OPEN PEER REVIEW

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Advantages of "Open Peer Review" process

- More transparency, constructiveness and tactful comments of the peer review process: leads to an increase in the quality of reviews
- More motivations for all involved roles in the review process
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- Prevents reviewers from following their individual agendas and leading to the detection of reviewers' conflicts of interests

You can find out more at:
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Peer Review Report for "Effect of Vitamin D Levels on Bone Remodeling in Healthy Women"

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Review Timeline:

Submit Date: 31 Dec 2019
Revised Date: 26 Mar 2020
Accepted Date: 30 Mar 2020

Revision (0)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Reviewer | Revision (0)

22 Jan 2020

Dear AE,
In this cross-sectional study, association of serum vitamin D with bone markers in 310 indian women have been evaluated.
Methodological issues:
- One of the most important issues in this study is the lack of information about the consumption of supplements containing vitamin D, this can justify some extra-ordinary findings such as a positive correlation of CTX (as a resorptive bone marker) with serum vitamin D level or significant lower serum calcium in vitamin D sufficient group compared to vitamin D deficient group.
Other issues:
- The bulk of the introduction section is related to the effect of vitamin D supplementation on bone markers. Regarding the aim of this study, these references should be replaced with more relevant studies and their controversies
- How were participants selected? The ways of selecting participants are totally unclear in this study.
- The result part is too long due to repeating table data in the text. Only the most important data should be written in this part.

- Detailed repeating results in the discussion should be avoided.

Tables:

- Using a Z score is preferred for premenopausal participants.
- There are too many tables. Tables 1, 2, and 3 can be merged.
- Post-hoc analysis should be performed and written in the footnotes of Table 4&5.

Thanks.

REFEREE: Reviewer | **Revision (0)**

26 Jan 2020

Dear AE,

I read the paper titled “Vitamin D levels affect bone remodeling in healthy women” with great interest. I would like to congratulate the authors for conducting this study. I would also like to thank the editor for giving me the opportunity to review this manuscript.

- The research focused on the effect of vitamin D levels on bone remodeling in healthy women. Although the topic has been widely discussed, this is an interesting study. It could represent a potentially valuable addition to the literature concerning the effect of vitamin D on bone remodeling and BMD.
- The manuscript reports interesting observations, the methodology is properly conducted and the analyses provided are accurate.
- However, there are some aspects that could be considered in order to strengthen this study and there are a few sentences that require rephrasing for clarity.

Abstract:

- Study design has not been mentioned in the title or abstract of the manuscript.

Methods:

- The time and duration of study and periods of recruitment have not been mentioned.
- How to select the participant in the study must be expressed in detail, and how to manage selection bias?
- What is the reason for choosing 25 to 65 years old? Application of osteopenia and osteoporosis for premenopausal group are not correct.
- The method of calculating study size is not mentioned.
- Classification of vitamin D levels in the method and result sections are different.

Results:

- The number of post-menopausal women is less than that of the premenopausal women (less than half) which can make results invalid in sub-groups.
- Very low number of subjects in vitamin D sub-groups in patients with osteoporosis can make the study results invalid.

Discussion:

- Repeating the results in the discussion section is not necessary and it is better to be eliminated.
- It is best to mention the key results of the study at the beginning of the discussion.
- One of the important limitations of the study is how to select participants in the study which can affect external validity.
- Another important limitation of this study is the number of patients in subgroup.
- Conclusion of the study is not mentioned

Thanks.

Farhad Hosseinpanah: Associate Editor | **Revision** (0) 30 Jan 2020

Dear EIC,
Based on the comments of two reviewers, the manuscript cannot be accepted in current format. Major revision is needed. The authors should respond to the comments raised by the reviewers. Moreover, sampling frame should be clearly defined. There is an unexpected finding regarding positive association between CTX and vitamin D, seriously threatening internal validity of the study. This finding needs explanation and discussion.
Thanks.

REFEREE: EIC | **Revision** (0) 1 Feb 2020

Dear Authors,
The manuscript needs major revision before considering for publication in the IJEM.
Thanks.

OPEN PEER REVIEW

Revision (1)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

Response to Reviewer's comments

Reviewer 1

In this cross-sectional study, association of serum vitamin D with bone markers in 310 indian women have been evaluated.

Methodological issues:
-One of the most important issues in this study is lack of information about consumption of supplements containing vitamin D, this can justify some extra-ordinary findings such as positive correlation of CTX (as a resorptive bone marker) with serum vitamin D level or significant lower serum calcium in vitamin D sufficient group compared to vitamin D deficient group.

Response: It is a cross-sectional study, where we have participants recruited on the basis of inclusion and exclusion criteria mentioned in the methodology section. We have not recruited participants taking any drugs or supplements. However this was questionnaire based, hence, recall bias cannot be eliminated and this point was mentioned in the discussion as limitation.

Other issues:
-The bulk of introduction section is related to effect of vitamin D supplementation on bone markers. Regarding the aim of this study, these references should be replaced with more relevant studies and their controversies.

Response: We can introduce few more studies in the introduction section to strengthen it.

-How were participants selected? The ways of selecting participants are totally unclear in this study.

Response: The participants were selected from the vicinity of the study site. Awareness related to osteoporosis and vitamin D deficiency was created and women willing to participate in the study were recruited. ***This study is a part of a broader project trying to explore biomarkers for osteoporosis and shows the preliminary results on 310 participants who were recruited so far.***

- The result part is too long due to repeating table data in the text. Only the most important data should be written in this part.
Detailed repeating results in discussion should be avoided.

Response: These points shall be considered and manuscript is being revised accordingly.

Tables:
Using Z score is preferred for premenopausal participants.

Response: We agree to this point. However, only frequencies were mentioned to maintain the uniformity in the table and no analysis

was done with respect to it.

There are too many tables. Tables 1, 2, and 3 can be merged.
Response: Tables 2 and 3 will be merged in the revised manuscript.

Post-hoc analysis should be performed and written in footnotes of tables 4&5.

Response: Dunn's Post-hoc analysis was done for both the tables and mentioned in the results section.

Reviewer 2

I read the paper titled "Vitamin D levels affect bone remodeling in healthy women" with great interest. I would like to congratulate the authors for conducting this study. I would also like to thank the editor for giving me the opportunity to review this manuscript.

The research focused on the effect of vitamin D levels on bone remodeling in healthy women. Although the topic has been widely discussed, this is an interesting study. It could represent a potentially valuable addition to the literature concerning the effect of vitamin D on bone remodeling and BMD.

The manuscript reports interesting observations, the methodology is properly conducted and the analyses provided are accurate.

However, there are some aspects that could be considered in order to strengthen this study and there are a few sentences that require rephrasing for clarity.

Abstract:

Study design has not been mentioned in the title or abstract of the manuscript.

Response: We will mention the study design in abstract of the revised version

Methods:

The time and duration of study and periods of recruitment have not been mentioned.

Response: The participants were recruited from November 2014-December 2019. The study was carried out for a period of 5 years

How to select the participants in the study must be expressed in detail, and how to manage selection bias?

Response: The participants were selected from the vicinity of the study site. Awareness related to osteoporosis and vitamin D deficiency was created and women willing to participate in the study were recruited based on strict inclusion exclusion criteria.

What is the reason for choosing 25 to 65 years old? Application of osteopenia and osteoporosis for premenopausal group are not correct.

The method of calculating study size is not mentioned.

Response: This study is a part of a broader project trying to explore biomarkers for osteoporosis. The sample size was calculated using the formula

$$N = \frac{t^2 x\ p(1-p)}{m^2}$$

Where N= required sample size

t=confidence level at 95%

p=estimated prevalence of osteoporosis

m= margin of error at 5%

Keeping in view presumed prevalence of osteoporosis (0.33), confidence level 95 % and margin of error 5%, 340 participants were tested. With probable drop-out of about 20%, about 408 participants had to be included in the project. Since the preliminary analysis of 310 participants yielded interesting results, we decided to publish it.

The project requires women between the age group of 18-65 years, however, the 310 recruited participants were all between 25-65 year..

Classification of Vitamin D level in the method and results section are different.

Response: This will be rectified in the revised manuscript

The number of post-menopausal women is less than that of the pre-menopausal women (less than half) which can make results invalid in sub-groups.

Response: The inclusion criterion for the project was apparently healthy women. ***Women on bone compromising drugs, with hepatic, cardiac or renal disorders, metabolic bone disease, hyper-cortisolism, sterility, oligomenorrhea, diabetes, malignancy, as well as pregnant and lactating women were excluded. The recruitment for the project is ongoing and it is difficult to find healthy postmenopausal women as majority of them are excluded on the basis of exclusion criteria.***

Very low number of subjects in vitamin D sub-groups in patients with osteoporosis, can make the study results invalid.

Response: Low number of vitamin D deficient osteoporotic subjects was only in premenopausal group. Table 3 denotes just the frequency and no statistical tests were applied. Actual classification of population was done on the basis of vitamin D levels for analysis.

Discussion:

Repeating the results in the discussion section is not necessary and it is better to be eliminated.

It is best to mention the key results of the study at the beginning of discussion.

One of the important limitations of the study is how to select participants in the study which can affect external validity.

Conclusion of the study is not mentioned

Response: We will consider these points and revise the manuscript accordingly

Another important limitation of this study is the number of patients in subgroup.

Response: We agree and this will be mentioned in the discussion.

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Revision (1)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Reviewer | **Revision** (1) 25 Feb 2020

Dear AE,
The study is reviewed carefully. According to comments and revisions by the author, this manuscript is accepted.
Thanks

Farhad Hosseinpanah: Associate Editor | **Revision** (1) 6 Mar 2020

Dear EIC,
In the revised manuscript the majority of comments given for the different sections have been responded to and accordingly altered. However, there is a major concern regarding an unexpected finding; a positive association between CTX and vitamin D; which needs to be more clarified. As the authors mentioned, most studies reported no or negative association. First of all in the abstract and the results absolute values of "r "should be corrected. it would be + not minus. Moreover, in terms of positive association, there is not any difference between premenopausal and postmenopausal women. Therefore reference number 31 can not justify the issue. Positive association in adolescents also can not be extrapolated to adults. Analytical error? or recent vitamin D supplementation? might explain it.
Thanks.

REFEREE: EIC | **Revision** (1) 6 Mar 2020

Dear Authors,
The manuscript needs another round of revision.
Thanks.

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Revision (2)

Reply to Reviewers

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You can read the authors' responses to the reviewers' comments in the next page.

Response to Associate Editor's Comments

Associate Editor 1:
In the revised manuscript the majority of comments given for the different sections have been responded to and accordingly altered. However, there is a major concern regarding an unexpected finding; positive association between CTX and vitamin D; which needs to be more clarified.As the authors mentioned, most studies reported no or negative association. First of all in the abstract and the results absolute values of "r "should be corrected. it would be + not minus. Moreover, in terms of positive association, there is not any difference between premenopausal and postmenopausal women. Therefore reference number 31 can not justify the issue. Positive association in adolescent also can not extrapolated to adults. Analytical error? or recent vitamin D supplementation? might explain it.

Response: We are glad that the reviewer has accepted the revised manuscript, which was altered according to the suggestions given earlier by the reviewers.

As rightly pointed out by the Associate Editor, the r value is positive and it has been rectified in the abstract part of the manuscript.

To the best of our knowledge, only Tehran study on healthy adolescent (reference 30) showed positive correlation of vitamin D with CTX, so we decided to quote it. However, the findings of that study were not extrapolated to our cohort.

There was no analytical error in terms of the quoting the positive correlation of vitamin D with CTX (reviewer 2 did mention that analyses were accurate). However, the only justification we can provide at the moment is that this finding could be due to recent intake of vitamin D supplement, which were not noted, since they were healthy women and apart of large cohort for the biomarker study as mentioned previously to the reviewers.

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Revision (2)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

Farhad Hosseinpanah: Associate Editor | **Revision** (2) 15 Mar 2020

Dear EIC,
Regarding the importance of this unexpected finding, first of all, mention the problem of extrapolation of adolescence findings to adults. Moreover, as I mentioned before, highlight the lack of difference in r values between pre-and postmenopausal women which is important regarding Ref. 31. Last but not least, refer to recent vitamin D supplementation.
Thanks.

Fereidoun Azizi & Dr. Azita Zadeh-Vakili: EIC | **Revision** (2) 16 Mar 2020

Dear Author,
Your article is reviewed by the reviewers carefully. According to their comments, this document needs minor revision. Please follow their comments as requested.
Thanks.

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Revision (3)

Reply to Reviewers

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You can read the authors' responses to the reviewers' comments in the next page.

Response to Associate Editor's Comments

Associate Editor 1:
Dear Authors

Regarding the importance of this unexpected finding, first of all, mention the problem of extrapolation of adolescence findings to adults. Moreover, as I mentioned before, highlight the lack of difference of r values between pre- and postmenopausal women which is important regarding Ref. 31. Last but not least, refer to recent vitamin D supplementation.

Response: We have justified the association of CTX with vit D in premenopausal women too and added a new reference with respect to it. Hope that will highlight the lack of difference of r values between pre- and postmenopausal women.

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Revision (3)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

Farhad Hosseinpanah: Associate Editor | **Revision** (3) 23 Mar 2020

Dear EIC
Based on the authors' answers to the reviewers' comments, the reviewer(s) have recommended publication.
Kind regards.

Fereidoun Azizi & Dr. Azita Zadeh-Vakili: EIC | **Revision** (3) 25 Mar 2020

Dear Authors,
The revised manuscript needs a minor change to be accepted for publication:
In the section of "Study design", the mode of recruitment of the study population is not clear; how were they called to participate in the study? Please explain about the selection of your study population with more details.
Can these 310 women be representative of an Indian women population? If not, this issue should be added as a study limitation in the paragraph of study limitations.
Thanks.

OPEN PEER REVIEW

Revision (4)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

Response to EIC

In the section of "Study design", the mode of recruitment of the study population is not clear; how were they called to participate in the study? Please explain about the selection of your study population with more details.

Response: ***For recruitment, camps were organized in the community near the study site where awareness related to osteoporosis and vitamin D deficiency was created amongst women. They were told about the study and its relevance and women willing to participate in the study were screened and following the inclusion and exclusion criteria, recruited in the study.***

Can these 310 women be representative of an Indian women population? If not, this issue should be added as a study limitation in the paragraph of study limitations.

Response: The study participants were recruited from Mumbai, Maharashtra and ICMR has recognized the population of this region as representative of Indian population in various studies.

Reference: **POPULATION BASED REFERENCE STANDARDS OF PEAK BONE MINERAL DENSITY OF INDIAN MALES AND FEMALES - AN ICMR MULTI-CENTRE TASK FORCE STUDY POPULATION BASED REFERENCE STANDARDS OF PEAK BONE MINERAL DENSITY OF INDIAN MALES AND FEMALES - AN ICMR MULTI-CENTRE TASK FORCE STUDY**

https://www.icmr.nic.in/sites/default/files/reports/ICMR_Tech_Report_BMDRefStds2010.pdf

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Revision (4)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: EIC | **Revision** (4) 30 Mar 2020

Dear Author,
The document is reviewed carefully by the reviewers. According to their comments and your revisions as requested, this manuscript is accepted.
Thanks.