Author’s response to reviews

Title: Prevalence of osteoporosis and osteopenia in men and premenopausal women with celiac disease: a systematic review

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Author’s response to reviews:

Dear Editor,

Thank you very much for reviewing our manuscript. We also greatly appreciate the reviewers for their complimentary comments and suggestions. We have revised the manuscript based on reviewer’s comments (by tracked changes and highlights). Please find a point-by-point response to the reviewer’s concerns as below. We hope that you find our responses satisfactory and that the manuscript is now acceptable for publication.

Yours Sincerely,

Azita

Reviewer #1:

Generally

How did you address or assess the effect of comorbid diseases? The prevalence/result the result of your selected studies were overestimated.
Answer: we excluded the studies with endocrine and metabolic disorder, age, smoking, and menopause which are known as the confounding factors for bone loss.

Abstract

Better if your rewrite the 1st 2 lines under the result section of the abstract

Answer: was done.

Since it is a pooled prevalence, you should have to add recommendation in the conclusion part of the abstract.

Answer: was done in abstract.

Background

Better if you review the usage of articles like the, a, an … etc. E.g. paragraph 1, line 3 " current ….." must be "the current …”

Answer: was done.

Better if you rewrite in 3 or 4 paragraphs, It is too long and difficult to grasp the main idea

Answer: we shortened as you commented.

How did you rule out other diseases that will cause this problem and what about the differential diagnosis as well as comorbidities with celiac diseases?

Answer: we just included studies with excluding confounding factors of age, menopause, endocrine disorder, history of corticosteroid use, and smoking. Bone loss is one of comorbidity of celiac disease with unknown etiology which can be due to cytokines or hyper parathyroidism or other nutrient deficiency.

Methods

Why only you focus on PubMed and Scopus Databases? What about Cochran library, Google scholar, etc.
Answer: Google is not scientific data base but we use that for hand searching in references. We searched Cochran and there was not any systematic review about prevalence of bone loss in celiac.

What will you do if you have got a publication with another language (other than English) because you stated that "No language or..." paragraph 1, line 6 under search strategy. It must be clearly stated.

Answer: We corrected that inside the manuscript.

Is there a possibility of hand searching?

Answer: Yes it was. We did it and we found one study which PRISMA chart shows.

Did you include or exclude reviews that reiterated findings from already included studies (you mention in the background section of the last lines, reference number 10 and 25)

Answer: Yes in first systematic was about bone fracture and not about prevalence of bone loss and in the second one there was systematic review about bone recovery after different interventions and their data was not common with us.

Result

What about heterogeneity and publication bias?

Answer: Heterogeneity of all meta-analyses have been reported as Cochrane Q and I square index. As the number of included studies in each meta-analysis is very limited (3 to 4 studies for each meta-analysis), publication bias using funnel plot would not provide any meaningful data. So, we omit the publication bias part.

What about the sensitivity analysis?

Answer: The number of included studies are very limited in each meta-analyses and subgroup analysis or any sensitivity analyses would not give a meaningful or useful results.

The 1st two Sentences under "Bone mineral density" title needs references

Answer: Reference was added as below:

Discussion

Better if you review the usage of articles like the, a, an … etc. E.g. paragraph 1, line “aim …..” must be "the aim …".

Answer: was done

Better if you rewrite in 5 or 6 paragraphs, it is too long and difficult to grasp the ideas for those who have similar ideas

Answer: we corrected as you commented.

Can you add a justification for the variation or similarity while you are trying to compare the findings?

Answer: I made some changes in discussion. Some study are similar in papulation age and some in separating femoral from lumbar densitometry. Confounding factors are not mention clearly in most of studies. We focused to exclude most important confounding factor which is age and in women menopausal age so we include studies which is done in young age or mention about menopause. Type of studies are different and just 2 are case control and others are cross sectional.

Conclusion

What is your recommendation as an intervention plan? Because this is a systematic review with a pooled prevalence? and do you think writing the percentage in the conclusion part is recommended

Answer: Thanks for your nice comment. Bone loss increase fracture risk and disability and has a high cost and if it is more prevalent among the CD cases compared with general papulation, it should be found and prevented. We changed the conclusion.

Generally, as you know osteoporosis is one of the most important reason of bone fracture which results to long term disabilities and huge costs for the governments. It has been shown that the prevalence of osteoporosis is varied between 14-45% among the CD cases, which is probably due to the lack of exclusion of confounding factors such as drug use, menopause, and …. Therefore, it was not clear that what the exact association between CD and osteoporosis is. In our study for the first time in the world we excluded such confounding factors to clarify this association independent from other confounding factors. We confirm that our systematic review may probably has some limitations, however we believe that this report is enough valuable to pave the way of similar jobs in future. Indeed such systematic reviews as the pilots will pave the way of introducing new preventive policies in the world to decrease such public health problems. We hope that you find our responses satisfactory.
List of abbreviations

better if you rewrite like this "CD: Celiac Disease"

Answer: was done.

Reviewer #2: There are a few grammatical errors through the manuscript which may be correct prior to publishing. I think it would be paramount to mention an important limitation in the study with regard to menopause. Many included studies are assuming an age at menopause as 50 or 55 without biochemical evidence of true menopause. Patients might have had menopause at age 45 and still be included in the study data. Overall it is an interesting observation and I agree that more controlled studies might be helpful to eliminate confounders.

Answer: Thanks for your nice comment. In two studies they have mentioned about their samples which was in premenopausal age and we don’t know about how they include this age. Is it by biochemical evidence of true menopause? Or just age of patients? And in most studies which we include in our systematic review, age of patients were less than 50 and just in 2 with small sample size (76 patients) they include age less than 55 for their studies whom probably are in early years of menopause. As you know age is most important confounding factor and there are lot of studies about bone loss in celiac patients and their results have wide range of variability because of not excluding age as most important confounding factor, as we write about it in abstract even in mean age up to 78 years old. We believe we need more case control study with exclusion of confounding factors to find out real prevalence of bone loss in celiac patients. However, indeed such systematic reviews can pave the way for future studies in this era. We hope that you find our responses satisfactory.