

Manuscript No: 88662

“Adult-Onset Hypophosphatemic Osteomalacia as a Cause of Widespread Musculoskeletal Pain: Retrospective Case Series of Single Center Experience.”

Dear Jin-Lei Wang,

Editor-in-Chief, *World Journal of Clinical Cases*

10.10.2023

Thank you for your email, in which you requested revisions to our manuscript. We have carefully considered the comment from the reviewer, and have revised and improved the manuscript accordingly. The detailed answers to the reviewers' comments were described in a separate page. The original referee comments are provided in black color, whereas our answers are given in blue. The appropriate changes made in the revised manuscript are highlighted.

Coauthors and I really appreciate your considerate comments on my submission, and will provide point-by-point answers to your peer-review issues. We sincerely hope that our revised manuscript is suitable for publication in *World Journal of Clinical Cases*. We appreciate your giving us the opportunity to revise our manuscript.

Sincerely,

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Professor

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Reply to Reviewer #1

1. This study is a single-center retrospective study including only 8 patients. Although the difficulty of identifying this disease is considered, the number of included patients is still too small, which greatly affects the credibility of the conclusions. Therefore, we hope that the authors will conduct multicenter research to expand the sample size. Prospective studies are also necessary.

Thank you for comment. We certainly agree with your comment. Small number of included patients and the retrospective nature of the study are major limitation of this study. Larger prospective multi-centered cohort studies are needed to further prove the conclusion of this study.

Therefore, we will add a discussion about the limitations of this study to the manuscript and engage in discussions with our colleagues to initiate prospective research on the detection of this rare condition in our country.

Line 381-383, P14, discussion

Another limitation was the inherent bias due to the retrospective nature of the study and the relatively small number of patients recruited in a single center. Larger prospective multi-centered cohort studies are needed to establish a more precise clinical picture of the disease entity.

2. This study was conducted in a country where the hepatitis B virus is endemic. Adefovir-induced Fanconi syndrome is the most common cause of hypocalcemic OM. This view is very interesting. If the authors can further prove this conclusion in a multicenter prospective study, it will have very important clinical significance. However, it should be noted that with the emergence of new drugs such as tenofovir, the clinical practice also tends to use drugs with better efficacy and safety. Authors need to consider whether the significance of the conclusions drawn in this study will be greatly discounted in future clinical practice.

Thank you for comment. I certainly agree with your comment. As the use of adefovir in HBV patients is decreasing, the clinical significance of adefovir-induced hypophosphatemic osteomalacia mentioned in this study may diminish in the future. However, a considerable number of patients in Korea are still taking adefovir for long-term maintenance therapy, and sporadic cases of hypophosphatemic osteomalacia associated with adefovir have been reported. Nevertheless, we have also experienced that many cases can be overlooked due to a lack of awareness of the disease. Therefore, we believe that physicians in HBV-endemic countries should be aware of these clinical cases, and the authors aim to present this study. However, we also acknowledge the points raised by the reviewer as practical considerations. Therefore, we have supplemented the discussion section of the paper to address the limitations of the study as follows:

Line 381-383, P14, discussion

Additionally, ADV has been used as a drug of choice for treating HBV infection for years. However, after the introduction of other anti-HBV medications with better efficacy including entecavir and tenofovir, ADV is not recommended for the treatment of chronic HBV infection in European and Korean clinical guidelines [28,29]. Thus, our conclusion that ADV-induced Fanconi syndrome is the most common etiology of adult-onset hypophosphatemic OM in HBV-endemic countries, may have little clinical significance in the future. However, as a considerable number of patients continue to receive ADV for their long-term maintenance therapy, physicians in HBV-endemic countries should be aware of this clinical entity.

Editorial Office

Before its final acceptance, please provide and upload the following important documents: Biostatistics Review Certificate, a statement affirming that the statistical review of the study was performed by a biomedical statistician.

Thank you for comment. However, in this study, we did not utilize any kind of statistical method for analysis of results. Thus, there are nothing to state on the biostatistics review.

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Thank you for comment. We will provide standard three-line tables for all tables included in the manuscript.