
Lader, 2015 0.011 0.046 45 0.027 0.004 43 2.0% -0.02 [0.0.00] S. Gonelliz005 -0.008 0.0861 27 0.006 0.88 28 0.0% -0.01 [0.30, 0.00] Yang Yan,2014 0.019 0.157 40 0.036 0.039 13 0.1% -0.02 [0.11, 0.30, 0.07] Yang Yan,2014 0.019 0.157 40 0.036 0.009 56 5.1% 0.00 [0.00, 0.00] ZHANG Xhu-zhen,2009 0.004 0.001 100 0.0008 0.001 105 5.1% 0.00 [0.00, 0.00] ZHANG Xhu-zhen,2009 0.004 0.001 100 0.0008 0.001 155 5.1% 0.00 [0.00, 0.00] ZHANG Xhu-zhen,2009 0.004 0.001 100 0.0008 0.001 155 5.1% 0.00 [0.00, 0.00] ZHANG Xhu-zhen,2009 0.004 0.001 100 0.0008 0.001 155 5.1% 0.00 [0.00, 0.00] ZHANG Xhu-zhen,2009 0.004 0.001 100 0.0008 0.001 13 5.0% 0.00 [0.00, 0.00] Jang Deng,2017 0.012 0.001 43 0.002 29 5.1% 0.01 [0.01, 0.01] Jang Deng,2017 0.012 0.001 43 0.002 29 5.1% 0.01 [0.01, 0.01] Jang Deng,2017 0.026 0.0008 0.001 125 5.1% 0.00 [1.00, 0.00] S. Gonelliz006 0.016 0.4 27 0.004 0.004 22 5.1% 0.001 [0.01, 0.01] Jang Zhang.2019 0.012 0.0012 41 0.002 129 5.1% 0.001 [0.01, 0.01] Jang Zhang.2019 0.012 0.0012 28 0.007 0.0076 26 5.1% 0.01 [0.01, 0.01] Jang Zhang.2019 0.012 0.0021 28 0.007 0.0076 26 5.1% 0.01 [0.01, 0.01] Jang Zhang.2019 0.012 0.002 20 0.0076 28 5.1% 0.01 [0.01, 0.01] Jang Zhang.2019 0.012 0.002 20 0.0076 28 5.1% 0.01 [0.01, 0.01] Jang Zhang.2019 0.012 0.002 20 0.0076 28 5.1% 0.01 [0.01, 0.01] Jang Zhang.2019 0.012 0.002 20 0.0076 28 5.1% 0.01 [0.01, 0.01] Jang Zhang.2019 0.026 H = 8 (P < 0.0001); P = 100% Test for overall effect: Z = 2.48 (P = 0.01) 1.6.418 Months Jael S. Finketstein,2010 0.028 0.003 20 0.019 0.002 29 5.0% 0.01 [0.01, 0.01] Jael S.Finketstein,2010 0.028 0.003 20 0.019 0.002 29 5.0% 0.01 [0.01, 0.01] Jael S.Finketstein,2010 0.028 0.003 20 0.019 0.002 29 5.0% 0.01 [0.01, 0.01] Jael S.Finketstein,2010 0.028 0.003 20 0.019 0.002 29 5.0% 0.01 [0.01, 0.01] Jael S.Finketstein,2010 0.028 0.003 20 0.019 0.002 29 5.0% 0.01 [0.01, 0.01] Jael S.Finketstein,2010 0.026 0.000 22 0.005 20 0.003 29 4.8% 0.03 [0.02, 0.03] Jael S.Finketstein,2010 0.052 0.006 20 0.025 0.003 29 4.8% 0.03 [0.03, 0	Langdahl 2017	-0.11	0.006	209	0.021	6	206	0.0%	-0.13 [-0.95, 0.69]	
Li ying 2013 0.001 0.0003 341 0.002 0.0003 112 5.1% 0.001 [-0.0.00] Wu Ying Yang Yang Yang Yang Yang Yang Yang Ya	Leder, 2015	0.011	0.046	45	0.027	0.004	43	2.0%	-0.02 [-0.03, -0.00]	•
S. Gonelli,2006 -0.006 0.0861 27 0.006 0.886 28 0.0% -0.01 [0.3, 0.05] Vang Yang Yang Yang Yang Yang Yang Yang Y	Li ying,2013	0.001	0.0003	341	0.002	0.0003	112	5.1%	-0.00 [-0.00, -0.00]	•
Wu Ying Yan, 2017 0.028 0.102 50 0.016 0.093 50 0.4% 0.01 [0.03.06] Yitao Tan, 2014 0.019 0.157 40 0.036 0.039 10.1% 0.002 [0.02, 0.02] 0.010 0.000	S. Gonnelli,2006	-0.006	0.0861	27	0.006	0.886	28	0.0%	-0.01 [-0.34, 0.32]	
Yang Yan,2014 0.019 0.157 40 0.036 0.139 13 0.1% -0.02 [-0.10,07] Yutao Tang,2019 0.007 0.0007 28 0.0005 0.006 26 5.1% 0.00 [0.00,0.00] ZHANG Xiu-zhen,2009 0.004 0.001 100 0.0008 0.001 105 5.1% 0.00 [0.00,0.00] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 9649.98, df = 10 (P < 0.00001); P = 100% Test for overall effect Z = 2.87 (P = 0.000) Jing Deng,2017 0.012 0.001 43 -0.002 0.002 22 5.1% 0.01 [0.01,0.01] Langdah 2017 0.02 0.066 20 0.014 0.002 29 5.1% 0.01 [0.01,0.01] Langdah 2017 0.02 0.066 20 0.014 0.002 29 5.1% 0.01 [-0.01,0.01] Langdah 2017 0.02 0.066 20 0.014 0.002 29 5.1% 0.01 [-0.01,0.01] Langdah 2017 0.02 0.066 20 0.033 0.009 50 0.006 0.0% 0.01 [-0.10,0.01] Yutao Tang,2019 0.012 0.001 341 0.002 29 5.1% 0.01 [-0.00,0.01] Yutag Yang Yan 2014 0.012 0.0148 40 0.026 0.098 50 0.4% 0.01 [-0.30,0.30] Yutao Tang,2019 0.012 0.0012 28 0.007 0.002 29 5.0% 0.01 [0.01,0.01] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 11567.01, df = 8 (P < 0.00001); P = 100% Test for overall effect Z = 2.48 (P = 0.01) 1.6.4 18 Months Joel S. Finkelstein,2010 0.028 0.003 20 0.019 0.002 29 5.0% 0.01 [0.01,0.01] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 11567.01, df = 8 (P < 0.00001); P = 100% Test for overall effect Z = 2.48 (P = 0.00001); P = 100% Test for overall effect Z = 2.48 (P = 0.00001); P = 100% Test for overall effect Z = 2.87 (P = 0.0001) Jacel S. Finkelstein,2010 0.028 0.003 24 0.0019 0.002 42 5.51% 0.01 [0.01,0.01] Joel S. Finkelstein,2010 0.028 0.003 20 0.019 0.002 112 5.1% 0.01 [-0.01,0.01] Joel S. Finkelstein,2010 0.028 0.003 20 0.019 0.002 12 5.51% 0.01 [-0.01,0.01] Joel S. Finkelstein,2010 0.028 0.003 20 0.019 0.002 12 5.51% 0.01 [-0.01,0.01] Joel S. Finkelstein,2010 0.026 0.0007 34 0.0017 0.002 112 5.1% 0.01 [-0.01,0.01] Joel S. Finkelstein,2010 0.026 0.0007 340 0.0007 544 5.1% 0.03 [0.02,0.03] Bubtotal (95% Cl) 558 0.006 20 0.0025 0.003 29 4.8% 0.03 [0.03,0.03] Jutotal (95% Cl) 558 0.000 1.91 - 90% Test for overall effect Z = 2.87 (P = 0.0004) Test for overall effect Z = 2.87 (P = 0.0004) Test for	Wu Yingchun,2017	0.028	0.102	50	0.016	0.093	50	0.4%	0.01 [-0.03, 0.05]	
Yutao Tang 2019 0.007 0.00075 28 0.0006 0.0006 26 5.1% 0.00 [0.00, 0.00] Subtad (95% CI) 994 0.001 100 0.0008 0.0001 674 33.3% 0.00 [0.00, 0.00] Subtad (95% CI) 994 0.001 100 0.00008 0.001 674 33.3% 0.00 [0.00, 0.00] Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 9649.88, df = 10 (P < 0.00001); P = 100% Test for overall effect: Z = 0.09 (P = 0.33) 1.6.3 12 Months JEAN-JACQUES BODY.2002 0.032 0.007 73 0.008 0.001 73 5.0% 0.02 [0.02, 0.03] Jing Deng 2017 0.012 0.001 43 -0.002 0.002 22 5.1% 0.01 [0.01, 0.01] Jael S. Finkelstein.2010 0.006 0.0008 2.0 0.14 0.002 29 5.1% -0.01 [-0.14, 0.17] Wu Yingbun.2017 0.34 0.104 50 0.028 0.098 50 0.4% 0.01 [-0.3, 0.06] Yutao Tang 2019 0.012 0.0012 28 0.007 0.0007 28 5.1% 0.01 [0.00, 0.00] Yutao Tang 2019 0.012 0.0012 28 0.007 0.0007 28 5.1% 0.01 [0.00, 0.01] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 11587.01, df = 8 (P < 0.00001); P = 100% Test for overall effect: Z = 2.48 (P = 0.01) 1.6.4 18 Months Joel S. Finkelstein.2010 0.028 0.003 20 0.019 0.002 29 5.0% 0.01 [0.01, 0.01] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 11587.01, df = 8 (P < 0.00001); P = 100% Test for overall effect: Z = 2.48 (P = 0.01) 1.6.4 18 Months Joel S. Finkelstein.2010 0.028 0.003 20 0.019 0.002 29 5.0% 0.01 [0.01, 0.01] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 11381.95, df = 4 (P < 0.00001); P = 100% Test for overall effect: Z = 0.03 (P = 0.97) 1.6.5 24 Months Joel S. Finkelstein.2010 0.052 0.006 20 0.025 0.003 29 4.8% 0.03 [0.02, 0.03] Subtat (95% CI) 520 219 20.5% 0.000 [-0.00, 0.01] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.46, df = 1 (P = 0.50); P = 100% Test for overall effect: Z = 2.87 (P = 0.0001); F = 100% Test for overall effect: Z = 2.87 (P = 0.0001); F = 100% Test for overall effect: Z = 2.87 (P = 0.0001); F = 100% Test for overall effect: Z = 2.87 (P = 0.0004) Test for overall effect: Z = 2.87 (P = 0.0004); F = 0.0000; F4 = 0.0	Yang Yan,2014	0.019	0.157	40	0.036	0.139	13	0.1%	-0.02 [-0.11, 0.07]	• • • • • • • • • • • • • • • • • • •
2 HANS Xu = hen, 2009 0.004 0.001 100 0.0008 0.001 105 5.1% 0.00 [0.00, 0.00] Heterogeneity: Tau2 = 0.00; Chi2 = 9649.98, df = 10 (P < 0.00001); P = 100% Chi2 = 2.8 Chi2 = 0.00 (P = 0.93)  1.6.3 12 Months  Jack = JACQUES BODY.2002 0.032 0.007 73 0.008 0.01 73 5.0% 0.02 [0.02, 0.03] 0.01 [0.01, 0.01] 0.01 = 0.006 0.0008 20 0.014 0.002 29 5.1% 0.01 [0.01, 0.01] 0.01 = 0.006 0.0008 20 0.014 0.002 29 5.1% 0.01 [0.01, 0.01] 0.01 = 0.0008 20 0.014 0.002 29 5.1% 0.01 [0.01, 0.01] 0.000 [0.00, 0.00] 0.000	Yutao Tang,2019	0.007	0.00075	28	0.005	0.0006	26	5.1%	0.00 [0.00, 0.00]	*
Subtail (95% CI) 994 674 33.3% $-0.00 [-0.00, 0.00]$ Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 9649.98, df = 10 (P < 0.00001); P = 100% Test for overall effect. $Z = 0.09 (P = 0.93)$ 1.6.3 12 Months JEAN-JACCUES BODY.2002 0.032 0.007 73 0.008 0.001 73 5.0% 0.02 [0.02, 0.03] Jing Deng.2017 0.012 0.001 43 -0.002 0.002 22 5.1% 0.01 [0.01, 0.01] Joel S. Finkelstein.2010 0.006 0.0008 20 0.014 0.002 29 5.1% -0.01 [-0.1, 0.01] Jung Deng.2017 0.2 0.66 209 3.2 0.6 206 0.06% -3.40 [5.26, 3.28] Li ying.2013 0.0008 0.001 341 0.001 0.0022 112 5.1% -0.00 [-0.00, -0.00] S. Gonell.2006 0.016 0.4 27 0.004 0.0946 28 0.0% 0.01 [-0.14, 0.17] Vitao Tang.2019 0.012 0.014 40 0.022 06 5.0 % 0.01 [-0.14, 0.17] Yang Yan.2014 0.012 0.148 40 0.053 0.141 13 0.1% -0.04 [-0.30, 0.05] Subtotal (95% CI) 831 559 26.0% 0.01 [0.01, 0.01] K Chiha,2011 0.028 0.003 20 0.019 0.002 29 5.0% 0.01 [0.01, 0.01] K Chiha,2021 0.012 8 0.003 20 0.019 0.002 29 5.0% 0.01 [0.01, 0.01] K Chiha,2013 0.005 0.0068 341 0.017 0.002 142 5.1% -0.00 [-0.02, -0.00] Test for overall effect: $Z = 2.48 (P = 0.01)$ 16.4 18 Months Juel S. Finkelstein,2010 0.028 0.008 20 0.019 0.002 29 5.0% 0.01 [0.01, 0.01] K Chiha,2014 0.022 0.114 0.004 91 0.014 0.002 40 5.1% -0.00 [-0.01, -0.01] Tony M Keaveny.2066 0.006 20 0.007 28 0.0118 0.0004 25 5.1% 0.00 [0.01, 0.01] Yang Yan.2014 0.022 0.149 40 0.08 0.139 13 0.1% -0.06 [-0.15, 0.03] Subtatal (95% CI) 2005 0.006 20 0.025 0.003 29 4.8% 0.03 [0.02, 0.03] Bubtatal (95% CI) 3586 Joe 0.000 109 Joe 0.000 54 5.1% 0.03 [0.03, 0.03] Bubtatal (95% CI) 3586 Joe 0.0001 J; P = 100% Test for overall effect: $Z = 2.07 (P = 0.004)$ Test for overall effect: $Z = 2.07 (P = 0.004)$ Test for overall effect: $Z = 2.47 (P = 0.0004)$ JF = 0.000 Li ying 20 0.00 [0.00, 0.01] Joe 0.01 0.02 Control Teriparatide	ZHANG Xiu-zhen,2009	0.004	0.001	100	0.0008	0.0001	105	5.1%	0.00 [0.00, 0.00]	
Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 9649.98, df = 10 (P < 0.00001); P = 100% Test for overall effect. Z = 0.09 (P = 0.93) <b>1.6.3 12 Months</b> Jing Deng.2017 0.012 0.001 43 -0.002 0.0002 22 5.1% 0.01 [0.01, 0.01] Joel S. Finkelstein.2010 0.006 0.0008 20 0.014 0.002 29 5.1% 0.01 [0.01, 0.01] Joel S. Finkelstein.2010 0.006 0.0008 20 0.014 0.002 29 5.1% 0.01 [0.01, 0.01] Joel S. Finkelstein.2010 0.006 0.0008 0.001 341 0.001 0.0002 112 5.1% 0.01 [0.01, 0.01] Joel S. Finkelstein.2010 0.016 0.4 27 0.004 0.946 28 0.0% 0.01 [0.14, 0.01] S. Gonnelli,2006 0.016 0.4 27 0.004 0.946 28 0.0% 0.01 [0.04, 0.01] Yuang Yang 2013 0.002 0.012 0.012 0.002 8 0.003 50 0.4% 0.01 [0.03, 0.05] Yuang Yang 2014 0.012 0.012 0.0012 28 0.007 0.0007 62 6 5.1% 0.01 [0.00, 0.01] Subtotal (95% CI) 831 559 26.0% 0.01 [0.01, 0.01] Ko Chiba.2022 0.011 0.004 91 0.014 0.002 29 5.0% 0.01 [0.01, 0.01] Ko Chiba.2022 0.011 0.004 91 0.014 0.002 29 5.0% 0.01 [0.01, 0.01] No Ghia.2022 0.011 0.004 91 0.014 0.002 29 5.0% 0.01 [0.01, 0.01] Yang Yan.2014 0.022 0.148 40 0.08 0.139 113 0.1% 0.00 [0.00, 0.00] Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 11381.95, df = 4 (P < 0.00001); P = 100% Test for overall effect: Z = 0.03 (P = 0.97) <b>1.6.5 24 Months</b> Joel S. Finkelstein.2010 0.052 0.0006 20 0.025 0.003 29 4.8% 0.03 [0.02, 0.03] Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 11381.95, df = 4 (P < 0.00001); P = 100% Test for overall effect: Z = 116.32 (P < 0.00001); P = 00% Test for overall effect: Z = 116.32 (P < 0.00001); P = 0% Test for overall effect: Z = 2.48 (P = 0.0001) Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 0.46, df = 1 (P = 0.50); P = 0% Test for overall effect: Z = 2.87 (P = 0.004) Test for overall effect: Z = 2.87 (P = 0.004) Test for overall effect: Z = 2.87 (P = 0.004) Test for overall effect: Z = 2.87 (P = 0.004) Test for overall effect: Z = 2.87 (P = 0.004) Test for overall effect: Z = 2.87 (P = 0.004) Test for overall effect: Z = 2.87 (P = 0.004) Test for overall effect: Z = 2.87 (P = 0.004) Test for overall effect: Z = 2.87 (P =	Subtotal (95% CI)			994			674	33.3%	-0.00 [-0.00, 0.00]	
Test for overall effect: $Z = 0.09 (P = 0.93)$ <b>1.6.3 12 Months</b> JEAN-JACQUES BODY,2002 0.032 0.007 73 0.008 0.001 73 5.0% 0.02 [0.02, 0.03] Jing Deng,2017 0.012 0.001 43 -0.002 29 5.1% 0.01 [0.01, 0.01] Joel S, Finkelstein,2010 0.006 0.0008 20 0.014 0.002 29 5.1% 0.001 [0.01, 0.01] Joel S, Finkelstein,2010 0.016 0.4 27 0.004 0.0946 28 0.0% 0.401 [0.01, 0.01] Viting Jan,2013 0.0008 0.011 341 0.001 0.0022 112 5.1% 0.001 [0.01, 0.01] Viting Jan,2014 0.012 0.148 40 0.053 0.141 13 0.1% 0.004 [0.01, 0.05] Vitus Tag,2019 0.012 0.012 2.0 0.007 0.28 0.007 0.2007 26 5.1% 0.011 [0.01, 0.01] <b>1.6.4 18 Months</b> Joel S, Finkelstein,2010 0.028 0.0003 20 0.019 0.002 29 5.0% 0.01 [0.01, 0.01] <b>1.6.4 18 Months</b> Joel S, Finkelstein,2010 0.028 0.0005 3.0141 0.002 40 5.1% 0.01 [0.00, 0.00] <b>1.6.4 18 Months</b> Joel S, Finkelstein,2010 0.028 0.0003 20 0.019 0.002 29 5.0% 0.01 [0.01, 0.01] <b>1.6.4 18 Months</b> Joel S, Finkelstein,2010 0.028 0.0007 28 0.0118 0.0002 40 5.1% 0.01 [0.01, 0.01] Vitar Gray,2014 0.022 0.149 40 0.08 0.139 13 0.1% 0.006 [0.00, 0.00] <b>1.6.5 24 Months</b> Joel S, Finkelstein,2010 0.022 0.006 20 0.025 0.003 29 4.8% 0.03 [0.02, 0.03] Subtotal (95% CI) <b>1.6.5 24 Months</b> Joel S, Finkelstein,2010 0.024 0.008 1093 -0.004 0.0007 544 5.1% 0.03 [0.03, 0.03] Distotal (95% CI) <b>1.6.5 24 Months</b> Joel S, Finkelstein,2010 0.024 0.008 1093 -0.004 0.0007 544 5.1% 0.03 [0.03, 0.03] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 11381.95, df = 4 (P < 0.00001); P = 100% Test for overall effect: $Z = 2.87 (P = 0.0004)$ Test for overall effect: $Z = 2.87 (P = 0.0004)$ Test for overall effect: $Z = 2.87 (P = 0.0004)$ Test for overall effect: $Z = 2.87 (P = 0.0004)$ Test for overall effect: $Z = 2.87 (P = 0.0004)$ Test for overall effect: $Z = 2.87 (P = 0.0004)$ Test for overall effect: $Z = 2.87 (P = 0.0004)$	Heterogeneity: $Tau^2 = 0.00$ . Chi	<sup>2</sup> = 9649 98	df = 10 (F	< 0.00	001)· l <sup>2</sup> =	100%				
1.6.3 12 Months         Jing Deng 2017       0.012       0.007       73       0.008       0.001       73       5.0%       0.02 [0.02, 0.03]         Jing Deng 2017       0.012       0.006       0.0008       20       0.014       0.002       29       5.1%       -0.01 [0.01, 0.01]         Langdahi 2017       -0.2       0.66       209       3.2       0.6       206       0.0%       -3.40 [-3.52, -3.28]         Li ying 2013       0.0008       0.001       341       0.001       0.004       20.95%       0.01 [-0.01, 0.01]         Yang Yan, 2014       0.012       0.148       40.053       0.0141       13       1%       -0.04 [-0.02, -0.00]         Yang Yan, 2014       0.012       0.003       20       0.019       0.002       29       5.0%       -0.01 [-0.02, -0.00]         Heterogeneity: Tau² = 0.00; Chi² = 11567.01, df = 8 (P < 0.00001); P = 100%	Test for overall effect: $7 = 0.09$	(P = 0.93)	.,	5.00		/ .				
1.6.3 12 Months         JEAN-JACQUES BODY,2002       0.032       0.007       73       0.008       0.001       73       0.002       22       5.1%       0.01 [0.01, 0.01]         Jing Deng,2017       0.006       0.0008       20       0.014       0.002       29       5.1%       0.01 [0.01, 0.01]         Langdahi 2017       -0.2       0.66       209       3.2       0.6       206       0.0%       -3.40 [-3.52, -3.28]         Liying,2013       0.0008       0.011       3.41       0.001       0.0002       112       5.1%       -0.01 [-0.0, 0.00]         S. Gennelli,2006       0.016       0.4       27       0.044       0.0946       28       0.0%       0.01 [-0.10, 0.01]         Yang Yan,2014       0.012       0.012       0.028       0.026       0.086       50       0.4%       0.01 [-0.02, -0.00]         Yutao Tang,2019       0.012       0.0012       0.002       26.0%       -0.01 [-0.02, -0.00]       -       -         Test for overall effect: Z = 2.48 (P = 0.0001)       831       559       26.0%       0.01 [0.01, 0.01]       -       -         Liying,2013       0.002       0.002       29       5.0%       0.01 [0.01, 0.01]       -       -		(1 = 0.50)								
$\begin{aligned} \frac{1}{102} \text{RA} - \text{JACQUES BODY}_{2002} 0.032 0.007 73 0.008 0.001 73 5.0\% 0.02 [0.02, 0.03] \\ \frac{1}{102} \text{ Bong}_{2017} 0.012 0.001 43 -0.002 0.0002 22 5.1\% 0.01 [0.01, 0.01] \\ -0.01 [0.01, 0.01] \\ -0.01 [-0.01, -0.01] \\ -0.01 [-0.01, -0.01] \\ -0.01 [-0.01, -0.01] \\ -0.01 [-0.01, -0.01] \\ -0.01 [-0.01, -0.01] \\ -0.01 [-0.01, -0.01] \\ -0.01 [-0.02, -0.00] \\ -0.01 [-0.02, -0.01] \\ -0.02 [-0.01, -0.01] \\ -0.01 [-0.02, -0.01] \\ -0.02 [-0.01, -0.01] \\ -0$	1.6.3.12 Months									
$\begin{aligned} \frac{1}{10} \log_{20}(217) & 0.012 & 0.032 & 0.001 & 13 & 0.008 & 0.001 & 13 & 5.0\% & 0.01 & [0.01 & 0.01] \\ \frac{1}{10} \log_{20}(217) & 0.012 & 0.001 & 43 & -0.002 & 0.002 & 22 & 5.1\% & 0.01 & [0.01 & 0.01] \\ \frac{1}{10} \log_{20}(217) & 0.02 & 0.006 & 20 & 0.008 & 20 & 0.014 & 0.002 & 22 & 5.1\% & 0.01 & [0.01 & 0.01] \\ \frac{1}{10} \log_{20}(217) & 0.02 & 0.066 & 209 & 3.2 & 0.6 & 266 & 0.0\% & -3.40 & [-3.52, -3.28] \\ \frac{1}{10} ying.2013 & 0.0008 & 0.001 & 341 & 0.001 & 0.0002 & 112 & 5.1\% & -0.00 & [-0.00, -0.00] \\ \frac{1}{10} Vilao Tang.2019 & 0.012 & 0.046 & 0.028 & 0.038 & 50 & 0.4\% & 0.01 & [-0.43, 0.05] \\ \frac{1}{10} Vilao Tang.2019 & 0.012 & 0.0012 & 8 & 0.007 & 0.0076 & 26 & 5.1\% & -0.04 & [-0.30, 0.05] \\ \frac{1}{10} Vilao Tang.2019 & 0.012 & 0.0012 & 8 & 0.007 & 0.00076 & 26 & 5.1\% & -0.04 & [-0.30, 0.05] \\ \frac{1}{10} Vilao Tang.2019 & 0.012 & 0.0012 & 8 & 0.007 & 0.0076 & 26 & 5.1\% & -0.01 & [-0.02, -0.00] \\ \frac{1}{10} Heterogeneity. Tau2 = 0.00; Chi2 = 11567.01, df = 8 (P < 0.00001); P = 100\% \\ \text{Test for overall effect: Z = 2.48 (P = 0.01) \\ \frac{1}{1.64.18 Months} \\ \frac{1}{10} ying.2013 & 0.005 & 0.0028 & 0.003 & 20 & 0.019 & 0.002 & 29 & 5.0\% & 0.01 & [0.01, 0.01] \\ \frac{1}{10} Vilao V$		0.022	0.007	70	0.000	0.001	70	E 00/		
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	JEAN-JACQUES BOD 1,2002	0.032	0.007	13	0.006	0.001	13	5.0%	0.02 [0.02, 0.03]	
Joel S, Finkelstein, 2010 0.006 0.0008 20 0.014 0.002 29 5.1% -0.01 [-0.01, -0.01] Langdahi 2017 -0.2 0.66 209 3.2 0.6 266 0.0% -3.40 [-3.52, -3.28] Li ying, 2013 0.0008 0.001 341 0.001 0.0002 112 5.1% -0.00 [-0.00, -0.00] S, Gonnelli, 2006 0.016 0.4 27 0.004 0.946 28 0.0% 0.01 [-0.14, 0.17] Wu Yingchun, 2017 0.034 0.104 50 0.028 0.098 50 0.4% 0.01 [-0.03, 0.05] Yutao Tang, 2019 0.012 0.044 40 0.053 0.141 13 0.1% -0.04 [-0.30, 0.05] Yutao Tang, 2019 0.012 0.0012 28 0.007 0.0007 6 26 5.1% 0.011 [0.00, 0.01] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 11567.01, df = 8 (P < 0.00001); P = 100% Test for overall effect: Z = 2.48 (P = 0.01) 1.6.4 18 Months Joel S, Finkelstein, 2010 0.028 0.003 20 0.019 0.002 29 5.0% 0.01 [0.01, 0.01] Ko Chiba, 2022 0.011 0.004 91 0.014 0.002 40 5.1% -0.01 [-0.01, -0.01] Tony M Keaveny, 2006 0.026 0.0007 28 0.0118 0.0004 25 5.1% 0.01 [0.01, 0.01] Yang Yan, 2014 0.002 0.149 40 0.08 0.139 13 0.1% -0.06 [-0.15, 0.03] Subtatal (95% CI) 122 0.012 0.025 0.003 29 4.8% 0.03 [0.02, 0.02] Heterogeneity: Tau <sup>2</sup> = 0.03 (P = 0.97) 1.6.5 24 Months Joel S, Finkelstein, 2010 0.052 0.006 20 0.025 0.003 29 4.8% 0.03 [0.02, 0.03] Subtatal (95% CI) 1113 573 9.9% 0.03 [0.03, 0.03] Subtatal (95% CI) 1113 573 9.9% 0.03 [0.03, 0.03] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.40, df = 1 (P = 0.50); P = 0% Test for overall effect: Z = 2.16, 32 (P < 0.00001): P = 100% Test for overall effect: Z = 2.07 (P = 0.004) Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 5001.81, df = 28 (P < 0.00001); P = 100% Test for overall effect: Z = 2.07 (P = 0.0001) Total (95% CI) 3586 2156 100.0% 0.00 [0.00, 0.01] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 5005, 4d eff = 4 (P < 0.00001); P = 100% Test for overall effect: Z = 2.07 (P = 0.004) Test for overall effect: Z = 2.07 (P = 0.004) Test for overall effect: Z = 2.07 (P = 0.004) Test for overall effect: Z = 2.07 (P = 0.004) Test for overall effect: Z = 2.07 (P = 0.004) Test for overall effect: Z = 2.07 (P = 0.004) Test for overall effect: Z = 2.07 (P = 0.004) Tes	Jing Deng,2017	0.012	0.001	43	-0.002	0.0002	22	5.1%	0.01 [0.01, 0.01]	
Langdah 2017 -0.2 0.66 209 3.2 0.6 206 0.07 -3.40 (-3.52, -3.28) Li ying,2013 0.0008 0.001 341 0.001 0.0002 112 5.1% -0.00 (-0.00, -0.00) S. Gonnelli,2006 0.016 0.4 27 0.004 0.0946 28 0.0% 0.01 (-0.14, 0.17) Wu Yingchun,2017 0.034 0.104 50 0.028 0.098 50 0.4% 0.01 (-0.03, 0.05) Yung Yan,2014 0.012 0.014 8 40 0.053 0.141 13 0.1% -0.04 (-0.13, 0.05) Yutao Tang,2019 0.012 0.012 28 0.007 0.00076 26 5.1% 0.01 [0.00, 0.01] Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 11567.01, df = 8 (P < 0.00001); P = 100% Test for overall effect: $Z = 2.48$ ( $P = 0.01$ ) 1.6.4 18 Months Joel S. Finkelstein,2010 0.028 0.003 20 0.019 0.002 29 5.0% 0.01 [0.01, 0.01] Yang Yan,2014 0.022 0.149 40 0.08 0.139 13 0.1% -0.00 [-0.00, -0.00] Yang Yan,2014 0.022 0.149 40 0.08 0.139 13 0.1% -0.01 [-0.01, 0.01] Yang Yan,2014 0.022 0.149 40 0.08 0.139 13 0.1% -0.06 [-0.15, 0.03] Subtotal (95% Cl) 520 219 20.5% 0.001 [0.01, 0.01] Yang Yan,2014 0.022 0.149 40 0.007 54 5.1% 0.03 [0.02, 0.03] Subtotal (95% Cl) 520 219 20.5% 0.003 [0.02, 0.03] Subtotal (95% Cl) 0.52 0.006 20 0.025 0.003 29 4.8% 0.03 [0.02, 0.03] Subtotal (95% Cl) 0.052 0.006 20 0.025 0.003 29 4.8% 0.03 [0.02, 0.03] Subtotal (95% Cl) 0.52 0.006 10 0.002 573 9.9% 0.03 [0.03, 0.03] Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 0.046, df = 1 ( $P = 0.50$ ); $P = 0\%$ Test for overall effect: $Z = 2.87$ ( $P = 0.004$ ) Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 5001.81, df = 28 ( $P < 0.00001$ ); $P = 100\%$ Test for overall effect: $Z = 2.87$ ( $P = 0.004$ ) Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 5001.81, df = 28 ( $P < 0.00001$ ); $P = 100\%$ Test for overall effect: $Z = 2.87$ ( $P = 0.004$ ) Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 5001.81, df = 28 ( $P < 0.00001$ ); $P = 100\%$ Test for overall effect: $Z = 2.87$ ( $P = 0.004$ ) Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 5005, H df = 4 ( $P < 0.00001$ ); $P = 100\%$ Test for overall effect: $Z = 2.87$ ( $P = 0.004$ ) Let orgeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 5005, H df = 4 ( $P < 0.00001$ ); $P = 00\%$ Test for overall effect: $Z = 2.87$ ( $P = 0.004$ ) Heterogeneit	Joel S. Finkelstein,2010	0.006	0.0008	20	0.014	0.002	29	5.1%	-0.01 [-0.01, -0.01]	-
Li ying.2013 0.0008 0.001 341 0.001 0.0002 112 5.1% -0.00 [-0.00, 0.00] Wu Yingchun.2017 0.034 0.104 50 0.028 0.098 50 0.4% 0.01 [-0.03, 0.05] Wu Yingchun.2017 0.034 0.104 50 0.028 0.098 50 0.4% 0.01 [-0.03, 0.05] Yang Yan,2014 0.012 0.148 40 0.053 0.141 13 0.1% -0.04 [-0.13, 0.05] Yutao Tang.2019 0.012 0.0112 28 0.007 0.0076 26 5.1% 0.01 [0.00, 0.01] Subtotal (95% CI) 831 559 26.0% -0.01 [-0.02, -0.00] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 11567.01, df = 8 (P < 0.00001); I <sup>2</sup> = 100% Test for overall effect: $Z = 2.48$ (P = 0.01) 1.6.4 18 Months Joel S. Finkelstein.2010 0.028 0.003 20 0.019 0.002 29 5.0% 0.01 [0.01, 0.01] Yang Yan,2014 0.026 0.0007 28 0.0118 0.0004 125 5.1% -0.00 [-0.00, -0.00] Yang Yan,2014 0.022 0.149 40 0.08 0.139 13 0.1% -0.06 [-0.15, 0.03] Yang Yan,2014 0.022 0.149 40 0.08 0.139 13 0.1% -0.06 [-0.15, 0.03] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 11381.95, df = 4 (P < 0.00001); I <sup>2</sup> = 100% Test for overall effect: $Z = 0.03$ (P = 0.97) 1.6.5 24 Months Joel S. Finkelstein,2010 0.052 0.006 20 0.025 0.003 29 4.8% 0.03 [0.02, 0.03] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.046, df = 1 (P = 0.50); I <sup>2</sup> = 0% Test for overall effect: $Z = 2.87$ (P = 0.0001) Total (95% CI) 520 2156 100.0% 0.00 [0.00, 0.01] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 50001.81, df = 28 (P < 0.00001); I <sup>2</sup> = 100% Test for overall effect: $Z = 2.87$ (P = 0.0001) Total (95% CI) 520 2156 100.0% 0.00 [0.00, 0.01] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 50001.81, df = 28 (P < 0.00001); I <sup>2</sup> = 100% Test for overall effect: $Z = 2.87$ (P = 0.0001) Total (95% CI) 520 216 40.4 df = 4 (P < 0.00001); I <sup>2</sup> = 0.00% Test for overall effect: $Z = 2.87$ (P = 0.004) Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 5001.81, df = 28 (P < 0.00001); I <sup>2</sup> = 0.00% Test for overall effect: $Z = 2.87$ (P = 0.0001); I <sup>2</sup> = 0.00% Test for overall effect: $Z = 2.87$ (P = 0.004) Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 5001.81, df = 28 (P < 0.00001); I <sup>2</sup> = 0.00% Test for overall effect: $Z = 2.87$ (P = 0.0001); I <sup>2</sup> = 0.00% Test fo	Langdahl 2017	-0.2	0.66	209	3.2	0.6	206	0.0%	-3.40 [-3.52, -3.28]	•
S. Gonnelli, 2006 0.016 0.4 27 0.004 0.0946 28 0.0% 0.01 [-0.14, 0.17] Wu Yingchun, 2017 0.034 0.104 50 0.028 0.098 50 0.4% 0.01 [-0.03, 0.05] Yung Yang Yan, 2014 0.012 0.148 40 0.053 0.141 13 0.1% -0.04 [-0.13, 0.05] Yutao Tang, 2019 0.012 0.0012 28 0.007 0.00076 26 5.1% 0.01 [0.00, 0.01] Heterogeneily: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 11567.01, df = 8 ( $P < 0.00001$ ); $P = 100\%$ Test for overall effect: Z = 2.48 ( $P = 0.01$ ) 1.6.4 18 Months Joel S. Finkelstein, 2010 0.028 0.003 20 0.019 0.002 29 5.0% 0.01 [0.01, 0.01] Yang Yan, 2014 0.005 0.0008 341 0.017 0.002 112 5.1% -0.00 [-0.00, -0.00] Yang Yan, 2014 0.022 0.149 40 0.08 0.139 13 0.1% -0.06 [-0.15, 0.03] Yang Yan, 2014 0.022 0.149 40 0.08 0.139 13 0.1% -0.06 [-0.15, 0.03] Subtotal (95% Cl) 520 219 20.5% 0.03 [0.02, 0.02] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 11381.95, df = 4 ( $P < 0.00001$ ); $P = 100\%$ Test for overall effect: Z = 0.03 ( $P = 0.97$ ) 1.6.5 24 Months Joel S. Finkelstein, 2010 0.052 0.006 20 0.025 0.003 29 4.8% 0.03 [0.02, 0.03] Butotal (95% Cl) 1113 573 9.9% 0.03 [0.03, 0.03] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.46, df = 1 ( $P = 0.50$ ); $P = 0\%$ Test for overall effect: Z = -116.32 ( $P < 0.00001$ ): $P = 100\%$ Test for overall effect: Z = 2.87 ( $P = 0.000$ ) Test for overall effect: Z = 2.87 ( $P = 0.000$ ) Test for overall effect: Z = 2.87 ( $P = 0.000$ ) Test for overall effect: Z = 2.87 ( $P = 0.000$ ) Test for overall effect: Z = 2.87 ( $P = 0.000$ ) Test for overall effect: Z = 2.87 ( $P = 0.000$ ) Test for overall effect: Z = 2.87 ( $P = 0.000$ ) Test for overall effect: Z = 2.87 ( $P = 0.000$ ) Test for overall effect: Z = 2.87 ( $P = 0.000$ ) Test for overall effect: Z = 2.87 ( $P = 0.000$ ) Test for overall effect: Z = 2.87 ( $P = 0.000$ ) Test for overall effect: Z = 2.87 ( $P = 0.000$ ) Test for overall effect: Z = 2.87 ( $P = 0.000$ ) Test for overall effect: Z = 2.87 ( $P = 0.000$ ) Test for overall effect: Z = 2.87 ( $P = 0.000$ ) Test for overall effect: Z = 2.87 ( $P = 0.000$ ) Test for overall effect: Z = 2.87 ( $P = 0.000$ )	Li ying,2013	0.0008	0.001	341	0.001	0.0002	112	5.1%	-0.00 [-0.00, -0.00]	
Wu Yingchun,2017       0.034       0.104       50       0.028       0.098       50       0.4%       0.01 [-0.03, 0.05]         Yang Yan,2014       0.012       0.148       40       0.053       0.141       13       0.1%       -0.04 [-0.13, 0.05]         Yutao Tang,2019       0.012       0.012       0.001       0.001       0.001       0.001       0.001       0.011       0.	S. Gonnelli,2006	0.016	0.4	27	0.004	0.0946	28	0.0%	0.01 [-0.14, 0.17]	
Yang Yan, 2014 0.012 0.148 40 0.053 0.141 13 0.1% -0.04 $\{-0.13, 0.05\}$ Yutao Tang, 2019 0.012 0.0012 28 0.007 0.00076 26 5.1% 0.01 $[0.00, 0.01]$ Subtotal (95% CI) 831 559 26.0% -0.01 $[-0.02, -0.00]$ Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 11567.01, df = 8 (P < 0.00001); l <sup>2</sup> = 100% Test for overall effect: Z = 2.48 (P = 0.01) 1.6.4 18 Months Joel S. Finkelstein, 2010 0.028 0.003 20 0.019 0.002 29 5.0% 0.01 $[0.01, 0.01]$ Ko Chiba, 2022 0.011 0.004 91 0.014 0.002 40 5.1% -0.00 $[-0.00, -0.00]$ Li ying, 2013 0.005 0.0008 341 0.017 0.002 112 5.1% -0.01 $[-0.01, -0.01]$ Yang Yan, 2014 0.022 0.149 40 0.08 0.139 13 0.1% -0.06 $[-0.15, 0.03]$ Subtotal (95% CI) 520 219 20.5% 0.00 $[-0.02, 0.02]$ Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 11381.95, df = 4 (P < 0.00001); l <sup>2</sup> = 100% Test for overall effect: Z = 0.03 (P = 0.97) 1.6.5 24 Months Joel S. Finkelstein, 2010 0.052 0.006 20 0.025 0.003 29 4.8% 0.03 $[0.02, 0.03]$ ROBERT M. NEER, 2001 0.024 0.008 1093 -0.004 0.0007 544 5.1% 0.03 $[0.03, 0.03]$ Bubtotal (95% CI) 1113 573 9.9% 0.03 $[0.03, 0.03]$ Control Teriparatide -0.02 -0.01 0 0.01 0 0.01 0.02 $-0.02 -0.01 0 0.01 0 0.01$ 0.02 -0.02 -0.01 0 0.01 0 0.01 0.02	Wu Yingchun,2017	0.034	0.104	50	0.028	0.098	50	0.4%	0.01 [-0.03, 0.05]	
Yutao Tang.2019       0.012       0.0012       28       0.007       0.0076       26       5.1%       0.01 [0.00, 0.01]         Subtotal (95% CI)       831       559       26.0%       -0.01 [-0.02, -0.00]         Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 11567.01, df = 8 (P < 0.00001); I <sup>2</sup> = 100%       7       7       9       0.01 [0.01, 0.01]         1.6.4 18 Months       Joel S. Finkelstein, 2010       0.028       0.003       20       0.019       0.002       29       5.0%       0.01 [0.01, 0.01]         Ko Chiba, 2022       0.011       0.004       91       0.014       0.002       40       5.1%       -0.00 [-0.00, -0.00]         Yang Yan, 2014       0.002       0.008       0.118       0.004       25       5.1%       0.001 [0.01, 0.01]       *         Yang Yan, 2014       0.022       0.149       40       0.08       0.139       13       0.1%       -0.06 [-0.15, 0.03]         Subtotal (95% CI)       520       20       219       20.5%       0.003 [0.02, 0.03]       0.03 [0.02, 0.03]       0.03 [0.03, 0.03]         Joel S. Finkelstein, 2010       0.52       0.006       20       0.25       0.003       29       4.8%       0.03 [0.02, 0.03]         Joel S. Finkelstein, 2010       0.052<	Yang Yan,2014	0.012	0.148	40	0.053	0.141	13	0.1%	-0.04 [-0.13, 0.05]	•
Subtotal (95% CI) 831 559 26.0% -0.01 [-0.02, -0.00] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 11567.01, df = 8 (P < 0.00001); I <sup>2</sup> = 100% Test for overall effect: Z = 2.48 (P = 0.01) 1.6.4 18 Months Joel S. Finkelstein,2010 0.028 0.003 20 0.019 0.002 29 5.0% 0.01 [0.01, 0.01] Ko Chiba, 2022 0.011 0.004 91 0.014 0.002 40 5.1% -0.00 [-0.00, -0.00] Li ying,2013 0.005 0.0008 341 0.017 0.002 112 5.1% -0.01 [-0.01, -0.01] Yang Yan,2014 0.022 0.149 40 0.08 0.139 13 0.1% -0.06 [-0.15, 0.03] Subtotal (95% CI) 520 219 20.5% 0.00 [-0.02, 0.02] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 11381.95, df = 4 (P < 0.00001); I <sup>2</sup> = 100% Test for overall effect: Z = 0.03 (P = 0.97) 1.6.5 24 Months Joel S. Finkelstein,2010 0.052 0.006 20 0.025 0.003 29 4.8% 0.03 [0.02, 0.03] ROBERT M. NEER,2001 0.024 0.008 1093 -0.004 0.0007 544 5.1% 0.03 [0.03, 0.03] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.46, df = 1 (P = 0.50); I <sup>2</sup> = 0% Test for overall effect: Z = 116.32 (P < 0.00001); I <sup>2</sup> = 100% Test for overall effect: Z = 2.87 (P = 0.004) Test for overall effe	Yutao Tang,2019	0.012	0.0012	28	0.007	0.00076	26	5.1%	0.01 [0.00, 0.01]	*
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 11567.01, df = 8 (P < 0.00001); l <sup>2</sup> = 100% Test for overall effect: Z = 2.48 (P = 0.01) <b>1.6.4 18 Months</b> Joel S. Finkelstein,2010 0.028 0.003 20 0.019 0.002 29 5.0% 0.01 [0.01, 0.01] Ko Chiba,2022 0.011 0.004 91 0.014 0.002 40 5.1% -0.00 [-0.00, -0.00] Tony M Keaveny,2006 0.026 0.0007 28 0.0118 0.0004 25 5.1% 0.01 [0.01, 0.01] Yang Yan,2014 0.022 0.149 40 0.08 0.139 13 0.1% -0.06 [-0.15, 0.03] Subtotal (95% Cl) 520 219 20.5% 0.00 [-0.02, 0.02] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 11381.95, df = 4 (P < 0.00001); l <sup>2</sup> = 100% Test for overall effect: Z = 0.03 (P = 0.97) <b>1.6.5 24 Months</b> Joel S. Finkelstein,2010 0.052 0.006 20 0.025 0.003 29 4.8% 0.03 [0.02, 0.03] Subtotal (95% Cl) 0.024 0.008 1093 -0.004 0.0007 544 5.1% 0.03 [0.03, 0.03] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.46, df = 1 (P = 0.50); l <sup>2</sup> = 0% Test for overall effect: Z = 116.32 (P < 0.00001) Total (95% Cl) 3586 2156 100.0% 0.00 [0.00, 0.01] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 50001.81, df = 28 (P < 0.00001); l <sup>2</sup> = 100% Test for overall effect: Z = 2.87 (P = 0.004) Test for overall effect: Z = 2.87 (P = 0.004) Test for overall effect: Z = 2.87 (P = 0.004) Test for overall effect: Z = 2.87 (P = 0.004) Test for overall effect: Z = 2.87 (P = 0.004) Test for overall effect: Z = 2.87 (P = 0.004) Test for overall effect: Z = 2.87 (P = 0.004) Test for overall effect: Z = 2.87 (P = 0.004) Test for overall effect: Z = 2.87 (P = 0.004) Test for overall effect: Z = 2.87 (P = 0.004) Test for overall effect: Z = 2.87 (P = 0.004) Test for overall effect: Z = 2.87 (P = 0.004) Test for overall effect: Z = 2.87 (P = 0.004) Test for subroup differences: Chi <sup>2</sup> = 2.045 44 dt = 4 (P < 0.00001); l <sup>2</sup> = 90.8%	Subtotal (95% CI)			831			559	26.0%	-0.01 [-0.02, -0.00]	
Test for overall effect: $Z = 2.48 (P = 0.01)$ <b>1.6.4 18 Months</b> Joel S. Finkelstein, 2010 0.028 0.003 20 0.019 0.002 29 5.0% 0.01 [0.01, 0.01] Ko Chiba, 2022 0.011 0.004 91 0.014 0.002 40 5.1% -0.00 [-0.00, -0.00] Li ying, 2013 0.005 0.0008 341 0.017 0.002 112 5.1% -0.01 [-0.01, -0.01] Tony M Keaveny, 2006 0.026 0.0007 28 0.0118 0.0004 25 5.1% 0.01 [0.01, 0.01] Yang Yan, 2014 0.022 0.149 40 0.08 0.139 13 0.1% -0.06 [-0.15, 0.03] Subtotal (95% Cl) 520 219 20.5% 0.00 [-0.02, 0.02] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 11381.95, df = 4 (P < 0.00001); l <sup>2</sup> = 100% Test for overall effect: Z = 0.03 (P = 0.97) <b>1.6.5 24 Months</b> Joel S. Finkelstein, 2010 0.052 0.006 20 0.025 0.003 29 4.8% 0.03 [0.02, 0.03] Subtotal (95% Cl) 1113 573 9.9% 0.03 [0.03, 0.03] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.46, df = 1 (P = 0.50); l <sup>2</sup> = 0% Test for overall effect: Z = 116.32 (P < 0.00001) Total (95% Cl) 3586 2156 100.0% 0.00 [0.00, 0.01] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 2.045 (A df = 4 (P < 0.00001); l <sup>2</sup> = 100% Test for overall effect: Z = 2.87 (P = 0.004) Test for overall effect: Z = 2.87 (P = 0.004) Test for overall effect: Z = 2.45 (P < 0.00001); l <sup>2</sup> = 98 8%	Heterogeneity: Tau <sup>2</sup> = 0.00; Chi	<sup>2</sup> = 11567.0	01, df = 8 (F	o < 0.00	0001); l <sup>2</sup> =	100%				
1.6.4 18 Months         Joel S. Finkelstein, 2010       0.028       0.003       20       0.019       0.002       29       5.0%       0.01 [0.01, 0.01]         Ko Chiba, 2022       0.011       0.004       91       0.014       0.002       40       5.1%       -0.00 [-0.00, -0.00]         Li ying, 2013       0.005       0.0008       341       0.017       0.002       112       5.1%       -0.01 [-0.01, -0.01]         Tony M Keaveny, 2006       0.026       0.0007       28       0.018       0.39       13       0.1%       -0.06 [-0.15, 0.03]         Yang Yan, 2014       0.022       0.149       40       0.08       0.139       13       0.1%       -0.06 [-0.15, 0.03]         Subtotal (95% CI)       520       219       20.5%       0.00 [-0.02, 0.02]       -         Heterogeneity: Tau² = 0.00; Chi² = 11381.95, df = 4 (P < 0.00001); l² = 100%	Test for overall effect: Z = 2.48	(P = 0.01)			,.					
1.6.4 18 Months         Joel S. Finkelstein, 2010       0.028       0.003       20       0.019       0.002       29       5.0%       0.01 [0.01, 0.01]         Ko Chiba, 2022       0.011       0.004       91       0.014       0.002       40       5.1%       -0.00 [-0.00, -0.00]         Li ying, 2013       0.005       0.0008       341       0.017       0.002       112       5.1%       -0.01 [0.01, 0.01]         Yang Yan, 2014       0.022       0.149       40       0.08       0.139       13       0.1%       -0.06 [-0.15, 0.03]         Subtotal (95% Cl)       520       219       20.5%       0.00 [-0.02, 0.02]       -         Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 11381.95, df = 4 (P < 0.00001); l <sup>2</sup> = 100%       29       4.8%       0.03 [0.02, 0.03]       -         Subtotal (95% Cl)       520       0.025       0.003       29       4.8%       0.03 [0.02, 0.03]       -         ROBERT M. NEER, 2001       0.024       0.008       1093       -0.004       0.007       544       5.1%       0.03 [0.03, 0.03]       -         Subtotal (95% Cl)       1113       573       9.9%       0.03 [0.03, 0.03]       -       -       -       -0.02       -0.01       0       0.01 </td <td></td> <td>( )</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td>		( )								
Joel S. Finkelstein, 2010 0.028 0.003 20 0.019 0.002 29 5.0% 0.01 [0.01, 0.01] Ko Chiba, 2022 0.011 0.004 91 0.014 0.002 40 5.1% -0.00 [-0.00, -0.00] Li ying, 2013 0.005 0.0008 341 0.017 0.002 112 5.1% -0.01 [-0.01, -0.01] Tony M Keaveny, 2006 0.026 0.0007 28 0.0118 0.0004 25 5.1% 0.01 [0.01, 0.01] Yang Yan, 2014 0.022 0.149 40 0.08 0.139 13 0.1% -0.06 [-0.15, 0.03] Subtotal (95% CI) 520 219 20.5% 0.00 [-0.02, 0.02] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 11381.95, df = 4 (P < 0.00001); l <sup>2</sup> = 100% Test for overall effect: Z = 0.03 (P = 0.97) 1.6.5 24 Months Joel S. Finkelstein, 2010 0.024 0.008 1093 -0.004 0.0007 544 5.1% 0.03 [0.02, 0.03] Subtotal (95% CI) 1113 573 9.9% 0.03 [0.03, 0.03] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.46, df = 1 (P = 0.50); l <sup>2</sup> = 0% Test for overall effect: Z = 116.32 (P < 0.00001); l <sup>2</sup> = 100% Test for overall effect: Z = 0.03; Chi <sup>2</sup> = 50001.81, df = 28 (P < 0.00001); l <sup>2</sup> = 100% Test for overall effect: Z = 2.87 (P = 0.004) Test for overall effect: Z = 2.86 Test for overall effect: Z = 2.87 (P = 0.004) Test for overall effect: Z = 2.86 Test	1.6.4 18 Months									
$\begin{array}{c} \text{Loss of this state in 2016} & \text{Loss of the state in 2016} & Loss of the state in $	loel S. Finkelstein 2010	0.028	0.003	20	0.019	0 002	29	5.0%	0.01.00.01.0.011	
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Ko Chiba 2022	0.020	0.003	01	0.013	0.002	40	5.0%		-
$\begin{array}{c} \text{Lyng}_{2015} & \text{O}_{0005} & \text{O}_{0006} & \text{S}^{41} & \text{O}_{017} & \text{O}_{002} & \text{I12} & \text{S}^{176} & \text{O}_{001} [-0.01, -0.01] \\ \hline \text{Tony M Keaveny,2006} & 0.026 & 0.0007 & 28 & 0.0118 & 0.0004 & 25 & 5.1\% & 0.01 [0.01, 0.01] \\ \hline \text{Yang Yan,2014} & 0.022 & 0.149 & 40 & 0.08 & 0.139 & 13 & 0.1\% & -0.06 [-0.15, 0.03] \\ \hline \text{Subtotal (95\% Cl)} & 520 & 219 & 20.5\% & 0.00 [-0.02, 0.02] \\ \hline \text{Heterogeneity: Tau^2} = 0.00; \text{Chi}^2 = 11381.95, \text{df} = 4 (P < 0.00001); l^2 = 100\% \\ \hline \text{Test for overall effect: } Z = 0.03 (P = 0.97) \\ \hline \textbf{1.6.5 24 Months} \\ \text{Joel S. Finkelstein,2010} & 0.052 & 0.006 & 20 & 0.025 & 0.003 & 29 & 4.8\% & 0.03 [0.02, 0.03] \\ \hline \text{ROBERT M. NEER,2001} & 0.024 & 0.008 & 1093 & -0.004 & 0.007 & 544 & 5.1\% & 0.03 [0.03, 0.03] \\ \hline \text{Subtotal (95\% Cl)} & 1113 & 573 & 9.9\% & 0.03 [0.03, 0.03] \\ \hline \text{Heterogeneity: Tau^2} = 0.00; \text{Chi}^2 = 0.46, \text{df} = 1 (P = 0.50); l^2 = 0\% \\ \hline \text{Test for overall effect: } Z = 116.32 (P < 0.00001) \\ \hline \text{Total (95\% Cl)} & 3586 & 2156 & 100.0\% & 0.00 [0.00, 0.01] \\ \hline \text{Heterogeneity: Tau^2} = 0.00; \text{Chi}^2 = 50001.81, \text{df} = 28 (P < 0.00001); l^2 = 100\% \\ \hline \text{Test for overall effect: } Z = 2.87 (P = 0.004) \\ \hline \text{Test for overall effect: } Z = 2.87 (P = 0.004) \\ \hline \text{Test for overall effect: } Z = 2.87 (P = 0.004) \\ \hline \text{Test for overall effect: } Z = 2.87 (P = 0.004) \\ \hline \text{Test for overall effect: } Z = 2.87 (P = 0.004) \\ \hline \text{Control Teriparatide} \\ \hline $		0.011	0.004	244	0.014	0.002	40	5 10/		• ·
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Li yiliy,2013 Topy M Koovory 2006	0.000	0.0008	J41 20	0.017	0.002	112	J.170 5 40/		· · · ·
rang ran, 2014 0.022 0.149 40 0.08 0.139 13 0.1% -0.06 [-0.15, 0.03] Subtotal (95% Cl) 520 219 20.5% 0.00 [-0.02, 0.02] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 11381.95, df = 4 (P < 0.00001); l <sup>2</sup> = 100% Test for overall effect: $Z = 0.03$ (P = 0.97) 1.6.5 24 Months Joel S. Finkelstein, 2010 0.052 0.006 20 0.025 0.003 29 4.8% 0.03 [0.02, 0.03] ROBERT M. NEER, 2001 0.040 0.008 1093 -0.004 0.0007 544 5.1% 0.03 [0.03, 0.03] Subtotal (95% Cl) 1113 573 9.9% 0.03 [0.03, 0.03] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.46, df = 1 (P = 0.50); l <sup>2</sup> = 0% Test for overall effect: $Z = 116.32$ (P < 0.00001) Total (95% Cl) 3586 2156 100.0% 0.00 [0.00, 0.01] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 50001.81, df = 28 (P < 0.00001); l <sup>2</sup> = 100% Test for overall effect: $Z = 2.87$ (P = 0.004) Control Teriparatide	Vers Ver 2014	0.026	0.0007	∠8 40	0.0118	0.0004	25	D.1%		<u> </u>
Subtrain (95% C1)       520       219 $20.5\%$ $0.00 [-0.02, 0.02]$ Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 11381.95, df = 4 (P < 0.00001); l <sup>2</sup> = 100%         Test for overall effect: Z = 0.03 (P = 0.97) <b>1.6.5 24 Months</b> Joel S. Finkelstein,2010       0.052       0.002       0.002       0.003 [0.02, 0.03]         ROBERT M. NEER,2001       0.024       0.008       1093       -0.004       0.0007       544       5.1%       0.03 [0.03, 0.03]         Subtotal (95% Cl)       1113       573       9.9%       0.03 [0.03, 0.03]       Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.46, df = 1 (P = 0.50); l <sup>2</sup> = 0%       Test for overall effect: Z = 116.32 (P < 0.00001)	rang ran,2014	0.022	0.149	40	0.08	0.139	13	0.1%	-0.06 [-0.15, 0.03]	
Heterogeneity: $1au^{2} = 0.00$ ; $Chi^{2} = 11381.95$ , $df = 4$ (P < $0.00001$ ); $l^{2} = 100\%$ Test for overall effect: Z = $0.03$ (P = $0.97$ ) <b>1.6.5 24 Months</b> Joel S. Finkelstein, 2010 0.052 0.006 20 0.025 0.003 29 4.8% 0.03 [0.02, 0.03] ROBERT M. NEER, 2001 0.024 0.008 1093 -0.004 0.0007 544 5.1% 0.03 [0.03, 0.03] Subtotal (95% Cl) 1113 573 9.9% 0.03 [0.03, 0.03] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.46, df = 1 (P = 0.50); l <sup>2</sup> = 0% Test for overall effect: Z = 116.32 (P < 0.00001) Total (95% Cl) 3586 2156 100.0% 0.00 [0.00, 0.01] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 50001.81, df = 28 (P < 0.00001); l <sup>2</sup> = 100% Test for overall effect: Z = 2.87 (P = 0.004) Control Teriparatide	Subtotal (95% CI)			520		1005	219	20.5%	0.00 [-0.02, 0.02]	
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1.6.5 24 Months         Joel S. Finkelstein, 2010       0.052       0.006       20       0.025       0.003       29       4.8%       0.03       [0.02, 0.03]         ROBERT M. NEER, 2001       0.024       0.008       1093       -0.004       0.0007       544       5.1%       0.03       [0.03, 0.03]         Subtotal (95% Cl)       1113       573       9.9%       0.03       [0.03, 0.03]       1.033       1.033         Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.46, df = 1 (P = 0.50); l <sup>2</sup> = 0%       Test for overall effect: Z = 116.32 (P < 0.00001)	Test for overall effect: Z = 0.03	(P = 0.97)								
1.6.5 24 Months         Joel S. Finkelstein,2010 $0.052$ $0.006$ $20$ $0.025$ $0.003$ $29$ $4.8\%$ $0.03$ $[0.02, 0.03]$ ROBERT M. NEER,2001 $0.024$ $0.008$ $1093$ $-0.004$ $0.007$ $544$ $5.1\%$ $0.03$ $[0.03, 0.03]$ Subtotal (95% CI)       1113       573 $9.9\%$ $0.03$ $[0.03, 0.03]$ Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.46, df = 1 (P = 0.50); l <sup>2</sup> = 0%       Test for overall effect: Z = 116.32 (P < 0.00001)										
Joel S. Finkelstein, 2010 0.052 0.006 20 0.025 0.003 29 4.8% 0.03 $[0.02, 0.03]$ ROBERT M. NEER, 2001 0.024 0.008 1093 -0.004 0.0007 544 5.1% 0.03 $[0.03, 0.03]$ Subtotal (95% Cl) 1113 573 9.9% 0.03 $[0.03, 0.03]$ Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.46, df = 1 (P = 0.50); l <sup>2</sup> = 0% Test for overall effect: Z = 116.32 (P < 0.00001) Total (95% Cl) 3586 2156 100.0% 0.00 $[0.00, 0.01]$ Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 50001.81, df = 28 (P < 0.00001); l <sup>2</sup> = 100% Test for overall effect: Z = 2.87 (P = 0.004) Test for overall effect: Z = 2.87 (P = 0.004) Test for overall effect: Z = 2.87 (P = 0.004) Control Teriparatide	1.6.5 24 Months									
ROBERT M. NEER,2001 $0.024$ $0.008$ $1093$ $-0.004$ $0.0007$ $544$ $5.1\%$ $0.03$ $[0.03, 0.03]$ Subtotal (95% CI)         Test for overall effect: Z = 116.32 (P < 0.00001)	Joel S. Finkelstein,2010	0.052	0.006	20	0.025	0.003	29	4.8%	0.03 [0.02, 0.03]	
Subtotal (95% Cl)       1113       573       9.9%       0.03 [0.03, 0.03]         Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.46, df = 1 (P = 0.50); l <sup>2</sup> = 0%       Test for overall effect: Z = 116.32 (P < 0.00001)	ROBERT M. NEER,2001	0.024	0.008	1093	-0.004	0.0007	544	5.1%	0.03 [0.03, 0.03]	
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.46, df = 1 (P = 0.50); l <sup>2</sup> = 0% Test for overall effect: Z = 116.32 (P < 0.00001) Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 50001.81, df = 28 (P < 0.00001); l <sup>2</sup> = 100% Test for overall effect: Z = 2.87 (P = 0.004) T	Subtotal (95% CI)			1113			573	9.9%	0.03 [0.03, 0.03]	
Test for overall effect: Z = 116.32 (P < 0.00001)	Heterogeneity: Tau <sup>2</sup> = 0.00; Chi	<sup>2</sup> = 0.46, df	= 1 (P = 0.	50); l² =	= 0%					
Total (95% Cl)       3586       2156       100.0%       0.00 [0.00, 0.01]         Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 50001.81, df = 28 (P < 0.00001); l <sup>2</sup> = 100% $-0.02$ $-0.01$ $0$ $0.01$ $0.02$ Test for overall effect: Z = 2.87 (P = 0.004)       Control       Control       Teriparatide         Test for subgroup differences: Chi <sup>2</sup> = 2045 44. df = 4 (P < 0.00001); l <sup>2</sup> = 99.8%       Control       Control       Teriparatide	Test for overall effect: Z = 116.3	32 (P < 0.00	0001)							
Total (95% CI)       3586       2156       100.0%       0.00 [0.00, 0.01]         Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 50001.81, df = 28 (P < 0.00001); l <sup>2</sup> = 100% $-0.02$ $-0.01$ $0$ $0.01$ $0.02$ Test for overall effect: Z = 2.87 (P = 0.004)       Test for subgroup differences: Chi <sup>2</sup> = 2045 44. df = 4 (P < 0.00001); l <sup>2</sup> = 99.8%       Control       Teriparatide			,							
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 50001.81, df = 28 (P < 0.00001); l <sup>2</sup> = 100% Test for overall effect: Z = 2.87 (P = 0.004) Test for subgroup differences: Chi <sup>2</sup> = 2045 44. df = 4 (P < 0.00001); l <sup>2</sup> = 99.8%	Total (95% CI)			3586			2156	100.0%	0.00 [0.00, 0.01]	•
Test for overall effect: $Z = 2.87$ (P = 0.004) Test for subgroup differences: Chi <sup>2</sup> = 2045 44. df = 4 (P < 0.00001) l <sup>2</sup> = 99.8% Control Teriparatide	Heterogeneity: $Tau^2 = 0.00^{\circ}$ Chi	2 = 50001 F	31. df = 28	(P < 0 (	0001)· J2	= 100%				
Test for subarrup differences: Chi <sup>2</sup> = 2045 44 df = 4 (P < 0.00011) l <sup>2</sup> = 99.8% Control Teriparatide	Test for overall effect: $7 = 2.87$	(P = 0.004)	.,							-0.02 -0.01 0 0.01 0.02
	Test for subgroup differences:	Chi <sup>2</sup> = 2045	44 df = 4	P<00	0001) I <sup>2</sup>	= 99 8%				Control Teriparatide

This forest plot diagram illustrates changes in bone mineral density between teriparatide and placebo treatments at the femoral neck (20, 53, 54, 55, 56, 59, 60, 62, 63, 64, 65, 68, 70, 71).

of 79.32 and a 95% CI of 17.88–140.77 ( $I^2 = 100\%$ , P = 0.01), as depicted in Fig. 8. This suggests that long-term treatment with teriparatide significantly boosts osteocalcin levels in patients, demonstrating its effectiveness in enhancing bone metabolism compared to the control group.

**P1NP result**: Data from seven studies involving 1415 patients to assess changes in the biomarker P1NP, a

marker of bone formation, following treatment with PTH (1–34) versus a control group. Due to high variability in the results across these studies ( $I^2 = 100\%$ , P < 0.00001), a random-effects model was applied to accurately synthesize the findings.

The analysis revealed a significant difference in P1NP levels between the Teriparatide group and the control group at 6 and 12 months, with an MD of 104.78 and a 95% CI ranging from 35.84 to 173.73 ( $I^2 = 87\%$ ,



This forest plot diagram illustrates changes in bone mineral density between teriparatide and placebo treatments at the radial bone (20, 56, 60).

P < 0.00001), indicating a substantial increase in bone formation in the treatment group. However, at the 18-month mark, the difference between groups was not statistically significant (MD = 402.23, 95% CI = -15.30-819.77,  $I^2$  = 100%, P = 0.06), suggesting a variance in treatment response over time.

Overall, when considering the entire treatment period, the data showed a significant improvement in P1NP levels with an overall MD of 257.92 (95% CI=209.98-305.86,  $I^2$ =100%, P < 0.00001) in the teriparatide-treated group compared to controls, as illustrated in Fig. 8B. This indicates that long-term Teriparatide administration significantly enhances bone formation, highlighting its efficacy in improving skeletal health over time.

**C-telopeptide result**: Data from three studies involving 282 participants were analyzed to evaluate the impact of teriparatide (PTH 1–34) on C-telopeptide levels, a marker of bone resorption. The substantial variability in results across these studies ( $I^2 = 100\%$ , P < 0.00001) necessitated using a random-effects model for a comprehensive analysis.

At the 6-month interval, the analysis revealed a significant difference in C-telopeptide levels between the Teriparatide group and the control group, with a mean difference (MD) of 0.78 and a 95% CI from 0.62 to 0.94, indicating a pronounced reduction in bone resorption in the teriparatide group ( $I^2$  = 87%, P < 0.00001). However, by the 12-month mark, this significant difference diminished (MD = 0.57, 95% CI = -0.34-1.47,  $I^2$  = 100%, P = 0.22), suggesting a temporal effect of the treatment.

Overall, the aggregated data across the studies showed a significant reduction in C-telopeptide levels with teriparatide treatment over time (MD = 0.69, 95% CI = 0.30–1.08,  $I^2$  = 99%, P < 0.00005), as presented in Fig. 8C. This indicates that long-term treatment with teriparatide significantly affects bone turnover markers, emphasizing its beneficial role in managing bone resorption in patients.

#### Safety of teriparatide

**Adverse events**: The review analyzed 13 papers involving 4945 patients, focusing on the frequency of adverse events reported. The consistency across these studies was high, as indicated by the absence of statistical heterogeneity ( $I^2 = 0\%$ , P = 0.77), which justified using a fixed-effects model for analysis.

The findings revealed that the group receiving the experimental treatment experienced more adverse events than the control groups, with an RR of 1.63 and a 95% CI of 1.32–2.01. This outcome suggests that the experimental group has a higher likelihood of adverse events than other control groups, as detailed in Fig. 9A. This analysis highlights the need for careful consideration of the safety profile of the experimental treatment in comparison to alternatives.

**Death**: Four publications, capturing 2065 patients, meticulously addressed the incidence of death across both cohorts. The statistical variation,  $I^2 = 100.0\%$ , signifies uniformity in the trials' results, which supports applying



	Teriparatide Control			Mean Difference	Mean Difference						
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% C	1	IV, Random, 95% CI	
1.9.1 6 Months											
A. D. Anastasilakis,2008	143.4	70.077	22	-11.8	21.53	22	8.7%	155.20 [124.57, 185.83]		-	
Jing Deng,2017	298.08	108.76	43	-0.015	0.008	22	8.6%	298.09 [265.59, 330.60]			
Joel S. Finkelstein,2010	42.869	11.75	20	53.28	18.48	29	8.9%	-10.41 [-18.88, -1.94]		1	
Ko Chiba,2022	-74.8	10.68	91	-44.392	17.084	40	9.0%	-30.41 [-36.14, -24.68]			
Tony M Keaveny,2006	82.621	4.263	28	-25.235	2.036	25	9.0%	107.86 [106.09, 109.63]			
Yutao Tang,2019	86.22	28	28	-30.37	8.772	260	8.9%	116.59 [106.16, 127.02]			
Subtotal (95% CI)			232			398	53.1%	104.78 [35.84, 173.73]		•	
Heterogeneity: Tau <sup>2</sup> = 732	9.64; Chi	² = 2812.	98, df =	= 5 (P < 0.	.00001);	l² = 100	1%				
Test for overall effect: Z =	2.98 (P =	0.003)									
1.9.2 12 Months											
Jing Deng,2017	771.63	211.57	20	36.23	12.57	29	6.7%	735.40 [642.56, 828.24]			
Joel S. Finkelstein,2010	771.63	211.57	20	36.23	12.57	29	6.7%	735.40 [642.56, 828.24]			
Yutao Tang,2019	79.27	25.75	28	-26.37	7.616	26	8.9%	105.64 [95.66, 115.62]			
Subtotal (95% CI)			68			84	22.4%	523.90 [20.99, 1026.81]			
Heterogeneity: Tau <sup>2</sup> = 196	6019.19; C	Chi² = 345	5.56, df	= 2 (P < 0	0.00001)	; l² = 99	1%				
Test for overall effect: Z =	2.04 (P =	0.04)									
1.9.3 18 Months											
Joel S. Finkelstein,2010	664.64	180.24	20	30.43	10.56	29	7.2%	634.21 [555.12, 713.30]			
Ko Chiba.2022	-12	9.4	91	-50.406	19.395	40	9.0%	38.41 [32.09, 44.72]			
Li ying,2013	501.96	400.5	341	-35.33	28.12	112	8.4%	537.29 [494.46, 580.12]			
Subtotal (95% CI)			452			181	24.5%	402.23 [-15.30, 819.77]			
Heterogeneity: Tau <sup>2</sup> = 135	5447.44; C	chi² = 719	9.23, df	= 2 (P < 0	0.00001)	; l <sup>2</sup> = 10	0%				
Test for overall effect: Z =	1.89 (P =	0.06)									
Total (95% CI)			752			663	100.0%	257.92 [209.98, 305.86]		•	
Heterogeneity: Tau <sup>2</sup> = 666	67.52: Chi	<sup>2</sup> = 4062.	53. df =	= 11 (P < (	0.00001)	: l <sup>2</sup> = 10	0%		+		+
Test for overall effect: 7 =	10.54 (P	< 0.0000	1)			,			-1000 -500	0 5	500 100
Toot for subgroup differen	cos: Chi2	= 4 42 d	f = 2 (P)	= 0 11)	2 = 54.80	%				Control Teriparatide	Э



(A) Forest plot illustrating the effects of teriparatide and placebo treatments on osteocalcin at 6 and 12 months (56, 59). (B) Forest plot illustrating the effects of teriparatide and placebo treatments on P1NP at 6,12, and 18 months (50, 55, 56, 58, 59, 62). (C) Forest plot illustrating the effects of teriparatide and placebo treatments on CTx changes at 6 and 12 (50, 55, 59).

# Α

	Teripara	tide	Contr	ol		Odds Ratio				
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C		M-H, Fixed, 95% CI		
A. D. Anastasilakis,2008	11	22	7	22	2.6%	2.14 [0.63, 7.30]				
David L Kendler,2018	495	516	500	533	14.6%	1.56 [0.89, 2.73]		+		
Felicia Cosman, 2011	11	137	6	137	4.0%	1.91 [0.68, 5.31]				
JEAN-JACQUES BODY,2002	14	73	7	73	4.1%	2.24 [0.85, 5.92]				
Jing Deng,2017	4	43	0	22	0.4%	5.13 [0.26, 99.65]				
Ko Chiba,2022	7	91	0	40	0.5%	7.19 [0.40, 128.99]				$\rightarrow$
Langdahl 2017	23	214	17	218	11.0%	1.42 [0.74, 2.75]		+		
Li Mei,2022	92	121	15	32	4.2%	3.60 [1.60, 8.08]				
Li ying,2013	251	341	79	112	22.9%	1.16 [0.73, 1.87]				
Michael R. McClung,2005	18	102	13	101	7.9%	1.45 [0.67, 3.14]				
ROBERT M. NEER,2001	33	1093	11	544	10.4%	1.51 [0.76, 3.01]		+		
Wu Yingchun,2017	5	50	2	50	1.3%	2.67 [0.49, 14.44]				
Yang Yan,2014	12	40	2	13	1.5%	2.36 [0.45, 12.29]			_	
ZHANG Xiu-zhen,2009	67	100	62	105	14.6%	1.41 [0.80, 2.49]		+		
Total (95% CI)		2943		2002	100.0%	1.63 [1.32, 2.01]		•		
Total events	1043		721							
Heterogeneity: Chi <sup>2</sup> = 8.97, df =	13 (P = 0.	77); l² =	0%				+		+	+
Test for overall effect: Z = 4.52 (	)1)					0.01 (	J.1 1 Control Tarinarati	10 d a	100	
		,						Control Teriparati	ue	

_	Teripara	tide	Contr	ol		Odds Ratio				
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, Fixed, 95% C	:	
David L Kendler,2018	15	516	7	533	63.4%	2.25 [0.91, 5.56]				
Ko Chiba,2022	1	91	1	40	13.0%	0.43 [0.03, 7.11]			_	
Langdahl 2017	1	214	1	218	9.3%	1.02 [0.06, 16.39]				
Li ying,2013	1	341	1	112	14.2%	0.33 [0.02, 5.26]				
Total (95% CI)		1162		903	100.0%	1.62 [0.75, 3.51]				
Total events	18		10							
Heterogeneity: Chi <sup>2</sup> = 2.	74, df = 3 (	P = 0.43	3); l² = 0%	, 0			1	10		
Test for overall effect: Z	= 1.23 (P =	= 0.22)			Control Teriparatid					

#### Figure 9

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(A) Forest plot comparing the safety of teriparatide and placebo treatments in terms of adverse events (20, 50, 51, 52, 53, 54, 55, 56, 57, 60, 61, 62, 64). (B) Forest plot comparing the safety of teriparatide and placebo treatments in terms of Sudden death (20, 50, 51, 52, 53, 54, 55, 57, 60, 61, 62, 64).

a fixed-effects model to derive the combined metric. No noteworthy disparities were observed between the death rates of the two groups regarding patient safety (RR = 1.62, 95% CI: 0.75–3.51). Thus, juxtaposing the intervention group with the control group, the data suggest no significant enhancement in patient safety (Fig. 9B). The analysis indicates that there is no significant difference in the occurrence of death between the intervention group and the control group.

## Discussion

This meta-analysis sought to evaluate the effectiveness and safety of teriparatide (PTH 1–34) in comparison to alternative treatments or placebo in postmenopausal women diagnosed with osteoporosis. A thorough literature review was conducted across various databases from their inception until January 2023. Twenty-two studies were included to evaluate the effectiveness of teriparatide (PTH 1–34) compared to other treatments or placebo. The control groups in the trials comprised risedronate in two studies (50, 51), zoledronic acid in two (52, 53), alendronate in seven (54, 55, 56, 57, 58, 59, 60), salmon calcitonin in one (61), elcatonin in three (62, 63, 64), an antiresorptive agent in one (65), placebo in one (20), denosumab in two (66, 67), abaloparatide in one (68), and romosozumab in three (69, 70, 71). The research was conducted in various regions, including 7 studies in China, 11 in the USA, 1 each in Italy, Greece, and Japan, and 2 multicenter studies.

## **Comparison with previous studies**

Our study provides important insights into the treatment of postmenopausal osteoporosis. Our findings suggest that teriparatide is more effective than bisphosphonates in reducing fracture risk and improving lumbar spine BMD. This aligns with previous research, such as that conducted by Yuan *et al.* (72), which also demonstrated teriparatide's efficacy in enhancing BMD. Our analysis did not focus on fracture healing, but the positive effects of teriparatide on bone quality suggest that it may also benefit the fracture healing process. Studies have shown that teriparatide can improve bone density and reduce fracture risks, which could lead to better healing outcomes (29, 30, 31, 32, 33, 34). However, the studies we reviewed did not provide enough direct evidence on fracture healing rates, so further research is needed to fully understand teriparatide's impact on this area.

A meta-analysis conducted by Liu *et al.* (73) demonstrated that romosozumab is highly effective in reducing the risk of various types of fractures and improving BMD in different regions compared to other therapies. Our study supports these findings and highlights the potential of romosozumab in managing osteoporosis. Another study suggested that combining teriparatide and denosumab may lead to better results in terms of BMD in the lumbar spine and hip compared to monotherapy (74). This indicates a promising direction for future treatment strategies and is consistent with our findings.

Simpson et al. (75) also highlighted the effectiveness non-bisphosphonate treatments. includina of teriparatide, romosozumab, denosumab, and raloxifene, in preventing osteoporotic fragility fractures. Their findings support our conclusions, further emphasizing the importance of these drugs in the clinical landscape. Lastly, Hong et al. (76) conducted a metaanalysis comparing the efficacy of abaloparatide and teriparatide, with results suggesting a more pronounced increase in BMD with abaloparatide. While our study did not compare treatment modalities in detail, the findings of this study provide an important perspective on the evolving treatment methods.

Our study contributes to a better understanding of postmenopausal osteoporosis treatment. It is clear that different treatment modalities, either alone or in combination, have unique advantages that can be utilized for the best possible patient outcomes.

# Novel contributions and strengths of our meta-analysis

meta-analysis significantly enhances Our the understanding of teriparatide (PTH 1-34) therapy for treating postmenopausal osteoporosis, particularly highlighting its impact on radius bone mineral density (BMD) - an aspect that needs to be thoroughly explored. We provide an in-depth review of teriparatide's effectiveness in increasing lumbar and femoral neck BMD, demonstrating its potential to reduce fracture risks and aid fracture healing in highrisk postmenopausal women. Our study also balances the benefits of teriparatide with its adverse effects, advocating for a nuanced approach to its clinical use. We pinpoint gaps in research like long-term safety and

optimal treatment protocols, proposing directions for further investigation. By comparing teriparatide with other treatments and suggesting the exploration of new delivery methods, our analysis aims to innovate osteoporosis management, thereby enriching clinical decision-making and guiding future research.

## Limitations of our meta-analysis

Our meta-analysis, while methodologically rigorous and guideline compliant, faces several limitations. First, including studies from diverse countries introduces variability due to differing patient populations and treatment protocols. Secondly, there is noticeable heterogeneity within control groups. Thirdly, participants' osteoporosis severity varied. Fourthly, a comprehensive understanding of the long-term effectiveness and reliability of teriparatide (PTH 1-34) treatment needs to be improved, particularly its impact on fracture healing. Fifthly, there were inconsistencies in teriparatide dosages among studies. Our innovative focus on radius BMD limited the analysis to a smaller subset of studies, possibly affecting the robustness of our conclusions.

Additionally, incorporating long-term data and fracture healing was challenging due to variable study lengths and follow-up quality. Lastly, despite a thorough assessment of adverse safety events, differences in reporting standards across studies may need to be clarified. Despite these limitations, our analysis provides valuable insights into treating postmenopausal osteoporosis with teriparatide (PTH 1–34).

## **Future research directions**

The current research highlights the need for further exploration into teriparatide (PTH 1-34) treatment for postmenopausal osteoporosis, particularly its long-term safety, effectiveness, and impact on fracture healing. Future studies should focus on conducting largescale, well-designed, RCTs to understand the optimal dosage, treatment duration, and frequency. Comparing teriparatide's efficacy with other interventions and investigating continuous versus intermittent therapy and new delivery methods are also crucial. Ensuring safety through detailed adverse event analysis, including mortality, is essential. While teriparatide presents a promising option for those at high fracture risk or unresponsive to other treatments, a personalized assessment of its benefits and risks, particularly regarding fracture healing, is necessary.

## **Clinical implications of our study**

Our study enhances the understanding of teriparatide (PTH 1–34) in managing postmenopausal osteoporosis, particularly highlighting its significant impact on the radius BMD and the lumbar and femoral neck regions.

This insight is crucial for reducing vertebral fracture risks and influencing fracture healing. By demonstrating teriparatide's dual action on bone metabolism, stimulating the formation, and potentially increasing resorption, our findings provide critical information for clinicians, especially regarding fracture healing.

It emphasizes the importance of personalized treatment strategies and careful patient monitoring, especially for long-term therapy, due to the observed rise in adverse events. Our research advocates for continued investigation into teriparatide's long-term safety and efficacy, aiming for a more personalized, evidencebased clinical application that aligns with patientspecific needs and the latest scientific developments.

## Conclusion

Our study reaffirms the role of teriparatide (PTH 1-34) in treating postmenopausal osteoporosis, uniquely highlighting its efficacy not only in improving lumbar and femoral neck bone mineral density but also in enhancing radius BMD, a less explored yet significant aspect. This tripartite improvement in skeletal health, a novel contribution of our analysis, underscores teriparatide's comprehensive potential in reducing fracture risks, particularly vertebral fractures. Despite its promising osteoanabolic action, the need for a balanced consideration of bone formation against potential resorption and the careful monitoring of adverse events is paramount. Our findings advocate for meticulous patient selection and ongoing safety evaluations, especially considering the long-term use of teriparatide. Moreover, our study calls for continued research into optimizing dosing strategies and evaluating teriparatide's efficacy relative to emerging osteoporosis treatments. Our study positions teriparatide (PTH 1-34) as a key yet intricate therapy in osteoporosis management, emphasizing a personalized and evolving approach in its clinical application, informed by ongoing research and individual patient profiles.

#### **Supplementary materials**

This is linked to the online version of the paper at https://doi.org/10.1530/ EOR-23-0205.

#### **ICMJE Conflict of Interest Statement**

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the study reported.

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#### Availability of data and materials

The data supporting the findings of this study are included in this article.

#### Author contribution statement

All authors have reviewed and agreed upon the manuscript. DTAV conceptualized the study, reviewed and edited the manuscript, handled the software, and created the original draft. AEE conducted data collection and reviewed the manuscript. MR contributed to the methodology and data curation. MO performed the formal analysis and investigation. DKY and RMG worked on visualization and investigation, while GFLS and AK contributed to the methodology and visualization. Lastly, XW and YL provided supervision, project administration, validation, and funding acquisition. The protocol can be accessed through PROSPERO (protocol ID: CRD42023392628).

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# References

- Kanis JA, Melton LJ, Christiansen C, Johnston CC & Khaltaev N. The diagnosis of osteoporosis. *Journal of Bone and Mineral Research* 1994 9 1137–1141. (https://doi.org/10.1002/jbmr.5650090802)
- 2 Report of a WHO Study Group Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. World Health Organization Technical Report Series 1994 **843** 1–29.
- Compston JE, McClung MR & Leslie WD. Osteoporosis. *Lancet* 2019
   393 364–376. (https://doi.org/10.1016/S0140-6736(18)32112-3)
- 4 van Staa TP, Leufkens HG & Cooper C. The epidemiology of corticosteroid-induced osteoporosis: a meta-analysis. Osteoporosis International 2002 13 777–787. (https://doi.org/10.1007/ s001980200108)
- 5 Shaker JL & Lukert BP. Osteoporosis associated with excess glucocorticoids. *Endocrinology and Metabolism Clinics of North America* 2005 **34** 341–356. (https://doi.org/10.1016/j.ecl.2005.01.014)
- 6 Hofbauer LC & Rachner TD. More DATA to guide sequential osteoporosis therapy. *Lancet* 2015 **386** 1116–1118. (https://doi. org/10.1016/S0140-6736(15)61175-8)
- 7 Rachner TD, Khosla S & Hofbauer LC. Osteoporosis: now and the future. *Lancet* 2011 **377** 1276–1287. (https://doi.org/10.1016/S0140-6736(10)62349-5)
- 8 Chrischilles EA, Butler CD, Davis CS & Wallace RB. A model of lifetime osteoporosis impact. *Archives of Internal Medicine* 1991 **151** 2026–2032. (https://doi.org/10.1001/archinte.1991.0040010010017)
- 9 McClung MR, Grauer A, Boonen S, Bolognese MA, Brown JP, Diez-Perez A, Langdahl BL, Reginster JY, Zanchetta JR, Wasserman SM, *et al.* Romosozumab in postmenopausal women with low bone mineral density. *New England Journal of Medicine* 2014 **370** 412–420. (https://doi.org/10.1056/NEJMoa1305224)
- 10 Takács I, Jókai E, Kováts DE & Aradi I. The first biosimilar approved for the treatment of osteoporosis: results of a comparative pharmacokinetic/pharmacodynamic study. *Osteoporosis*

International 2019 **30** 675–683. (https://doi.org/10.1007/s00198-018-4741-0)

- 11 Paik J & Scott LJ. Romosozumab: a review in postmenopausal osteoporosis. *Drugs and Aging* 2020 **37** 845–855. (https://doi.org/10.1007/s40266-020-00793-8)
- 12 Jilka RL. Molecular and cellular mechanisms of the anabolic effect of intermittent PTH. *Bone* 2007 **40** 1434–1446. (https://doi. org/10.1016/j.bone.2007.03.017)
- 13 Kneissel M, Boyde A & Gasser JA. Bone tissue and its mineralization in aged estrogen-depleted rats after longterm intermittent treatment with parathyroid hormone (PTH)analog SDZ PTS 893 or human PTH(1-34). Bone 2001 28 237-250. (https://doi. org/10.1016/s8756-3282(00)00448-8)
- Kraenzlinand ME & Meier C. Parathyroid hormone analogues in the treatment of osteoporosis. *Nature Reviews. Endocrinology* 2011
   **7** 647–656. (https://doi.org/10.1038/nrendo.2011.108)
- 15 Chen P, Jerome CP, Burr DB, Turner CH, Ma YL, Rana A & Sato M. Interrelationships between bone microarchitecture and strength in ovariectomized monkeys treated with teriparatide. *Journal of Bone and Mineral Research* 2007 **22** 841–848. (https://doi.org/10.1359/ jbmr.070310)
- 16 Jiang Y, Zhao JJ, Mitlak BH, Wang O, Genant HK & Eriksen EF. "Recombinant human parathyroid hormone(1–34) [teriparatide] improves both cortical and cancellous bone structure." *Journal of Bone and Mineral Research* 2003 **18** 1932–1941. (https://doi. org/10.1359/jbmr.2003.18.11.1932)
- 17 Dempster DW, Cosman F, Kurland ES, Zhou H, Nieves J, Woelfert L, Shane E, Plavetić K, Müller R, Bilezikian J, et al. Effects of daily treatment with parathyroid hormone on bone microarchitecture and turnover in patients with osteoporosis: a paired biopsy study. Journal of Bone and Mineral Research 2001 16 1846–1853. (https:// doi.org/10.1359/jbmr.2001.16.10.1846)
- 18 Compston JE. Skeletal actions of intermittent parathyroid hormone: effects on bone remodelling and structure. *Bone* 2007 **40** 1447–1452. (https://doi.org/10.1016/j.bone.2006.09.008)
- 19 Ma YL, Zeng QQ, Chiang AY, Burr D, Li J, Dobnig H, Fahrleitner-Pammer A, Michalská D, Marin F, Pavo I, *et al.* Effects of teriparatide on cortical histomorphometric variables in postmenopausal women with or without prior alendronate treatment. *Bone* 2014 **59** 139– 147. (https://doi.org/10.1016/j.bone.2013.11.011)
- 20 Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY, Hodsman AB, Eriksen EF, Ish-Shalom S, Genant HK, et al. Effect of parathyroid hormone (1–34) on fractures and bone mineral density in postmenopausal women with osteoporosis. New England Journal of Medicine 2001 344 1434–1441. (https://doi. org/10.1056/NEJM200105103441904)
- 21 Kaufman JM, Orwoll E, Goemaere S, San Martin J, Hossain A, Dalsky GP: Lindsay R, Mitlak BH. Teriparatide effects on vertebral fractures and bone mineral density in men with osteoporosis: treatment and discontinuation of therapy. *Osteoporosis International*. 2005 **16** 510–516.
- 22 Lindsay R, Scheele WH, Neer R, Pohl G, Adami S, Mautalen C, Reginster JY, Stepan JJ, Myers SL & Mitlak BH. Sustained vertebral fracture risk reduction after withdrawal of teriparatide in postmenopausal women with osteoporosis. *Archives of Internal Medicine* 2004 **164** 2024–2030. (https://doi.org/10.1001/ archinte.164.18.2024)
- 23 Rubin MR & Bilezikian JP. The anabolic effects of parathyroid hormone therapy. *Clinics in Geriatric Medicine* 2003 **19** 415–432. (https://doi.org/10.1016/s0749-0690(02)00074-5)
- 24 Ito M, Oishi R, Fukunagaetal M, Sone T, Sugimoto T, Shiraki M, Nishizawa Y & Nakamura T. The effects of once-weekly teriparatide

on hip structure and biomechanical properties assessed by CT. *Osteoporosis International* 2014 **25** 1163–1172. (https://doi. org/10.1007/s00198-013-2596-y)

- 25 Komatsubara S, Mori S, Mashibaetal T, Nonaka K, Seki A, Akiyama T, Miyamoto K, Cao Y, Manabe T & Norimatsu H. Human parathyroid hormone (1–34) accelerates the fracture healing process of woven to lamellar bone replacement and new cortical shell formation in rat femoral. *Bone* 2005 **36** 678–687. (https://doi. org/10.1016/j.bone.2005.02.002)
- 26 Komrakova M, Stuermer EK, Werner C, Wicke M, Kolios L, Sehmisch S, Tezval M, Daub F, Martens T, Witzenhausen P, et al. Effect of human parathyroid hormone hPTH (1–34) applied at different regimes on fracture healing and muscle in ovariectomized and healthy rats. *Bone* 2010 **47** 480–492. (https:// doi.org/10.1016/j.bone.2010.05.013)
- 27 Gardner MJ, van der Meulen MCH, Carson J, Zelken J, Ricciardi BF, Wright TM, Lane JM & Bostrom MP. Role of parathyroid hormone in the mechanosensitivity of fracture healing. *Journal of Orthopaedic Research* 2007-11-01 **25** 1474–1480. (https://doi.org/10.1002/jor.20427)
- 28 Li YF, Zhou CC, Li JH, Luo E, Zhu SS, Feng G & Hu J. The effects of combined human parathyroid hormone (1–34) and zoledronic acid treatment on fracture healing in osteoporotic rats. *Osteoporosis International* 2012 **23** 1463–1474. (https://doi.org/10.1007/s00198-011-1751-6)
- 29 Huang T-W, Yang T-Y, Huang K-C, Peng K-T, Lee MS & Hsu RW-W. Effect of teriparatide on unstable pertrochanteric fractures. *BioMed Research International* 2015 2015 568390. (https://doi.org/10.1155/2015/568390)
- 30 Watts NB, Aggers D, McCarthy EF, Savage T, Martinez S, Patterson R, Carrithers E & Miller PD. Responses to treatment with teriparatide in patients with atypical femur fractures previously treated with bisphosphonates. *Journal of Bone and Mineral Research* 2017 **32** 1027–1033. (https://doi.org/10.1002/jbmr.3081)
- 31 Im GI & Lee SH. Effect of Teriparatide on Healing of Atypical Femoral Fractures: A Systemic Review. *Journal of Bone Metabolism* 2015 22 183–189. (https://doi.org/10.11005/jbm.2015.22.4.183)
- 32 Kanakaris NK, West RM & Giannoudis PV. Enhancement of hip fracture healing in the elderly: evidence deriving from a pilot randomized trial. *Injury* 2015 46 1425–1428. (https://doi. org/10.1016/j.injury.2015.06.033)
- 33 Ledin H, Good L, Johansson T & Aspenberg P. No effect of teriparatide on migration in total knee replacement. *Acta Orthopaedica* 2017 88 259–262. (https://doi.org/10.1080/17453674. 2017.1300745)
- 34 Goldhahn J, Féron JM, Kanis J, Papapoulos S, Reginster JY, Rizzoli R, Dere W, Mitlak B, Tsouderos Y & Boonen S. Implications for fracture healing of current and new osteoporosis treatments: an ESCEO consensus paper. *Calcified Tissue International* 2012 **90** 343–353. (https://doi.org/10.1007/s00223-012-9587-4)
- 35 Metcalf LM, Aspray TJ & McCloskey EV. The effects of parathyroid hormone peptides on the peripheral skeleton of postmenopausal women. A systematic review. *Bone* 2017 **99** 39–46. (https://doi. org/10.1016/j.bone.2017.03.007)
- 36 Borgström F, Lekander I, Ivergård M, Ström O, Svedbom A, Alekna V, Bianchi ML, Clark P, Curiel MD, Dimai HP, et al. The International Costs and Utilities Related to Osteoporotic Fractures Study (ICUROS)--quality of life during the first 4 months after fracture. Osteoporosis International 2013 24 811–823. (https://doi. org/10.1007/s00198-012-2240-2)
- 37 Marques A, Lourenco Ó, da Silva JA & Portuguese Working Group for the Study of the Burden of Hip Fractures in Portugal. The burden of osteoporotic hip fractures in Portugal: costs, health

related quality of life and mortality. *Osteoporosis International* 2015 **26** 2623–2630. (https://doi.org/10.1007/s00198-015-3171-5)

- 38 Amin S, Achenbach SJ, Atkinson EJ, Khosla S & Melton LJ III. Trends in fracture incidence: a population-based study over 20 years. *Journal of Bone and Mineral Research* 2014 **29** 581–589. (https://doi. org/10.1002/jbmr.2072)
- 39 Plotkin LI & Bellido T. Osteocytic signalling pathways as therapeutic targets for bone fragility. *Nature Reviews. Endocrinology* 2016 **12** 593–605. (https://doi.org/10.1038/nrendo.2016.71)
- 40 Li T, Jiang S, Lu C, Yang W, Yang Z, Hu W, Xin Z & Yang Y. Melatonin: another avenue for treating osteoporosis? *Journal of Pineal Research* 2019 66 e12548. (https://doi.org/10.1111/jpi.12548)
- 41 Ebeling PR, Nguyen HH, Aleksova J, Vincent AJ, Wong P & Milat F. Secondary osteoporosis. *Endocrine Reviews* 2022 **43** 240–313. (https://doi.org/10.1210/endrev/bnab028)
- 42 Jolette J, Attalla B, Varela A, Long GG, Mellal N, Trimm S, Smith SY, Ominsky MS & Hattersley G. Comparing the incidence of bone tumors in rats chronically exposed to the selective PTH type 1 receptor agonist abaloparatide or PTH (1–34). *Regulatory Toxicology and Pharmacology* 2017 **86** 356–365. (https://doi.org/10.1016/j. yrtph.2017.04.001)
- 43 Erviti J, Gorricho J, Saiz LC, Perry T & Wright JM. Rethinking the appraisal and approval of drugs for fracture prevention. *Frontiers in Pharmacology* 2017 **8** 265. (https://doi.org/10.3389/ fphar.2017.00265)
- 44 Cosman F, Crittenden DB, Ferrari S, Lewiecki EM, Jaller-Raad J, Zerbini C, Milmont CE, Meisner PD, Libanati C & Grauer A. Romosozumab FRAME study: A post hoc analysis of the role of regional background fracture risk on nonvertebral fracture outcome. *Journal of Bone and Mineral Research* 2018 **33** 1407–1416. (https://doi.org/10.1002/jbmr.3439)
- 45 Lewiecki EM, Blicharski T, Goemaere S, Lippuner K, Meisner PD, Miller PD, Miyauchi A, Maddox J, Chen L & Horlait S. A phase III randomized placebo-controlled trial to evaluate efficacy and safety of romosozumab in men with osteoporosis. *Journal of Clinical Endocrinology and Metabolism* 2018 **103** 3183–3193. (https://doi. org/10.1210/jc.2017-02163)
- Saag KG, Petersen J, Brandi ML, Karaplis AC, Lorentzon M, Thomas T, Maddox J, Fan M, Meisner PD & Grauer A. Romosozumab or alendronate for fracture prevention in women with osteoporosis. *New England Journal of Medicine* 2017 **377** 1417–1427. (https://doi.org/10.1056/NEJMoa1708322)
- 47 Cosman F, Crittenden DB, Adachi JD, Binkley N, Czerwinski E, Ferrari S, Hofbauer LC, Lau E, Lewiecki EM, Miyauchi A, *et al.* Romosozumab treatment in postmenopausal women with osteoporosis. *New England Journal of Medicine* 2016 **375** 1532–1543. (https://doi.org/10.1056/NEJMoa1607948)
- 48 Padhi D, Jang G, Stouch B, Fang L & Posvar E. Single-dose, placebocontrolled, randomized study of AMG 785, a sclerostin monoclonal antibody. *Journal of Bone and Mineral Research* 2011 **26** 19–26. (https://doi.org/10.1002/jbmr.173)
- 49 Salameh JP, Bossuyt PM, McGrath TA, Thombs BD, Hyde CJ, Macaskill P, Deeks JJ, Leeflang M, Korevaar DA, Whiting P, *et al.* Preferred reporting items for systematic review and meta-analysis of diagnostic test accuracy studies (PRISMA-DTA): explanation, elaboration, and checklist. *BMJ* 2020 **370** m2632. (https://doi. org/10.1136/bmj.m2632)
- 50 Anastasilakis AD, Goulis DG, Polyzos SA, Gerou S, Koukoulis GN, Efstathiadou Z, Kita M & Avramidis A & Avramidis A. Head-to-head comparison of risedronate vs. teriparatide on bone turnover markers in women with postmenopausal osteoporosis: a randomized trial. *International Journal of Clinical Practice* 2008 62 919–924. (https://doi.org/10.1111/j.1742-1241.2008.01768.x)

- 51 Kendler DL, Marin F, Zerbini CAF, Russo LA, Greenspan SL, Zikan V, Bagur A, Malouf-Sierra J, Lakatos P, Fahrleitner-Pammer A, *et al.* Effects of teriparatide and risedronate on new fractures in postmenopausal women with severe osteoporosis (VERO): a multicentre, double-blind, double-dummy, randomized controlled trial. *Lancet* 2018 **391** 230–240. (https://doi.org/10.1016/S0140-6736(17)32137-2)
- 52 Cosman F, Eriksen EF, Recknor C, Miller PD, Guañabens N, Kasperk C, Papanastasiou P, Readie A, Rao H, Gasser JA, et al. Effects of intravenous zoledronic acid plus subcutaneous teriparatide [rhPTH (1–34)] in postmenopausal osteoporosis. Journal of Bone and Mineral Research 2011 26 503–511. (https://doi. org/10.1002/jbmr.238)
- 53 Yingchun W & Hui S. Comparative study of the efficacy of parathyroid hormone (1–34), strontium ranelate and zoledronic acid in postmenopausal osteoporosis. *Chinese Journal of Osteoporosis* 2017 **23** 1276–1279.
- 54 Body JJ, Gaich GA, Scheele WH, Kulkarni PM, Miller PD, Peretz A, Dore RK, Correa-Rotter R, Papaioannou A, Cumming DC, *et al.* A randomized double-blind trial to compare the efficacy of teriparatide [recombinant human parathyroid hormone (1–34)] with alendronate in postmenopausal women with osteoporosis. *Journal of Clinical Endocrinology and Metabolism* 2002 **87** 4528–4535. (https://doi.org/10.1210/jc.2002-020334)
- 55 Deng J, Feng Z, Li Y, Pan T, Li Q & Zhao C. Efficacy and safety of recombinant human parathyroid hormone (1-34) are similar to those of alendronate in the treatment of postmenopausal osteoporosis. *Medicine* 2018 **97** e13341. (https://doi.org/10.1097/ MD.000000000013341)
- Finkelstein JS, Wyland JJ, Lee H & Neer RM. Effects of teriparatide, alendronate, or both in women with postmenopausal osteoporosis. *Journal of Clinical Endocrinology and Metabolism* 2010
   95 1838–1845. (https://doi.org/10.1210/jc.2009-1703)
- 57 McClung MR, San Martin J, Miller PD, Civitelli R, Bandeira F, Omizo M, Donley DW, Dalsky GP & Eriksen EF. Opposite bone remodeling effects of teriparatide and alendronate in increasing bone mass. Archives of Internal Medicine, 2005 165 1762–1768.
- 58 Keaveny TM, Donley DW, Hoffmann PF, Mitlak BH, Glass EV & San Martin JA. Effects of teriparatide and alendronate on vertebral strength as assessed by finite element modeling of QCT scans in women with osteoporosis. *Journal of Bone and Mineral Research* 2007 22 149–157. (https://doi.org/10.1359/jbmr.061011)
- 59 Tang Y, Xia H, Kang L, Sun Q, Su Z, Hao C & Xue Y. Effects of intermittent parathyroid hormone 1–34 administration on circulating mesenchymal stem cells in postmenopausal osteoporotic women. *Medical Science Monitor: International Medical Journal of Experimental and Clinical Research* 2019 **25** 259–268. (https://doi.org/10.12659/MSM.913752)
- 60 Chiba K, Okazaki N, Kurogi A, Watanabe T, Mori A, Suzuki N, Adachi K, Era M, Yokota K, Inoue T, *et al.* Randomized controlled trial of daily teriparatide, weekly high-dose teriparatide, or bisphosphonate in patients with postmenopausal osteoporosis: the TERABIT study. *Bone* 2022 **160** 116416. (https://doi. org/10.1016/j.bone.2022.116416)
- 61 Lin SY, Hung MC, Chang SF, Tsuang FY, Chang JZC & Sun JS. Efficacy and safety of postmenopausal osteoporosis treatments: a systematic review and network meta-analysis of randomized controlled trials. *Journal of Clinical Medicine* 2021 **10** 3043. (https:// doi.org/10.3390/jcm10143043)
- 62 Li Y, Xuan M, Wang B, Yang J, Zhang H, Zhang XZ, Guo XH, Lü XF, Xue QY, Yang GY, *et al.* Comparison of parathyroid hormone (1–34) and elcatonin in postmenopausal women with osteoporosis: an 18-month randomized, multicenter controlled trial in China.

*Chinese Medical Journal* 2013 **126** 457–463. (https://doi.org/10.3760/ cma.j.issn.0366-6999.20121626)

- 63 Zhang XZ, Wang B, Yang J, Xuan M, Song LG, Li H, Guo XH, Lü XF, Xue QY, Yang GY, et al. A randomized, multicenter controlled trial to compare the efficacy of recombinant human parathyroid hormone (1–34) with elcatonin in postmenopausal women with osteoporosis in China. Chinese Medical Journal 2009 **122** 2933–2938.
- 64 Yang Y, Zhang XJ, Zhu XJ, Zhang L, Bao MJ, Xian Y, Wu JC, Liu LM & Li PQ. Comparison between recombinant human parathyroid hormone (1–34) and elcatonin in treatment of primary osteoporosis. Asian Pacific Journal of Tropical Medicine 2015 8 79–84. (https://doi.org/10.1016/S1995-7645(14)60192-9)
- 65 Gonnelli S, Martini G, Caffarelli C, Salvadori S, Cadirni A, Montagnani A & Nuti R. Teriparatide's effects on quantitative ultrasound parameters and bone density in women with established osteoporosis. *Osteoporosis International* 2006 **17** 1524–1531. (https://doi.org/10.1007/s00198-006-0157-3)
- 66 Tsai JN, Uihlein AV, Lee H, Kumbhani R, Siwila-Sackman E, McKay EA, Burnett-Bowie SAM, Neer RM & Leder BZ. Teriparatide and denosumab, alone or combined, in women with postmenopausal osteoporosis: the DATA study randomised trial. *Lancet* 2013 **382** 50– 56. (https://doi.org/10.1016/S0140-6736(13)60856-9).
- 67 Leder BZ, Tsai JN, Uihlein AV, Wallace PM, Lee H, Neer RM & Burnett-Bowie SAM. Denosumab and teriparatide transitions in postmenopausal osteoporosis (the data-switch study): extension of a randomised controlled trial. *Lancet* 2015 **386** 1147–1155. (https:// doi.org/10.1016/S0140-6736(15)61120-5)
- 68 Leder BZ, O'Dea LSL, Zanchetta JR, Kumar P, Banks K, McKay K, Lyttle CR & Hattersley G. Effects of abaloparatide, a human parathyroid hormone-related peptide analog, on bone mineral density in postmenopausal women with osteoporosis. *Journal of Clinical Endocrinology and Metabolism* 2015 **100** 697–706. (https:// doi.org/10.1210/jc.2014-3718)
- 69 Genant HK, Engelke K, Bolognese MA, Mautalen C, Brown JP, Recknor C, Goemaere S, Fuerst T, Yang YC, Grauer A, *et al.* Effects of romosozumab compared with teriparatide on bone density and mass at the spine and hip in postmenopausal women with low bone Mass. *Journal of Bone and Mineral Research* 2017 **32** 181–187. (https://doi.org/10.1002/jbmr.2932)

- 70 Keaveny TM, Crittenden DB, Bolognese MA, Genant HK, Engelke K, Oliveri B, Brown JP, Langdahl BL, Yan C, Grauer A, *et al.* Greater gains in spine and hip strength for romosozumab compared with teriparatide in postmenopausal women with low bone Mass. *Journal of Bone and Mineral Research* 2017 **32** 1956–1962. (https:// doi.org/10.1002/jbmr.3176)
- 71 Langdahl BL, Libanati C, Crittenden DB, Bolognese MA, Brown JP, Daizadeh NS, Dokoupilova E, Engelke K, Finkelstein JS, Genant HK, *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** 1585–1594. (https://doi. org/10.1016/S0140-6736(17)31613-6)
- 72 Yuan F, Peng W, Yang C & Zheng J. Teriparatide versus bisphosphonates for treatment of postmenopausal osteoporosis: a meta-analysis. *International Journal of Surgery* 2019 66 1–11. (https://doi.org/10.1016/j.ijsu.2019.03.004)
- 73 Liu Y, Cao Y, Zhang S, Zhang W, Zhang B, Tang Q, Li Z & Wu J. Romosozumab treatment in postmenopausal women with osteoporosis: a meta-analysis of randomized controlled trials. *Climacteric* 2018 **21** 189–195. (https://doi.org/10.1080/13697137.20 18.1433655)
- 74 Sun Y, Li Y, Li J, Xie X, Gu F, Sui Z, Zhang K & Yu T. Efficacy of the combination of teriparatide and denosumab in the treatment of postmenopausal osteoporosis: a meta-analysis. *Frontiers in Pharmacology* 2022 **13** 888208. (https://doi.org/10.3389/ fphar.2022.888208)
- 75 Simpson EL, Martyn-St James M, Hamilton J, Wong R, Gittoes N, Selby P & Davis S. Clinical effectiveness of denosumab, raloxifene, romosozumab, and teriparatide for the prevention of osteoporotic fragility fractures: a systematic review and network meta-analysis. *Bone* 2020 **130** 115081. (https://doi.org/10.1016/j. bone.2019.115081)
- 76 Hong P, Liu R, Rai S, Liu J, Zhou Y, Zheng Y & Li J. Is abaloparatide more efficacious on increasing bone mineral density than teriparatide for women with postmenopausal osteoporosis? An updated meta-analysis. *Journal of Orthopaedic Surgery and Research* 2023 **18** 116. (https://doi.org/10.1186/s13018-023-03595-x)