International Journal of Pharmacology

ISSN 1811-7775

science alert

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Asian Network for Scientific Information

OPEN ACCESS International Journal of Pharmacology

ISSN 1811-7775
DOI: 10.3923/ijp.2024.690.697

Research Article
Comparison of the Effectiveness of Teriparatide and Zoledronic Acid in Osteoporosis Treatment: A Meta-Analysis

Xin Zhang, Xinzhong Xu, Chun Zhang, Chungui Xu, Fei Huang and Wukun Xie

Department of Orthopaedics, The Second Affiliated Hospital of Anhui Medical University, Heifei 230601, China

Abstract

Background and Objective: Osteoporosis (OP) is a systemic metabolism-related complication associated with lowering the mass of bone, the altered microstructure of bone, decreased bone tissue capacity, high fragility of bone and prone to systemic fractures. This meta-analysis is intended to assess the effectiveness of TPTD and ZOL in treating osteoporosis. **Materials and Methods:** The 8 databases that are related to the controlled clinical trials are collected. The 95% confidence interval (CI) is set for determining the relative risk or the differences of mean in this study. Moreover, the heterogeneity of obtained results was estimated using the I^2 in this study. **Results:** According to our criteria, an overall total of 6 papers have been involved in this meta-analysis. According to the six studies, the experimental group's Bone Mineral Density (BMD) is noticeably higher than that of the corresponding untreated group (standardised mean difference (SMD): 0.12; 95% CI: 0.07, 0.17 and p<0.01). After investigating, it is observed that the VAS-score (SMD:-0.72; 95% CI:-1.86,0.42 and p- 0.218), Serum procollagen type I N-propeptide (PINP) (SMD: 67.71 and 95% CI: 13.44,121.99), β-isomerized C-terminal telopeptides (β-CTX) (SMD: 0.43 and 95% CI: 0.17,0.68) and adverse reactions (OR: 0.52 and 95% CI: 0.25, 1.06) in this meta-analysis. **Conclusion:** Meta-analysis investigations demonstrated that both TPTD and ZOL are effective in OP. The TPTD showed more effectiveness than ZOL in enhancing BMD and promoting the formation of bone. However, TPTD is less effective than ZOL in inhibiting osteoclasts.

Key words: Zoledronic acid, teriparatide, bone mineral density, osteoporosis, systemic fractures

Citation: Zhang, X., X. Xu, C. Zhang, C. Xu, F. Huang and W. Xie, 2024. Comparison of the effectiveness of teriparatide and zoledronic acid in osteoporosis treatment: A meta-analysis. Int. J. Pharmacol., 20: 690-697.

Corresponding Author: Wukun Xie, Department of Orthopaedics, The Second Affiliated Hospital of Anhui Medical University, Heifei 230601, China

Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Osteoporosis (OP) is a systemic metabolism-related complication associated with lowering the mass of bone, altering the microstructure of bone, decreasing the capacity of bone tissue, augmenting bone fragility and being prone to systemic fractures of bone[1,2]. With the population ageing and a large number of elderly people, the functions of various organs in middle-aged and elderly people gradually decline, so that the resorption of bone significantly surpasses bone formation, which is ultimately related to bone loss and relaxation[3,4], eventually leading to Osteoporotic Vertebral Compression Fractures (OVCFs)[5,6]. During bone metabolism, osteoclasts perpetually absorb bone matrix to generate depressions, while osteoblasts synthesize bone matrix continuously to fill in depressions. When the human body enters old age, women are postmenopausal or bedridden for a long time, the formation and resorption of bone tissue balance are gradually broken and the quantity of bone resorption is compared to bone remodeling[7]. The OP is often caused by various factors. Studies have shown that ageing of the body, decreased estrogen levels, long-term lack of mechanical stimulation, neurological diseases, hypogonadism and autoimmune diseases may all cause OP[8-10]. This research conducted a systematic assessment to compare the effects of TPTD and ZOL in individuals with OP.

Zoledronic acid (ZOL), a potent bisphosphonate, effectively inhibits bone turnover by significantly reducing biochemical markers of bone turnover. It also has strong anti-resorptive properties and effectively suppresses bone formation and calcification[11]. Upon IV injection, osteoclasts readily uptake and efficiently disseminate it to the bone tissue. Annually, a 5 mg dose of ZOL is administered IV to promote the attachment and durability of the bisphosphonate over 12 months[12,13].

Teriparatide (TPTD) or recombinant human parathyroid hormone 1-34, consists of the first 34 amino acid segments of the parathyroid hormone molecule. It may significantly improve bone production and increase bone density in people with osteoporosis[14]. Several studies have shown that TPTD exhibited better effectiveness than other therapeutic drugs for improving the Bone Mineral Density (BMD) of people with osteoporosis[15]. Consequently, a systematic review was conducted to investigate the comparison of the effects of TPTD and ZOL in OP.

MATERIALS AND METHODS

Study area: The present study was performed in the Second Affiliated Hospital of Anhui Medical University, Hefei, China from August to November, 2023.

Study design: In this study, controlled clinical trials were included that investigated the association of TPTD combined with other therapies versus ZOL for treating OP.

Research object: In this meta-analysis, a total of 1020 research articles were involved with the OP patients who were on TPTD or ZOL treatment. Patients with a T $\leq$-2.5 BMD score calculated by dual-energy X-ray (DXA) concerning the WHO recommended diagnostic criteria, regardless of gender.

Intervention measures: The experimental group was defined as the patients treated with TPTD or TPTD combined with other therapeutic strategies, whereas the control group was defined as those treated with ZOL or ZOL combined with other therapeutic strategies for the intervention. Meanwhile, exclusion criteria were as below: (1) Trials without a control group, (2) Studies that did not use TPTD and ZOL as intervention, (3) The research studied without authentic data or having no appropriate research information, (4) Studies with no consistent outcome indicators or computational methodology and (5) Review articles or studies with the animal.

Outcome measures: Those clinical trial articles published in various databases and scientific journals for evaluating OP patient treatments were observed. The frequently used parameters for assessing the OP consisted of BMD, VAS score, PINP, β-CTX and adverse reactions.

Search strategy: Multiple databases were employed to search for the relevant randomized controlled trials up to the end of 2022, including Web of Science, PubMed, Scopus, Cochrane Library, Embase, CNKI, VIP, WanFang and CBM Libraries. Frequently used terms are "Teriparatide" or "Teriparatide combined therapy" or "Zoledronic acid" or "Zoledronic acid combined therapy" or "Osteoporosis" or "treatment of Osteoporosis".

Screening of studies and extraction of proper data: The two authors independently selected the relevant studies according

to both inclusion and exclusion criteria using the NoteExpress software version 3.9.0. After selecting the studies, the authors read the abstract and full text of the articles whether to include them and collect the data for exporting into the Excel table. In the event of a dispute among the writers involved in the collection process, the third author resolves the issue by providing counsel.

Statistical assessment: The software Stata 15.1 was employed to conduct the meta-analysis. For both the relative risk (RR) of categorical factors and the mean difference (MD) of continuous factors, the 95% confidence interval (CI) was computed. Heterogeneity was estimated using the statistic I^2. The fixed effects (FE) approach was used for $I^2 \leq 50$, whereas the random effects (RE) model was applied for $I^2 > 50\%$. A sensitivity assessment was conducted to examine the origin of data heterogeneity.

RESULTS

Searching results: The investigation produced a total of 1020 references based on the specified inclusion and exclusion criteria. After the exclusion of duplicated studies, 502 studies were used for further analysis. Afterwards, 10 studies were evaluated to extract the key information from the whole text. Next, four studies were further exempted due to mismatch of data (n = 1) or missing value of data (n = 3). Finally, 6 studies were included in the systematic review (Table 1). The PRISMA statement was followed and the flow chart of PRISMA for this analysis was revealed in Fig. 1.

Result of BMD investigation: Our investigation revealed that the 5 studies provided the BMD of the experimental and control groups. The BMD level was observed to be remarkably greater (SMD: 0.12, 95% CI: 0.07, 0.17, p<0.01 and Fig. 2) in the investigational group than in the untreated group. A higher level of heterogeneity was found in these trials and thus the sensitivity analysis was further performed (Fig. 3). Among patients with osteoporosis (OP), TPTD administration resulted in a substantial increase in BMD in the experimental group compared to the control group.

Analysis of VAS score: Our observation revealed that the 4 studies provided the VAS score of the investigational and

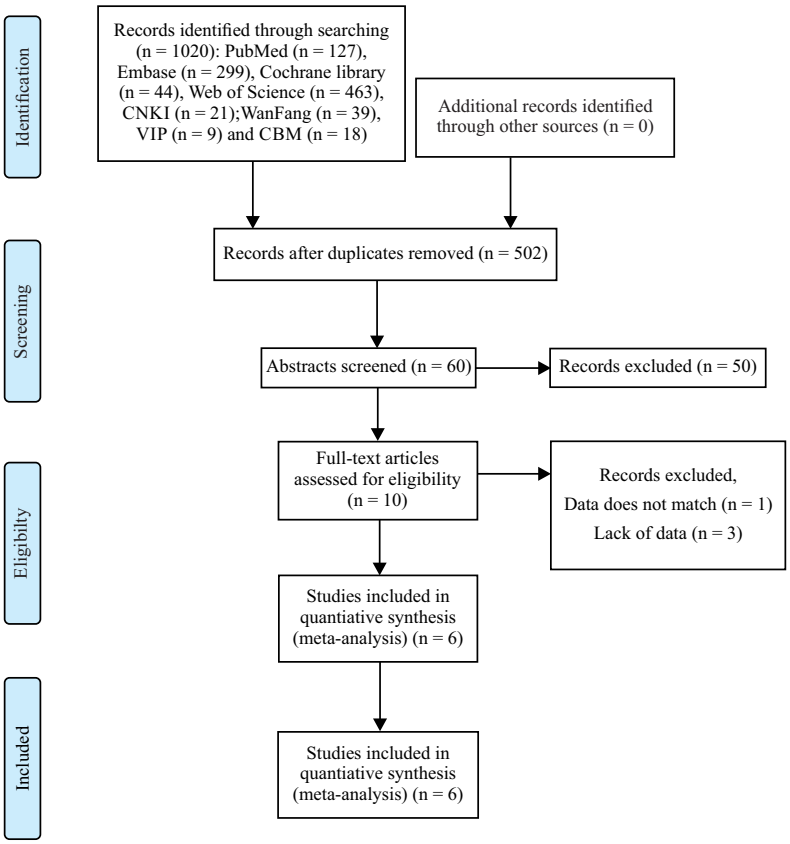

Fig. 1: Flowchart for screening for inclusion in the literature of meta-analyses (PRISMA)

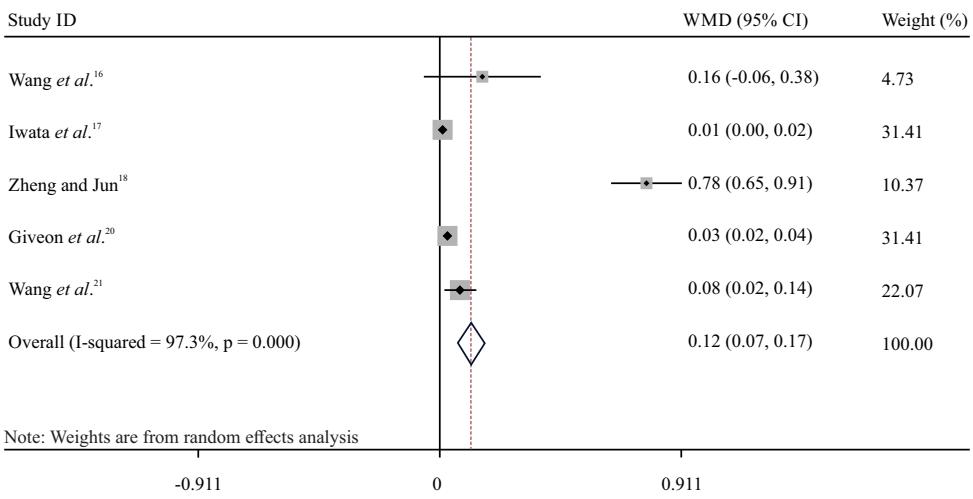

Fig. 2: Forest illustration of the BMD

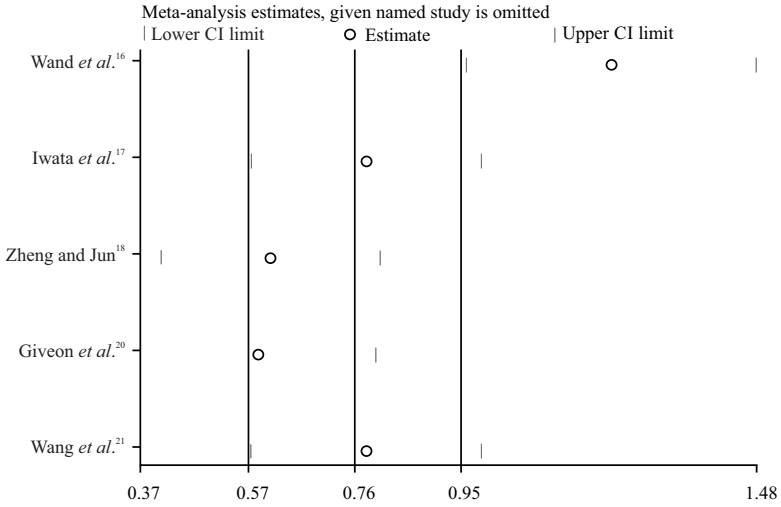

Fig. 3: Sensitivity analysis of the BMD

Table 1: Basic characteristics of the included studies

Sample size (T/C)	Man/Woman	Age (years) (Mean±SD) (T/C)	T	C	Main outcomes	Study (Reference)
84/120	204 woman	66.8±8.1/68.1±7.4	TPTD	ZOL	①, ②, ③ and ⑤	Wang *et al.*[16]
32/32	27/37	64.5±6.6/65.8±7.2	TPTD	ZOL	①, ②, ④ and ⑤	Iwata *et al.*[17]
20/40	60 woman	70.14±15.43/68.31±13.12	TPTD	ZOL	①, ③ and ④	Zheng and Jun[18]
26/37	26/37	65.4±6.7/66.5±5.8	TPTD	ZOL	②	Xiong *et al.*[19]
53/50	103 woman	68.02±5.26/68.16±6.23	TPTD	ZOL	①, ②, ③, ④ and ⑤	Giveon *et al.*[20]
29/38	7/60	66.34±8.13/65.89±6.13	TPTD	ZOL	①, ③ and ④	Wang *et al.*[21]

T: Trial group, C: Control group, TPTD: Teriparatide, ZOL: Zoledronic acid, BMD: Bone mineral density, VAS: Visual analogue scale score, β-CTX: β-cross-linked C-telopeptide of type 1 collagen, PINP: N-terminal propeptide of type 1 collagen and Adverse effects

untreated groups. Our investigation identified that the VAS score is not significantly differentiated between the experimental group and the untreated group (SMD:-0.72, 95% CI:-1.86, 0.42, p = 0.218 and Fig. 4). Compared to ZOL, TPTD had no obvious advantage in improving VAS scores in patients with OP.

Analysis of PINP: Four studies provided information on PINP in the investigational group and the untreated group. Our systematic review result revealed that the level of PINP was significantly greater in the investigational group (SMD: 67.71, 95% CI: 13.44, 121.99, p<0.05 and Fig. 5) when compared with untreated samples.

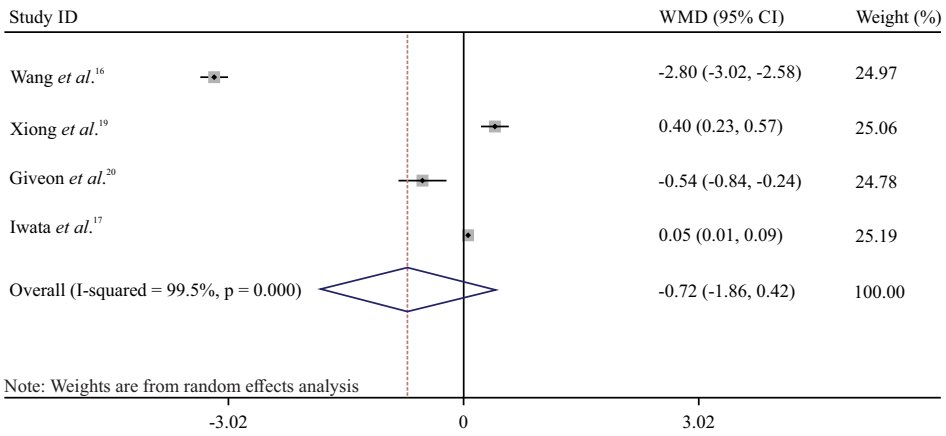

Fig. 4: Forest illustration of the VAS score

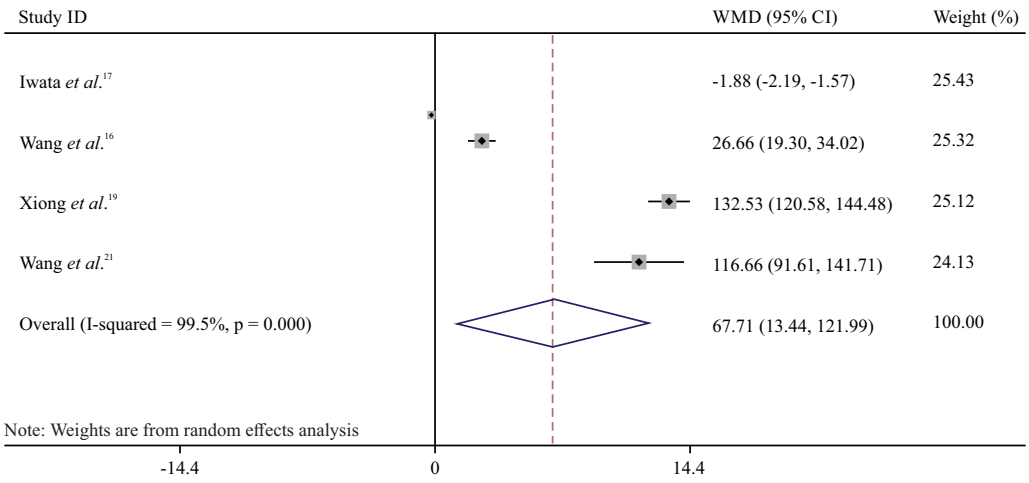

Fig. 5: Forest illustration of the PINP

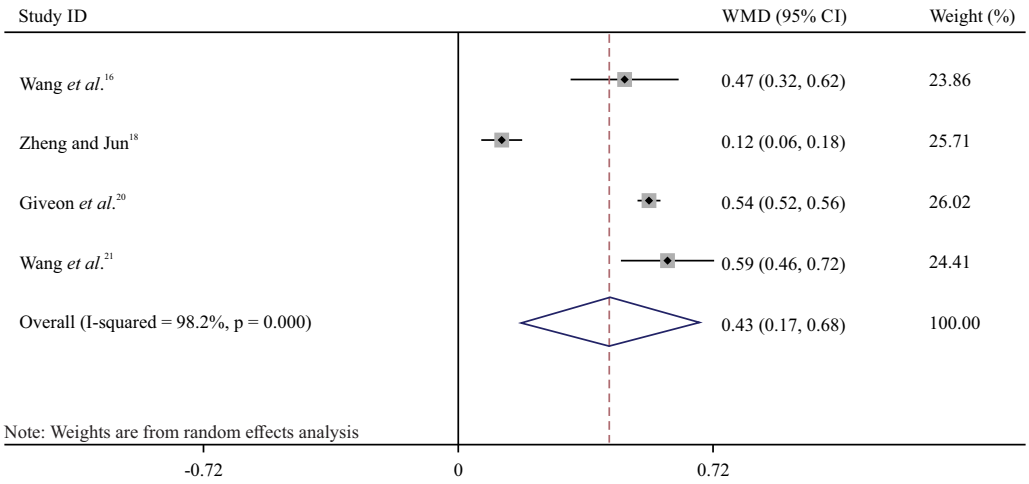

Fig. 6: Forest illustration of the β-CTX

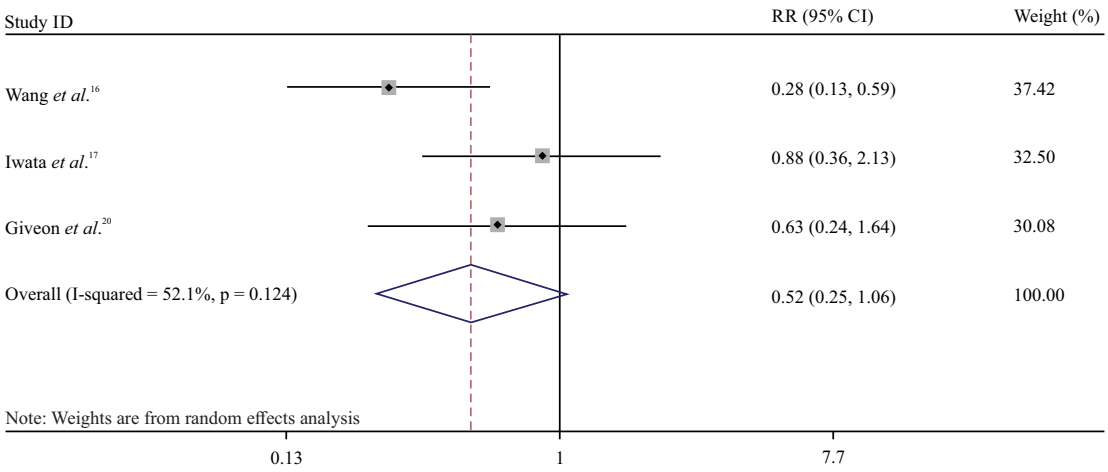

Fig. 7: Forest illustration of the adverse reactions

Analysis of β-CTX: Four studies were observed to provide information on β-CTX in the experimental and untreated groups. There was a remarkably higher β-CTX level in the experimental group (SMD: 0.43, 95% CI: 0.17, 0.68, p<0.01 and Fig. 6) during the comparison with the untreated group.

Investigation of adverse reactions: In the investigational and untreated groups, three studies were determined to provide adverse reaction information. The study did not find any notable disparity in adverse responses between the experimental group and the untreated group (odds ratio: 0.52, 95% confidence interval: 0.25, 1.06, p>0.05 and Fig. 7).

DISCUSSION

With increasing age, the calcium salts and organic components in the human bone tissue continue to decrease, microstructure degenerates or is destroyed, bone density decreases and bone fragility increases. Hence, most elderly people have osteoporosis, which leads to lumbar vertebral compression fractures and the occurrence risk is increased. As a third-generation bisphosphonate drug, ZOL is currently significantly used to prevent and treat the various types of osteoporosis due to its good affinity for bone tissue and its significant ability to inhibit osteoclast-mediated bone resorption. Stone *et al.*[22] and Ding *et al.*[23] reports have confirmed that bisphosphonates positively maintain the stability of the internal fixation system, reducing fracture complications and spinal interbody fusion. Unlike ZOL, which mainly acts on osteoclasts, TPTD mainly promotes the formation of new bone and accelerates bone remodeling by activating osteoblasts in the bone microenvironment. The results of some clinical randomized controlled have revealed that TPTD can effectively enhance bone density, inhibit the resorption of bone and improve the outcome in osteoporotic patients[24].

Osteoporosis can be classified as primary osteoporosis, which consists of menopausal osteoporosis and idiopathic osteoporosis, senile osteoporosis, with postmenopausal osteoporosis being the most common type of primary osteoporosis. Secondary osteoporosis, often known as the other group, refers to osteoporosis that is induced by a disease or medicine. This study focuses on patients with osteoporosis, a metabolic disease caused by an imbalance in bone formation and bone resorption balance. The development of osteoporosis is intricate and some studies suggest that it may be related to oxidative stress, dysbiosis of the intestinal flora and abnormal bone marrow mesenchymal stem cell differentiation. According to the mechanism of action, anti-osteoporosis drugs can be classified as the categories of inhibitors of bone resorption, bone formation enhancers, drugs with other mechanisms and herbal medicines. Bisphosphonates, such as ZOL, alendronate and ibandronate, are widely used as bone resorption inhibitors in therapeutic settings. Among them, ZOL is the third generation of bisphosphonate with the strongest effect. Its anti-osteoporotic effect has been proven in many clinical trials at home and abroad and it is also important in preventing osteoporotic fractures and secondary fractures. The TPTD, a recombinant human parathyroid hormone amino-terminal 1-34 active fragment, has been marketed in China. The TPTD, when administered in low doses and used intermittently, may effectively stimulate osteoblast activity, promote bone formation, increase bone density and quality and decrease the incidence of both vertebral and non-vertebral fractures[25].

The TPTD is a recombinant human parathyroid hormone amino-terminal 1-34 active fragment that retains the same osteoblast-promoting effect of the PTH-1 receptor as the amino-terminal end of PTH, while eliminating the pro-apoptotic effect caused by the C-terminal peptide chain of PTH[26]. In a prospective retrospective study by Seibel[27], 197 postmenopausal patients with osteoporosis who received ZOL were followed for BMD and total BMD of the femoral neck, lumbar spine and hip at years 1 and 2. Within a research investigation including 139,647 individuals diagnosed with osteoporosis, the average age of the participants was 64 years. Sooragonda *et al.*[28] determined that TPTD had superior efficacy compared to ZOL, raloxifene and denosumab in lowering the incidence of both vertebral and non-vertebral fractures among anti-osteoporosis medications. A systematic review of seven studies comparing the efficacy and safety of TPTD and risedronate in the therapy of osteoporosis revealed that teriparatide is superior in improving bone mineral density in the femoral neck, lumbar spine and total hip. Additionally, teriparatide reduces the incidence of clinical fractures, new vertebral fractures and non-vertebral fractures. Furthermore, there was no significant disparity in the prevalence of adverse events between the two medicines[29]. This may be because teriparatide promotes the formation of cortical and reticular bone by promoting bone metabolism, but does not significantly increase bone mass in cancellous bone sites like the femoral neck and hip[30].

This meta-analysis included six trials, with the test group including 244 patients and the control group comprising 371 individuals. The research found that patients with OP who were treated with TPTD had greater levels of BMD (standardized mean difference: 0.12, 95% confidence interval: 0.07, 0.17 and $p<0.01$) compared to the control group. Nevertheless, the VAS score did not exhibit any noteworthy disparity between the two groups (SMD: -0.72, 95% confidence Interval:-1.86, 0.42 and $p = 0.218$). Furthermore, the treatment of OP patients with TPTD showed a significantly higher content of PINP and β-CTX (SMD: 67.71, 95% CI: 13.44, 121.99 and $p<0.05$) and (SMD: 0.43, 95% CI: 0.17, 0.68 and $p<0.01$). There were no notable disparities in negative responses seen among the two groups (OR: 0.52, 95% CI: 0.25, 1.06 and $p>0.05$).

There are several limitations associated with this research. The limited size of the sample is a significant constraint. This research specifically chose single-centric controlled trials due to the absence of multicenter studies, which therefore had an impact on the accuracy of the results to some degree. Furthermore, this reduced sample size inadequately assesses the safety of TPTD or ZOL.

CONCLUSION

This systematic review demonstrated that TPTD and ZOL are effective in patients with OP. The TPTD showed more effectiveness than ZOL for enhancing BMD and promoting the formation of bone tissue. However, TPTD is less effective than ZOL in inhibiting osteoclasts. Last but not least, big data, multicenter studies, clinical studies with a lower risk of bias and basic clinical studies, are warranted.

SIGNIFICANCE STATEMENT

Osteoporosis (OP) interferes with the body's metabolism and causes bone mass loss, structural alterations, lower bone strength, increased bone fragility and a greater risk of fractures. This meta-analysis compares TPTD with ZOL for osteoporosis therapy. This extensive investigation found that TPTD and ZOL help OP sufferers. The findings showed that TPTD increased BMD and bone tissue growth more than ZOL. In inhibiting osteoclasts, TPTD is less effective than ZOL. Finally, substantial data analysis, multicenter studies, bias-free clinical trials and basic clinical research are needed.

ACKNOWLEDGMENT

The authors express their gratitude for the facilities provided by the higher officials.

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