

Dear Editors and Reviewers:

Thank you for your letter and for the reviewers' comments concerning our manuscript entitled "Treatment for subtrochanteric fracture and subsequent nonunion in an adult patient with osteopetrosis"(Manuscript Number: 67788). Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction which we hope meet with approval. Revised portion are marked in yellow background in the paper. The main corrections in the paper and the responds to the reviewer's comments are as flowing:

Responds to the reviewer's comments:

**Reviewer 1:**

The framework of writing is unusual. Normally, the Abstract of a case report does not require to be structured. Consequently, it is easier to be read and understood. Besides, it will not repeat the description in the text. Although the authors also submitted an English-editing certificate concomitantly, numerous errors still appeared (e.g., line 126- proximal left femur or left proximal femur? present or past tense, singular or plural, --- etc.). Re-checking is absolutely necessary.

**Response:** Thank you very much for your kind comments. We have revised and repolished the manuscript according to your suggestions. All manuscript changes have been marked in yellow.

**1.** The Abstract form requires to be re-checked with corresponding to the guidelins of

this journal.

**Response:** Thank you for your kind comments. we are very sorry for our negligence of the abstract's format. We have revised it according to the instructions for authors of the journal.

**2.** In the text, osteopetrosis and osteosclerosis are mingled erroneously. e.g., lines-74, 79, 85,109,135,169,175,186.

**Response:** We apologize for our negligence, We have checked the full text and replaced osteosclerosis with osteopetrosis.

**3.** In Introduction, line-99, the follow-up period should be 10 months, and not one year. Although the difference is only 2 months, the definition is quite different. Is nonunion confirmed or not?

**Response:** We apologize for our negligence. We changed one year to 10 months. The U.S. Food and Drug Administration (FDA) defines a non-union as a fracture that is at least 9 months old and has not shown any signs of healing for 3 consecutive months. In our case, at 2, 3 and 10 months postoperatively, the plain radiography showed the fracture line was still clearly visible and no obvious signs of fracture healing were observed, So we think the definition of nonunion is certain.

**4.** In lines 131-133, the normal value at your Lab. should be supplemented.

**Response:** Thanks for your suggestion. We've rewritten the Lab, the rewriting part

has also been marked with a yellow background in the article.

#### Laboratory examinations

Main abnormal indicators: parathyroid hormone 111.90 pg/ml, urine specific gravity 1.010, uric acid 520  $\mu\text{mol/L}$ , D-dimer 1.39  $\mu\text{g/ml}$ , fibrinogen degradation product 6.8  $\mu\text{g/ml}$ , blood phosphorus 1.61 mmol/l, WBC  $10.6 \times 10^9/\text{L}$ , NE% 84.1%, LYM% 11.3%, D-dimer 1.39ug/ml, FIB 6.8ug/ml.

Main normal indicators: Hb 152g/L, PLT  $144.5 \times 10^9/\text{L}$ , PT 11.0s, APTT 25.6s, TT 13.6s, U-BIL(-), UBG(-), KET(-), BLD(+/-), Calcitonin 3.86pg/ml, TPOAb 36U/ml, TG-Ab <15.0U/ml, FT3 4.45pmol/L, FT4 13.34pmol/L.

5. In Discussion, lines-225-227, autogenous bone graft may aggravate the trauma? and expensive? Is it true?

**Response:** Thanks for your suggestion. We have adjusted the relevant statements, hoping to meet your requirements. it may cause complications and additional treatment costs <sup>[24]</sup>. Relevant expressions can be seen in the 24th reference. e.g., In the complications part ‘Although the iliac crest remains the most frequently harvested donor site, morbidity is a concern.’

6. In Discussion, the authors require to comment the technique: In the initial treatment with locked plating, is supplementary cancellous bone graft from the pelvis helpful?

**Response:** Thanks for your positive comments. We have added relevant content to the discussion, hoping to meet your requirements. There is no doubt that autogenous bone

graft can promote fracture healing, but for patients with no obvious defect after fracture reduction<sup>[25]</sup>, whether it is necessary to use autogenous bone graft even reamed and bone graft at the first operation remains to be further discussed.

7. In Discussion, the authors require to comment the aftercare: After the initial internal fixation, is supplementary teriparatide (Forteo) necessary? The reason is similar to treatment of atypical femur fractures.

**Response:** Thank you for your comments. For patients with postoperative use of teriparatide, our view is that although teriparatide is widely used in the treatment of osteoporosis and atypical femoral fractures, to reduce the incidence of fracture and improve the fracture healing rate, it has not formed a systematic standard treatment concept. In particular, the experience of treating atypical fractures is applied to the treatment for fracture with osteopetrosis. We did not find relevant literature support, We will further explore the relevant aspects in the future. (Reference 1 Greenspan SL, Vujevich K, Britton C, Herradura A, Gruen G, Tarkin I, Siska P, Hamlin B, Perera S: Teriparatide for treatment of patients with bisphosphonate-associated atypical fracture of the femur. *Osteoporos Int* 2018, 29(2): 501-506 [PMID: 29085957 DOI: 10.1007/s00198-017-4286-7] Reference 2 Ralston SH, Gaston MS: Management of Osteogenesis Imperfecta. *Front Endocrinol (Lausanne)* 2019, 10: 924 [PMID:32117044 DOI: 10.3389/fendo.2019.00924])

8. If combined 4. and 5. techniques in the initial operation are used, can the better

outcome be achieved?

**Response:** Thanks for your suggestion. There is no doubt that more interventions at the beginning may increase the probability of postoperative fracture healing. But we still want to emphasize that this is not necessary, this may lead to excessive medical treatment. I hope our answer can meet your requirements. If you have further questions, please contact us. We will make corrections with an open mind.

**9.** In Discussion, please comment the optimal length of a locked plate. The longer is a plate, the better is the outcome? Or, what is the optimal distance from the farthest screw to the fracture site?

**Response:** Thanks for your positive comments. We have added relevant content to the discussion, hoping to meet your requirements. The fixation of steel plate follows AO principles, a plate length greater than three times the fracture in comminuted fractures, and greater than eight to ten times the fracture length in simple fractures has been advocated. Screw to plate hole ratios of less than 0.5 create a long lever arm and decrease the bending loads on the distal screws. In addition, a span of at least two or three screw holes should be left open over the fracture to decrease stress concentration<sup>[22,23]</sup>.

**10.** The styles of References should be consistent. e.g., p.123-7 or 123-127?

**Response:** We apologize for our negligence. We have revised it according to the instructions for authors of the journal.

**11.** Based on pre- and post-operative radiographs, the femur has the narrow medullary canal without complete obliteration. Before a locked plate is inserted, the narrow medullary canal may be reamed for a short segment and cancellous bone graft is filled. Whether the union chance may be upgraded? Please give a comment in Discussion.

**Response:** Thanks for your suggestion. In our opinion, reamed and bone graft may increase the probability of fracture healing, but it may cause iatrogenic fractures and prolong the operation time. Its necessity needs to be further discussed.

**12.** Osteopetrosis with fractures is very rare. Using possible techniques to upgrade the success rate of treatment is always invaluable. Have the authors an ideal protocol for treatment of this issue?

**Response:** Thanks for your positive comments. Osteosynthesis is regarded as the first-choice of treatment approach for fractures in patients with osteopetrosis, especially peritrochanteric fractures. Meanwhile, if the condition of medullary canal permits, the preferred choice is closed reduction and intramedullary nailing. However, for most patients with osteopetrosis, only open reduction and plate fixation are allowed. Regardless of whichever operation method is selected, extra attention must be paid to timely replacement of drill bits and adequate cooling with physiological saline during operation. This additional attention is effective at protecting the blood supply and avoiding operation failure and iatrogenic fracture. In addition, the use of PRP might be more efficient in combination with physical stimulation therapy such as

rESWT at treating fractures in patients with osteopetrosis.

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Responds to the reviewer's comments:

1. Chief complaints in Case Presentation section repeat the description of Introduction section. What happens?

**Response:** We apologize for our negligence, this is an upload error.

2. In Imaging examinations, proximal left femur? Or left proximal femur?

**Response:** I'm sorry I don't know the difference. It is left proximal femur.

3. The time period between the operative treatment and diagnosis of nonunion with PRP treatment is inconsistent at Case summary in Abstract (12 months) and Outcome and follow-up (10 months)?

**Response:** "Case summary in Abstract (12 months)" is the time of receiving further treated with PRP+rESWT

4. The first paragraph of Discussion section repeats Outcome and follow-up.

**Response:** We apologize for our negligence, this is an upload error.

5. There is no true Discussion section in the text.

**Response:** We apologize for our negligence, this is an upload error.

6. The Conclusion is overlong and should be condensed.

**Response:** Thanks for your positive comments. We have condensed relevant content to the conclusion, hoping to meet your requirements.

7. The reviewer's comments and suggestions are not responded in the text despite that the authors perfectly reply the queries.

**Response:** We apologize for our negligence, we uploaded a wrong version, we reuploaded a correct version, and sent the version marked with the modified content to you as an attachment for viewing.