Author’s response to reviews

Title: Effect of duration of diabetes on bone mineral density : A population study on East Asian males

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Neil Gittoes
Editor-in-Chief
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Dear. Neil Gittoes

We would like to thank you for considering our manuscript entitled “Effect of duration of diabetes on bone mineral density: A population study on East Asian males” for publication in “BMC Endocrine Disorders ”. We would also like to thank the reviewers for the thorough examination of our manuscript and excellent comments which have helped us to improve our manuscript. We hope that you and the reviewers will find the revision satisfactory. We thank the
reviewers for their constructive suggestions and look forward to having our manuscript published in "BMC Endocrine Disorders"

Sincerely yours,

RESPONSES TO Jennie Walsh (Reviewer 1):

Jennie Walsh (Reviewer 1): This is a topical and interesting area. There isn't so much published on the effect of diabetes on bone in South Asian populations so this is a useful addition to the literature.

The study has good numbers of subjects, the data analysis is appropriate and thoughtful, and the paper is reasonably well-written.

The association of type 2 diabetes with higher BMD, but increased fracture risk is well-recognised so the description of higher BMD in T2DM is not novel. However it does need to be presented to put the data on duration of diabetes into context.

The observation of lower femoral neck BMD with greater duration of diabetes is interesting. There have been similar findings in another study, but not in men and women or all ethnicities, so again this study adds useful information.

1. I'm surprised that BMI is not more different between the groups. If I understand the methods correctly, all KHANES participants with complete measurements were included, and participants for this analysis were not selected or matched by BMI. The similar BMI across groups is good for isolating the effect of DM from the effects of obesity, and reduces DXA artefact. But is this typical of the Korean T2DM population? If so, it would be good to explain this for readers in the USA and Europe.
Response:

Thank you for the comment. We agree with the reviewer about that, we have described this in the DISCUSSION section as following (Page 10, line 13-18) and added pertinent references.

“People in Asia develop diabetes at a lower degree of obesity and at younger ages, suffer longer with chronic diabetic complications [16]. And some studies in Japan [17] and Korea [18] have showed that Asian patients with type 2 DM have lower BMI and decreased β-cell function compared with European and American patients. Current study showed that each groups had similar BMI in overweight range not obesity. Therefore a study of relation of type 2 diabetes and osteoporosis in Asian population would be good for isolating the effect of obesity.”

2. It is difficult to justify pursuing the thread about insulin deficiency in longstanding T2DM as the cause of lower BMD when insulin was not different between the diabetes duration groups. Other possible mechanisms should be considered: What about the effect of glucose which was higher in the longer duration group? The existing literature on mechanisms of diabetes action on bone suggests that AGEs and low turnover are important - with a long time of high glucose, could the low turnover result in unfavourable bone balance?

Response:

Thank you for the comment. We agree with the reviewer about that, we have described this in the DISCUSSION section as following (Page 11, line 17 - Page 12, line 1).

“In the present study, insulin levels were similar in prediabetes and diabetes and in two groups with different duration of disease. It was significantly different that fasting glucose levels in prediabetes and diabetes, and HbA1c levels between diabetic men with a disease duration of ≤5 years and those with a disease duration >5 years. High blood glucose induces formation of advanced glycation end-products (AGE), with negative effects on structural proteins such as type I collagen, the main bone matrix protein. AGE may also reduce bone strength by impairing bone formation [27]. Most of the recent studies have confirmed decreased levels of bone turnover
markers in patients with DM [3]. The previous research on mechanisms of type 2 DM showed that action on bone with a long time of high glucose could the low turnover result in unfavorable bone balance.”

3. Why femoral neck only significantly affected site? Degenerative change at the LS obscuring bone loss? Current evidence suggests cortical porosity is an important factor in T2DM bone fragility and might be picked up better at the hip than the spine?

Response:

Thank you for the comment. We agreement with the reviewer about that degenerative change at the LS obscuring bone loss. We have described this in the DISCUSSION section as following (Page 12, line 16-22 ) and added the pertinent references.

“Possible explanations for significant reduction of femoral BMD are existing literature on bone loss and cortical porosity. Pentosidine is the best studied AGEs to date. The pentosidine content of cortical and trabecular bone derived from patients with a femoral neck fracture is higher than those of age-matched controls [3]. These women with prior fractures have significantly lower femoral neck volumetric BMD, a trend towards larger volumetric BMD on quantitative CT and higher serum levels of sclerostin than diabetic women without fractures and nondiabetic controls with fractures(increases of 31.4% and 25.2%, respectively) [31].”

4. The lipid profile results probably aren't relevant to this story and could be removed.

Response:

Thank you for the comment. We agreement with the reviewer about that the lipid profile results aren’t relevant to current study. However, some studies have showed relation of bone mineral density and adiponectin in patients with metabolic syndrome, and association of nonalcoholic
fatty liver disease with low bone mass. We have discussed your suggestion and it is useful to leave lipid profile results

5. Table 1 needs a font/text formatting tidy.

Response:

Thank you for the comment. We have done that in the revised manuscript as suggested.

6. Ref 24 is duplicated as 25

Response:

Thank you for the comment. We have corrected the error.

RESPONSES TO Lee Shepstone, PhD (Reviewer 2):

Lee Shepstone, PhD (Reviewer 2): Overall, this is an interesting paper that has been well written.

1. From the tables (and a lesser extent the text), it would appear that the authors have applied weights to individual observations. Table 1, for example, indicates that 3383 individuals were included in the study but the number 4 370 109 is also included. Could the authors clarify exactly what has been done here? Does the 4 370 109 merely indicate the size of the population represented? The size of the standard errors indicate that the sample size used is 3383 but has some weighting system been used in anyway?
Response:

Thank you for the comment. We agreement with the reviewer about that. The presented N is the size of Korean population estimated using sample weights. The sample weights were constructed for sample participants to represent the Korean population by accounting for the complex survey design, survey non-response and post-stratification. The weights based on the inverse of selection probabilities and inverse of response rates were modified by adjusting them to the sex- and age-specific Korean populations (post-stratification). We have provided detailed description in the revised manuscript METHODS and Table footnote section as following (Page 4 lines 16-20 and Page 7 lines 21-23, Page 21-25 table footnote) and added the pertinent reference.

“. A complex, stratified, multistage probability sampling design was used, and sampling units were selected based on geographical area, age and sex. Each sampled participant is assigned a numerical sample weight that measures the number of people in the population represented by that specific participant. A complex sampling design and sample weights facilitate the production of nationally representative data [12].”

“Statistical analyses were carried out using STATA 14.0 (StataCorp, College Station, TX, USA) with the SVY commands to account for the complex sampling design and include sample weight, which enabled the results to represent the entire national male population who were older than 50 years [12].”

“N = the size of Korean population estimated using sample weights”

2. Page 3 line 37 "...so determining the BMD is the best approach." This needs expanding. From the sentences above this, it appears clear that BMD is not necessarily a good predictor of fracture risk in type 2 DM patients. The authors have chosen to assess BMD rather than bone microstructure as the latter is not possible. The implications need some discussion here in the Background and perhaps more so in the Discussion.
Response:

Thank you for the comment. We agree with the reviewer's comment that we have done that in the revised manuscript BACKGROUND (Page 3 line 15-17) and DISCUSSION (Page 11 line 3-7) section as suggested.

“Clinically, assessing the bone microstructure of type 2 DM patients is difficult because CT or MRI should be used [3]. Therefore determining the BMD is the best approach for now.”

“Bone fragility result from decreased BMD and alterations in bone microstructure [3]. Assessing the macrogeometry of cortical bone and the microarchitecture of trabecular bone is difficult due to using quantitative CT or MRI. In clinical setting, Gold Standard of bone strength measurement is DXA and BMD remains a significant predictor of fracture risk in Type 2 DM, that is, independent of trabecular bone score and diabetes mellitus itself [26].”

3. A large number of individuals were excluded due to missing BMD values. Could the authors comment on this? Is there any reason why those missing BMD values would be different from those with BMD values? Is there a possible bias here?

Response:

Thank you for the comment. We agreement with the reviewer about that. We have corrected the error (2479 → 2489) and Figure 1. We have provided more detailed description in the METHODS section as following (Page 5 lines 2-4) and Figure 1.

“In July 2008, the whole-body dual-energy x-ray absorptiometry (DXA) survey was newly introduced and tested until May 2011. People who were tested before July 2008 and after May 2011 have not received the DXA.” This is only the number of exceptions caused by the date of the test the start and the end, and is not relevant to a selection bias.

“Missing BMD (n = 1862), Missing fasting glucose data (n = 209)”
Some more minor points:

1. Page 3 lines 49 - 53. "Generally, men have worse smoking and..." A reference may be useful if possible.

Response:

Thank you for the comment. We agree with the reviewer about that. The results of recent Korean health behavior report showed that males have more dangerous lifestyles than females, unlike the results of the US. At a general level, male participants are more likely to take risks than female participants. We added the pertinent reference (Page 3, line 22-24).

“Generally, men have worse smoking and alcohol drinking habits and higher risk of fall than women [8], which may contribute to bone health deterioration.”

2. Page 3 line 54. "...men are approximately 70% less frequently screened for ..." Do the authors mean 'less frequently' or 'less likely'?

Response:

Thank you for the comment. The reviewer raises an interesting concern. We mean ‘less frequently’. Reference article (Alswat K, Adler SM (2012) Gender differences in osteoporosis screening: retrospective analysis. Archives of osteoporosis 7:311-313) showed that osteoporosis screening rates performing DXA have been 18.4% in men and 60% in women.

3. Page 4 line 40. "...and sampling unit were selected..." should be "...and sampling units..."

Response:
Thank you for the comment. We have corrected the error (Page 4 line 17).

“sampling units were selected based on geographical area, age and sex.

4. Page 6 line 29. A reference for the Friedewald equation may be useful.

Response:

We agree with the reviewer about that. We have added the Friedwald equation and the pertinent reference (Page 6 line 13-15).

“The direct measurement of low-density lipoprotein (LDL) cholesterol was limited, and it was mainly calculated using the Friedewald equation (i.e., LDL cholesterol = total cholesterol – HDL cholesterol – triglyceride/5) [13].”

5. Page 8 and Table 2. Presumably the authors have applied the classic Bonferroni correction, simply dividing the initial significance level by 3 (the number of between group comparisons)? This would imply that, when comparing groups, a p-value of 0.0167 would be taken as statistically significant. This seems at odds with the value in table 2 footnote - is the latter a typo?

Response:

We agree with the reviewer about that. We applied the classic Bonferroni correction, simply dividing the initial significance level by 3. We have corrected the error in table 2 footnote.

“* P<0.0167 compared to 3 groups by Bonferroni’s correction.”
6. Page 11 line 50. "Hip fracture is the most risky osteoporotic fracture..." This needs rewording. Most serious fracture, perhaps?

Response:
we agree with the reviewer's comment. We have replaced “risky” words to “serious” in the revised manuscript (Page 13 line 1).

“Hip fracture is the most serious osteoporotic fracture,..”

7. Page 12 line 13 - 16. "This study is the first to indicate decreased femoral neck BMD in diabetic patients..." Surely this is exactly what it didn't do? The reverse is true.

Response:
Thank you for the comment. There is some reason in what the reviewer pointed out. This study pointed out the association of disease duration and BMD. We have corrected the sentence in the revised manuscript. (Page 13 line 10-12)

“This study is the first to indicate decreased femoral neck BMD in long-time diabetic patients in Asia, which is consistent with the findings of previous studies. Current study demonstrated decreased BMD by DXA with duration of type 2 DM different from the earlier studies.”

8. Page 12 lines 31-35 "Moreover, femoral neck BMD declined ..." This sentence is very unclear and ambiguous in meaning. Could the authors please clarify.

Response:
We agree with the reviewer about that. The point has been discussed. This study showed that participants with a duration of more than 5 years of type 2 diabetes had a significantly lower femoral neck bone mineral density. Type 2 DM is a disease with a long duration of disease and has recently increased in younger generations. Therefore, the duration of the five-year disease is relatively short. We have corrected the sentence in the revised manuscript as suggested. (Page 13 line 19-21).

“Moreover, femoral neck BMD declined in participants with type 2 DM relatively short disease durations, so caution is needed when interpreting the results.”

Tables: The summary of continuous variables as means and standard errors would be more useful as means and standard deviations.

9. Table 1: There is a p-value missing from the 6th line (i.e. comparing proportions in low income).

Response:

Thank you for the comment. We have added the p-value.

“0.003”