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14.02. 2014

Re.: Journal: World Journal of Gastroenterology
ESPS Nr.: #7758
Title: Osteoporosis and fractures in liver disease:
Relevance, pathogenesis and therapeutic implications
Author: Inaam A. Nakchbandi
Submission of revised manuscript

Dear Dr. Wang,

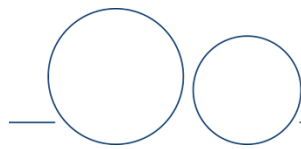
Thank you for allowing us to resubmit our manuscript entitled: Osteoporosis and fractures in liver disease: Relevance, pathogenesis and therapeutic implications.

We greatly appreciate the helpful comments of the reviewers. In response to the questions raised by the three reviewers we have revised the manuscript and believe that the manuscript has been strengthened. A point-by-point response follows this letter. In addition, the references and typesetting were adjusted as required. The manuscript has been reviewed by two English language native-speaker colleagues. Therefore, I am not willing to pay for English language editing.

We hope you find this revised version acceptable for publication in World Journal of Gastroenterology and look forward to your review.

Sincerely,

Inaam Nakchbandi



Response to Reviewers

We greatly appreciate the reviewers' comments. In response to the questions raised, we have revised the manuscript and believe that the manuscript has been strengthened.

Please note that the reviewers' comments are provided in italics, and our response is indented and provided in standard font. New additions to the text of the manuscript are bolded.

Reviewer Nr. 02520219

Dr. Nakchbandi in this review discussed the details on the patients who suffer liver diseases are accompanied with bone loss and the involvement of associated factors. This is a great review with good writing and easy understanding. this review should be accepted for publication.

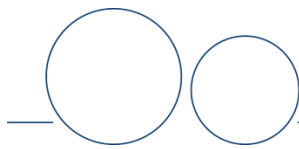
We thank the reviewer for the kind comments.

Reviewer Nr. 00002777

The review of Nakchbandi describes the relationship between liver disease and development of bone disease. The review is well written and well documented. In order to complete the chapter "The pathogenesis of osteoporosis in liver disease", a paragraph on the role of hyperhomocysteinemia in osteoporosis could be added.

We thank the reviewer for pointing this out. We added the following text in the paragraph entitled "Other players" on page 14:

Another potential player is homocysteine, which is elevated in liver disease [111]. It is detected in bone, and mostly indirect evidence suggests effects on osteoblasts, osteoclasts and collagen crosslinking [112-114]. Some studies reported a relationship between increased homocysteine levels and increased fracture risk, while others reported only a relationship between increased circulating homocysteine levels and decreased bone mineral density [115, 116].



Minor point: Page 3 of the introduction, last paragraph, since in these studies (delete “the”)

This was done. Thank you.

Last sentence before the conclusion, “in view of the currently available data on bisphosphonate, it seems reasonable”.

This was also done.

Reviewer Nr. 02527647

In this review, the authors analyzed the estimated prevalence for liver-related osteoporosis and fractures; the evidence available with regard to the pathogenesis of bone loss in liver disease, the diagnostic steps required in all patients, and the therapeutic options available, which will be very helpful for all hepatologists. Some parts need revise:

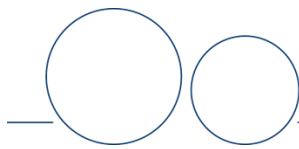
1. List the references in some parts of the descriptions:

(1)The general population started first associating this condition with menopause and loss of estrogen, even though it was clear from the beginning that it is a condition associated with a great variety of diseases ranging from inadequate calcium intake or uptake to abnormalities in various bone-associated cell functions.

(2)Most of the bone consists of a collagen matrix, but a great number of proteins and growth factors such as insulin like growth factor-I (IGF-I) have also been found in this matrix and affect osteoblast function as they are produced or osteoclast function when resorbed.

The following references were added (Cooke 1957, Neale 1974, Nordin 1979; Robey et al. 1996; Kawai et al 2012), these are numbered 2-4 for the first sentence and 6 and 7 for the second sentence.

2.In the sentence “Thus the potential for bone loss associated with chronic liver diseases amounts in the most conservative calculations to 2.23% and



can reach almost two fifths of the population.”, please explain how you get the results: 2.23% and two fifths.

In the related paragraph on pages 4 and 5, the following text was added. Please note that the statement about two fifths was adjusted upward based on the new calculation, which is also found in Table 1. Following is the text, with the new additions in bold font:

Thus the potential for bone loss associated with chronic liver diseases amounts in the most conservative calculations to 2.23% (**This number was obtained by adding the numbers at the lower ranges of the prevalence of different types of liver disease: $0.1+2+0.1+0.003+0.03=2.233$**) and can reach **up to half** the population (**This number was obtained by adding the numbers at the upper ranges of the prevalence of different types of liver disease: $0.1+44+0.7+4.5+0.03=49.33$**).

3. The title of table 1 "Epidemiology of bone abnormalities in liver disease", should revise as "Epidemiology of bone abnormalities in liver disease in Europe"

The Reviewer is correct that the prevalence of liver disease is restricted to Europe. However, the data in references 8 and 9 were obtained from worldwide studies. Thus adding the word in Europe in the title might be misleading. Instead we added a the foot note for Table 1 with the following wording:

***The data on the prevalence of liver diseases are obtained from a study limited to Europe.**