Author’s response to reviews

Title: Annual Alveolar Bone Loss in Older Adults Taking Oral Bisphosphonate: A Retrospective Cohort Study

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Author’s response to reviews:

August 2, 2019

Dear Professor Ganz,

Our manuscript entitled Annual Alveolar Bone Loss in Older Adults Taking Oral Bisphosphonate: a Case-Control Study” (OHEA-D-19-00400) has now been revised per the recommendations by the Reviewer and resubmitted (uploaded) for publication in BMC Oral Health.

Each of the recommendations by the Reviewers has been addressed and the manuscript has been revised accordingly. Please see the revised manuscript and our Response to the Reviewers. Please note that the changes made in the revised manuscript are identified by yellow highlights. We thank the Reviewers for their thorough reviews that have assisted us greatly in clarifying points of uncertainty thereby resulting in a significantly improved manuscript. We have fully addressed the Reviewers’ recommendations, and we look forward to your review of this revised manuscript.
Best regards,

Zuhair Natto, BDS, MBA, MPH, MS, MSc, DrP
Manuscript Number: OHEA-D-19-00400

Technical Comments:

Editor Comments:

dear authors please revise your paper following the reviewers' indications.

BMC Oral Health operates a policy of open peer review, which means that you will be able to see the names of the reviewers who provided the reports via the online peer review system. We encourage you to also view the reports there, via the action links on the left-hand side of the page, to see the names of the reviewers.

Reviewer reports:

Fabian Cieplik (Reviewer 1): This study investigates the annual alveolar bone loss in a cohort of patients taking oral bisphosphonates (BIS) as compared to a control cohort without BIS over a period of 2 years. Although the topic of this study is interesting in general, there are a few aspects that need revision before this study may be ready for publication.

Introduction:

- In. 55-62: Most of the Ref.s cited here are quite old. Aren't there more recent studies on that topic?

The beginning of this manuscript was talking about the relationship between aging and periodontal disease which has mixed literature since this known. Then, more recent literature was used. We used again mixed literature when we evaluated the relationship between osteoporosis and periodontal disease which is known again.
- In. 70-94: I would expect to add some detailed information about the BIS-related risks like osteonecrosis of the jaw (MRONJ)

Done.

- In. 96: "older adult patients" Please add information on the gender of these patients as most of the studies cited above included post-menopausal women

We have clarified this point in the results section descriptive analysis since we thought it will be strange to add this information in the introduction.

Material & Methods:

- please add information about ethical approval here (although this is also stated later in the Declarations section)

Done

- In. 106/107: "as well as to show at least 2 posterior approximating teeth" Does this mean that most of your analyses are based on data from two teeth (i.e. one inter proximal bone loss) only? Is this really representative for a whole patient?

We have discussion this point as a limitation of the study at the end of the discussion. It is known as partial mouth periodontal examination and is used in the literature.

- The sample size of 26 patients in each group seems to be quite small for a case-control study. Furthermore, I am a bit surprised that there were only 30 patients with medical history of BIS-intake in the electronic health record of the Harvard Dental Center between 2008 and 2015?!

Although we are celebrating 150 years, we are a small school with about 250 students only. In addition, we want bitewings for patients with multiple visits (one year of interval) which ended to very few patients. For this reason, 2 years was OK with about 30 patients with completed medical history. This number dropped severely if we go to 3 years or more.

- In. 135/136: "one trained examiner" Please state initials of this examiner

Done.
Discussion:

- In 200: mentioned instead of "mention"

Done

- Please add much more detailed discussion and careful consideration of potential benefits of BIS in Perio patients as opposed to the risks of MRONJ with BIS. What about the risk of MRONJ with locally administered BIS (e.g. 1% alendronate gel)? Is there any data on that as compared to systemic intake of BIS?

We have added more information and potential benefits about local delivery of 1% alendronate gel page 9 line 217.

- Please add a more detailed conclusion on whether BIS may be worthwhile further investigation as an adjunct in periodontal therapy.

Thank you for this comment. Yes, we added a sentence in the conclusion.

Tables/Figures:

- Table 1: Instead of mean age, I would suggest to state median age as well as 25/75% percentiles. It is not clear to me, why a standard error is given for percentage of females or percentage of mild, moderate or severe periodontitis? This seems not be necessary?! (also applicable to the other tables)

Yes true. It was a mistake and we have removed the females column and SE.

For the mean or median, it will not change anything since it is a match data on age and gender

- Table 4: What do these codes mean?! Why are they stated here? Were these periodontal therapies related to the measured teeth? For example if only teeth 36/37 and 46/47 were measured for alveolar bone loss in a patient, a periodontal surgery with GTR on tooth 16 may be not relevant.
This is Current Dental Terminology (CDT) codes and they are just for insurance claims and to populate an electronic health record. We mentioned these codes because several patients received these treatments since the first included x-ray which can increase/decrease the bone loss. In addition, some of these treatments were wide in definitions and we included which codes we used since we are using electronic health record. Yes, it is in the measured teeth. We have added more clarification in the manuscript.

- Figure 1: it may be better to show this data as a dot plot with one axis stating house income and the other stating periodontitis severity.

We agreed. We did both ways. However, the authors found it will be easier to present it in the current way for visual comparison.

- Figure 2: is this figure really necessary?! Furthermore, it seems implausible to me that the measured values are only at baseline (timepoint "0") and after 2 years (timepoint "2") because (as far as I understood from the materials & methods section, ln. 105) patients were included when they had radiographs with an at least one-year interval. Therefore, there may be several values between baseline and 2 years?

We thought for visual comparison this figure will be necessary because it showed there is increasing in bone loss among bisphosphonate group until become comparable to non bisphosphonate group regarding bone loss.

Yes, this is true. However, we think what will be matter is the long term effect of bisphosphonate which it turned to be almost comparable to non bisphosphonate group regarding bone loss as we can see in the confidence interval.

Rohana de Silva (Reviewer 2): Thank you for submitting this manuscript, however I would like to put you attention to the following shortcomings of your research project and the manuscript.

I feel very superficially you have divided you patients to two groups depending on the age, sex and whether they are taking bisphosphonate or not, without taking the other important factors involved in alveolar bone loss. Your article does not clearly indicate the types of the bisphosphonate drugs, purpose for receiving it (For example; as a part of the treatment for osteoporosis, to reduce bone destruction in a bone invading malignant condition or to reduce bone loss in those who are on long term systemic steroids.) and the duration of time they were on that drug. Please also indicate how many of your patients were on the bisphosphonate treatment during your investigation period.
Thank you for this good and valid point. We are using electronic health records of a dental school which it has several limitations. All patients received oral bisphosphonate (Alendronate) as we mentioned in the manuscript as (BIS). However, duration, dose and purpose were missing. We have added all these points as limitations of this study.

Explain how can you compare the bone levels of BIS and no BIS groups and come into a conclusion after they had different types of periodontal treatment during the investigative period? (In table 4 you haven't clearly mention when these treatment procedures were performed.)

We have mentioned in the conclusion that the group who reported receiving oral bisphosphonates showed no improvement in maintaining alveolar bone level. We have added that further investigation may need to investigate the effect of treatment modalities on bone response. We have justified our results that it could be due to periodontal treatments received. However, nobody know. This is why we have suggested further investigation. We have added that these patients received the treatments after first included x-ray.

The implication of this study, however, may indicate that the route of administration of bisphosphonate play an important role for its effectiveness to be achieved. Emerging evidence of several studies indicate that local delivery of bisphosphonate can help in maintaining periodontal health and alveolar bone level for patients who are more prone to the disease.

This is true. This is why we have added that we need to investigate its role as an adjunct in periodontal therapy.

In table 2 why you need to mention the patients under 57 years of age if your sample only consists of patients aged from 57 to 88 years. Please omit the unnecessary data.

Yes, this true. We have removed the unnecessary data. Thank you

Please add the missing details to the reference 12 and address the spelling and grammatical mistakes in the manuscript.

Done