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Reviewer Comments

This study is relatively well-written and informative to readers, however, there are some points to be advanced or fixed as bellows.

Comment 1: In abstract line 44, this study compared Teriparatide group and controlled group. In method, the patients in Teriparatide group also took calcium plus vitamin D supplements as controlled group. Clear definition is required in abstract and entire manuscript.

Reply 1: We appreciate this valuable comment, and apologize sincerely for our unclear description of Teriparatide group and control group in this study. According to the guidelines, adequate calcium and vitamin D intake is recognized as an important component of bone health (1). Teriparatide is a highly effective injectable treatment option with a unique mechanism of action in that it is anabolic and with demonstrated reduction in risk of vertebral and nonvertebral fractures (1,2). Yet, to date, sparse data exists regarding the efficacy of Teriparatide on relieving back pain and improving health related quality of life (HRQoL) of postmenopausal females with osteoporotic vertebral compression fractures (OVCFs) compared with calcium and vitamin D supplements, which was the purpose of this study. In our study, the Teriparatide group included patients treated with 20ug Teriparatide, once daily, while the control group included patients treated with 500 mg calcium and 400-800 IU Vitamin D per day.

Changes in the text: we have modified our text as advised.

1. In a 12-month, retrospective study, 112 postmenopausal women with OVCFs were assigned to Teriparatide group (20ug Teriparatide, subcutaneous, once daily, n=38) or control group (500 mg calcium and 400-800 IU Vitamin D per day, oral administration, n=74) according to patients' choices between January 2016 and October 2018. (Line 45-49)

2. Treatments with Teriparatide or calcium plus vitamin D supplements had significant effect on improvement of patients' back pain as well as HRQoL, with

significantly reduced VAS and ODI and increased SF-36 PCS and MCS scores. (see Page 3, Line 52-54)

3. Changes in ODI scores are shown in Table 2 and Fig. 1. This value declined in bath Teriparatide group and control group. (see Page 11, Line 231-232)

Comment 2: In result of abstract, PCS and MCS scores are not defined in the method. The sudden emerging of abbreviations confuses the readers.

Reply 2: We appreciate this considerate comment and apologize for the not enough detail of the concepts of PCS and MCS scores in our study, which made their sudden emerging abrupt. Based on your comment, we supplemented some details regarding "PCS and MCS scores" in the Methods part. The SF-36 has eight scales measuring eight domains of HRQoL: physical functioning (PF); role-physical (RP), or limitation in daily role functioning due to physical problems; role-emotional (RE), or limitation in daily role functioning due to emotional problems; bodily pain (BP); general health perception (GH); vitality (VT); social functioning (SF); and mental health perception (MH). Each scale consists of 2 to 10 items, and each item is rated on a two- to six-point Likert scale. The scale score is calculated by summation of all the scores of items belonging to the same scale. The physical health summary (PCS) and mental health summary (MCS) scales summarize the eight SF-36 scale scores into two summary scores that give an overall assessment of HRQoL related to physical and mental health, respectively. The physical component summary (PCS) includes four domains: physical functioning (PF, 10 questions), role physical functioning (RP, four questions), bodily pain (BP, two questions), and general health (GH, five questions). The mental component summary (MCS) includes four domains: vitality (VT, four questions), role emotional functioning (RE, three questions), social functioning (SF, two questions), and mental health (MH, five questions). It has been proved that the SF-36 PCS and MCS scales are valid, reliable, and equivalent for Chinese adult population (3).

Changes in the text: we have modified our text as advised.

The SF-36, a generic HRQoL questionnaire, consists of 36 self-administered questions which measure health status in eight domains of HRQoL: physical functioning (PF); role-physical (RP), or limitation in daily role functioning due to physical problems; role–emotional (RE), or limitation in daily role functioning due to

emotional problems; bodily pain (BP); general health perception (GH); vitality (VT); social functioning (SF); and mental health perception (MH). The physical health summary (PCS) and mental health summary (MCS) scales summarize the eight SF-36 scale scores into two summary scores that give an overall assessment of HRQoL related to physical and mental health, respectively. The physical component summary (PCS) includes four domains: physical functioning (PF), role physical functioning (RP), bodily pain (BP), and general health (GH). The mental component summary (MCS) includes four domains: vitality (VT), role emotional functioning (RE), social functioning (SF), and mental health (MH). It has been proved that the SF-36 PCS and MCS scales are valid, reliable, and equivalent for the Chinese adult population. (see Page 8-9, Line 153-174)

Comment 3: There is no sufficient definition of AEs. In particular, you did not compare the incidences of AEs between two groups, which cannot support your conclusion that Teriparatide increase the incidence of AEs than controlled group.

Reply 3: We appreciate this considerate comment and apologize for the lack of detail of sufficient definition of AEs in the Methods part, and the lack of the comparison of the incidences of AEs between two groups. The definition of AEs is as follows.

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment (4), including side effects to medicines and vaccines, and problems or incidents involving medical devices. Examples of adverse events are any unfavorable and unintended sign, symptom or disease associated with the use of a therapeutic good. The severity of AEs can be categorized as mild, moderate or severe. Mild is defined as no change in physical activity with occasional medication use for relief of symptoms. Moderate includes mild disruptions in daily physical activities and regular medication use for the alleviation of symptoms. Criteria for severe are major disruptions in normal daily activities, additional medication use and additional treatment above and beyond normal that may have included hospitalization.

In additional, we found that 12 (31.6 %) patients complained of slight nausea and dizziness in Teriparatide group, while no AEs was recorded in control group. In short, more AEs were documented in Teriparatide group ($p<0.0001$).

Changes in the text: we have modified our text as advised.

1. An adverse event (AE) was defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment (4). AEs were recorded at each study visit and were given instructions for the assignment of AE severity as mild, moderate or severe. Mild was defined as no change in physical activity with occasional medication use for relief of symptoms. Moderate included mild disruptions in daily physical activities and regular medication use for the alleviation of symptoms. Criteria for severe were major disruptions in normal daily activities, additional medication use and additional treatment above and beyond normal that may have included hospitalization. Treatment would be discontinued if serious AEs occurred. All of them completed the observation period and no patients withdrew from the trial for this reason. (see Page 9-10, Line 177-197)

2. Adverse events were systematically recorded at all patient visits. Overall, self-administered injections of Teriparatide and the oral calcium plus vitamin D supplements were well tolerated in spite of some cases of slight discomforts. 12 (31.6 %) patients complained of slight nausea and dizziness in Teriparatide group. Discomfort generally resolved as the study progressed with no further consequences and did not result in any drop-out. By contrast, all patients in the control group were satisfied with therapy and no side effect was reported. In short, more AEs were documented in Teriparatide group ($p<0.0001$). (see Page 12, Line 250-257)

Comment 4: In line 111-112, this sentence mean that the patients with a history of taking anti-resorptive drugs were excluded in this study? Overall correction in English is required.

Reply 4: We appreciate this comment and apologize for not providing sufficient detail about some exclusion criteria, such as the patients with a history of taking anti-resorptive drugs. As we know, maintenance of the mechanical integrity of bones depends on the homeostasis of osteogenesis and the homeostatic bone resorption. An imbalance between these phenomena is the primary contributor of osteoporosis (5). Osteoporosis treatment predominantly involves anti-resorptive agents (6) and anabolic agents, like Teriparatide, a synthetic and active fragment of parathyroid hormone (PTH) (7,8). Daily subcutaneous injections of Teriparatide stimulate more

osteogenesis than bone resorption by directly acting on osteoblasts to promote osteoblastogenesis and reduce osteoblast apoptosis (9-11). Furthermore, another mechanism underlying the anabolic effect of Teriparatide is the stimulation of proliferation and differentiation of bone marrow MSCs into the osteoblast lineage upon short-term administration (12,13). However, several osteoporosis treatment guidelines, mainly in Europe, recommend the use of Teriparatide for the treatment of severe established osteoporosis as a second-line treatment (14). Thus, many patients initiating Teriparatide therapy have often been previously treated with antiresorptives for long periods of time. An important clinical question is whether the response to Teriparatide induces positive effects on bone mass and osteoblast function regardless of previous exposure to antiresorptive therapies in postmenopausal women with established osteoporosis (15). To address this problem, some researchers put out that the previous anti-resorptive drugs may influence the anabolic effects of Teriparatide. Researchers reported that in individuals who have previously been treated with an antiresorptive agent, the subsequent actions of teriparatide on bone density are transiently delayed if bone turnover has been markedly suppressed (16,17). Thus, in order to avoid the possible blunted aftereffects of previous anti-resorptive treatments on Teriparatide in improvement of pain relief, and quality of life in postmenopausal females with osteoporotic vertebral compression fractures, we excluded the patients with a history of taking anti-resorptive drugs in this study.

In addition, our language has been modified and polished. See the full text for details.

Changes in the text: N/A.

Comment 5: In line 116-120, some of the exclusion criteria are not relevant to this study. What are the standard for exclusion criteria?

Reply 5: We appreciate this insightful comment, which has greatly improved the quality of the article. In our study, subjects were excluded from the study if they had metabolic bone disease other than postmenopausal osteoporosis; imminent need for kyphoplasty or vertebroplasty; and evidence of significant pathology related to back pain which was difficult to be interpreted by osteoporotic vertebral fracture. Besides, subjects with uncontrolled high blood pressure, liver disease, secondary osteoporosis or abnormal thyroid function, renal and hepatic dysfunction, medical conditions such as cancer, severe sleep apnea, chronic obstructive pulmonary disease, severe lactose

intolerance, and current use of tobacco were excluded. Actually, in this study, as your valuable recommendations, some of the exclusion criteria in the methods part seemingly were not directly relevant to the purpose of this study, such as uncontrolled high blood pressure, liver disease, secondary osteoporosis or abnormal thyroid function, renal and hepatic dysfunction, medical conditions such as cancer, severe sleep apnea, chronic obstructive pulmonary disease, severe lactose intolerance, and current use of tobacco. However, in fact, these exclusion criteria, like uncontrolled high blood pressure, renal and hepatic dysfunction and liver disease, medical conditions such as cancer, severe sleep apnea, chronic obstructive pulmonary disease, severe lactose intolerance can influenced the life quality of patients severely, and this effect may be even greater than that of drugs. Besides, secondary osteoporosis is referred to osteoporosis that is caused or exacerbated by other disorders or medication exposures, which had an impact on the results of this study. Furthermore, thyroid disease is a common disease of the endocrine system and one of the important causes of secondary osteoporosis (18). Thyroid hormone can affect mineral salt metabolism in human body, and it is involved in bone maturation and transformation. It was found that abnormal manifestations of bone metabolism, calcium and phosphorus substitution in patients with abnormal thyroid function led to decreased bone volume, leading to osteopenia (19,20). In conclusion, it is wise to exclude the patients with these exclusion criteria to especially assure the efficiency and credibility of these results.

Changes in the text: N/A.

Comment 6: In blood samples, bone turnover markers such as P1NP were not included in this study, which was described as the limitation at the end of manuscript. If you did not assess the effect of Teriparatide with evaluating bone turnover markers, I think the improvements of pain and quality of life could not be proved by the effect of Teriparatide. What is your opinion to overcome these shortcomings?

Reply 6: We appreciate this valuable comment and apologize for lacking the content of bone turnover markers in this study. We really appreciate it. As we all know, biochemical markers of bone turnover have the potential to provide early feedback to patients and prescribers during osteoporosis treatments as early as 1 to 3 months of initiating osteoporosis therapy (21-23). Among them, procollagen type I N-terminal propeptide (PINP) and serum C-terminal cross-linking telopeptide of type I collagen

(β-CTX I) is considered as the reference standard for bone formation and bone resorption respectively (21,22). You're on the right track, and the positive biochemical marker response after treatment of Teriparatide has been proved in many previous studies (24,25), which can receive confirmation of an anabolic biologic response in the bone.

However, in clinical practice, routine blood tests of bone turnover markers were very difficult to achieve for various reasons, especially in the orthopaedics clinic or during the outpatient follow-up. We acknowledged these data of our included patients were patchy, from which the impact of Teriparatide so far was hard to assess. Secondly, the aim of this study was to focuse mainly on the effect of Teriparatide on reducing back pain, and improving HRQoL for postmenopausal women with OVCFs. And we found that in postmenopausal women with OVCFs, the consequent persistent back pain and impaired HRQoL, treatment with Teriparatide was associated with more profound therapeutic effects and more AEs compared with calcium plus vitamin D supplements. But the interaction between bone turnover markers and the effect of Teriparatide, and the mechanism of action in depth were not explored in this study. That’s why these bone turnover markers were not included in our study.

In order to overcome the above mentioned shortcomings, we set strict inclusion and exclusion criteria trying to ensure that improvements in HRQoL were due to treatment of Teriparatide and calcium plus vitamin D supplements as much as possible. We believed that the improvements of pain and HRQoL could be proved by the effect of Teriparatide. The interaction between bone turnover markers and the effect of Teriparatide was needed in further clinical trials

And we have added some related discussion in the discussion section.

Changes in the text: The main drawback of our study include the relatively small number of subjects, which were groups two groups according to their choices on different treatments, but the numbers were sufficient to detect statistically significant differences in the outcomes of interest. Secondly, a relatively short observation window limits the extrapolation of our final results to the generalization of a 24-month course to certain extent. Finally, in blood samples, bone turnover markers were not included; however, the positive biochemical marker response after treatment of Teriparatide has been proved an anabolic biologic response in the bone (24,25). What’s more, routine blood tests of bone turnover markers were very difficult to achieve, especially in the orthopedics clinic or during the outpatient follow-up.

Furthermore, the aim of this study was to focus mainly on the effect of Teriparatide on reducing back pain, and improving HRQoL for postmenopausal women with OVCFs, rather than to explore the mechanism of action in depth. That's why these bone turnover markers were not included in our study. To overcome these shortcomings, we set strict inclusion and exclusion criteria trying to ensure that improvements in HRQoL were due to treatment as much as possible. We believed that the improvements of pain and HRQoL could be proved by the effect of Teriparatide. (see Page 15-16, Line 308-329)