

Reviewer #1

The manuscript entitled “Hepatic osteodystrophy - An underrecognized metabolic bone disease” provides a comprehensive minireview of the role of hepatic osteodystrophy. Hepatic osteodystrophy is a common and frequently untreated complication, manifested as osteoporosis or osteopenia, encountered in the evolution of chronic liver diseases. The authors have done an extensive literature review, covering various aspects of hepatic osteodystrophy, such as pathogenesis, management and further research direction. The topic is highly relevant and interesting. However, there are several areas where the manuscript could be improved to enhance its quality.

1. Do different types of chronic liver disease lead to hepatic osteodystrophy through different pathogenetic pathway or mechanism?

Authors’ reply: Though the pathogenesis of hepatic osteodystrophy is multifactorial, disease specific possible pathological factors leading to bone loss have been summarized in table 1 and added in the manuscript.

2. The authors discussed a lot of molecular pathways in the pathogenesis of hepatic osteodystrophy, such as IGF-1, IGFBP-3, Wnt/ β -catenin signaling pathway and RANKL/OPG. Please show these mechanisms more clearly in **Figure 1**.

Authors’ reply: We thank the reviewer for this valuable suggestion. Figure 1 has been revised

3. Are there any interactive effects among different physiological events during the pathogenesis of hepatic osteodystrophy?

Authors’ reply: Yes, several interactive physiological effects that contribute to the pathogenesis of hepatic osteodystrophy. Both hepatokines and osteokines interact together and can affect both hepatic tissue as well as bone. This physiological crosstalk is collectively referred as liver-bone axis.

4. Please review **figure 2**. Does parathyroid hormone only have the positive effects on osteoblast? How about the effects of parathyroid hormone on osteoclast?

Authors’ reply: Parathyroid hormone (PTH) has direct actions on osteoblasts and osteocytes and indirect effects on osteoclast through its action on osteoblast/osteocytes. While PTH stimulates both bone resorption and bone formation, the outcome on bone, either catabolic or anabolic, will depend on the duration and periodicity of exposure to PTH. In cholestatic animal model, a reduction in bone formation and osteoblast number was observed in male bile-duct-ligated rats. In addition, bone formation and trabecular bone volume in this model could be increased by administration of PTH, which predominantly affects the osteoblast.

5. In **figure 2**. Please add how hepatic stellate cells transform into activated hepatic stellate cells. Please add the source of tumor necrosis factors which activate T cells.

Authors' reply: The liver microenvironment of patients with CLD undergo changes that involve inflammation, altered blood flow, activation of stellate cells and loss of normal hepatic function. Activation of Toll-like receptor signalling pathways on hepatic stellate cells leads to production of a variety of inflammatory factors with bone absorption effect. Osteoclast precursors are activated by proinflammatory cytokines such as TNF, the levels of which are increased in patients with viral hepatitis and alcoholic liver disease. Activated tissue macrophages and monocytes are major sources of TNF.

Figure 2 has been updated

6. Please further discuss how to integrate hepatic osteodystrophy therapy into regular chronic hepatic disease management?

Authors' reply: Bone densitometry needs to be assessed in patients with cholestatic diseases or if any of the risk factors are found, and in cirrhotics. In patients within normal BMD, it is advisable to repeat DEXA after 2-3 years, as is suggested in the non-cirrhotic population. Recognition of the risk factors for bone loss including those for osteoporosis and fractures in patients with CLD is recommended. This part is included in the revised manuscript

Overall, the manuscript entitled "Hepatic osteodystrophy - An underrecognized metabolic bone disease" is a valuable contribution to the field, providing a detailed overview of the pathogenesis and management of hepatic osteodystrophy. **However, it would benefit from a more critical analysis of the existing literature, a deeper discussion of treatment options, and a more detailed roadmap for future research**

With these improvements, the manuscript could serve as a more comprehensive and balanced review for researchers and clinicians interested in hepatic osteodystrophy and modern molecular biology.

Authors' reply: Thank you for the suggestion. A deeper discussion of treatment options and a more critical analysis of the existing literature have been included in the revised manuscript.

Reviewer #2

The manuscript provides a concise yet comprehensive overview of hepatic osteodystrophy (HO), a significant but underrecognized complication of chronic liver disease (CLD). It covers the epidemiology, pathogenesis, diagnosis, and management of HO, emphasizing its multifactorial nature and the need for targeted interventions. The review is well-structured, with clear sections and a logical flow, making it accessible to readers in hepatology and endocrinology. However, there are areas where clarity, precision, and additional details could enhance the manuscript's impact and scientific rigor. Below are specific comments and suggestions for improvement.

1. In abstract section, clarify the statement “bisphosphonates are the most efficient drugs” by specifying their efficacy in increasing BMD or reducing fracture risk.

Authors' reply: The statement has been modified.

The primary medical intervention for the treatment of osteoporosis in CLD remains bisphosphonates though a benefit in terms of fracture reduction has never been shown.

2. Simplify complex sentences and define ambiguous terms. For instance, clarify what “liver-specific considerations” entail (e.g., unique risk factors or altered pharmacokinetics in CLD).

Authors' reply: The language has been changed to make it simple.

“Despite its significant contribution to morbidity in CLD patients, therapeutic strategies are often extrapolated from osteoporosis guidelines. These guidelines are based on data on general population excluding patient with CLD and thus limits its applicability in this population.”

3. The diagnosis section mentions the use of DXA and FRAX but does not address limitations specific to CLD patients, such as the impact of ascites on DXA accuracy.

Authors' reply: It has already been included. “In cirrhotic patients with ascites, paracentesis should be done before BMD measurements as fluid can falsely lower lumbar spine BMD values during a DXA scan”

4. The management section relies heavily on bisphosphonates and mentions denosumab and raloxifene but provides limited data on their long-term efficacy or safety in CLD patients. The role of anabolic agents like teriparatide is mentioned briefly without sufficient context.

Authors' reply: There is paucity of data on long-term efficacy or safety of bisphosphonates or denosumab in CLD patients due to the small number of studies with small sample size and short follow-up. However, serious adverse events have not been reported. Recombinant human PTH 1-34 (Teriparatide) has not been studied specifically in humans with CLD.

5. The prevalence data are compelling, but the section could benefit from a table summarizing rates across different CLD etiologies (e.g., PBC, viral hepatitis, ALD). Consider adding a sentence on the economic or clinical burden of HO to underscore its importance.

Authors' reply: A table on prevalence of hepatic osteodystrophy according to different CLD etiologies has been included in the revised manuscript

6. The screening recommendations (e.g., BMD every 1–2 years for PBC, 2–3 years for cirrhosis) are presented without referencing specific guidelines or consensus statements. Consider adding a table summarizing prevalence data or a flowchart for screening and management to enhance clinical utility.

Authors' reply: The screening recommendations are from the EASL Clinical Practice Guidelines published in 2018. The corresponding reference has been added. We thank the reviewer for this valuable suggestion. A flowchart for screening and management has been included in the revised manuscript.

7. The reference list is robust, but some citations (e.g., Ref. 7, a 2025 study) are listed as “e-pub ahead of print” without full publication details, which may limit accessibility for readers.

Authors' reply: The same has been taken care of. Thanks for pointing out this mistake.

8. Elaborate on key mechanisms (e.g., how sclerostin inhibits Wnt/ β -catenin signaling) and their relevance to bone loss in CLD.

Authors' reply: Thank you for the suggestion. The mechanism of sclerostin induced low bone mass by inhibition of WNT pathway and its relevance in hepatic osteodystrophy now added in the manuscript.

9. For genetic factors, clarify whether identified polymorphisms (e.g., VDR, COLIA1) are actionable in clinical practice or require further validation.

Authors' reply: Thank you for pointing this possibility. Currently the polymorphisms are not actionable from clinical practice point of view and need further future studies to explore its therapeutic potential.

10. Briefly address whether other emerging osteoporosis therapies have been studied in CLD or are under investigation, even if data are preliminary.

Authors' reply: Emerging osteoporosis therapies in CLD have been included in revised manuscript