

Many thanks for the precious suggestions of the reviewers to our manuscript with the title of " Association between body mass index and lumbar spine volumetric bone mineral density in diabetic and non-diabetic patients: a cross-sectional study" (Manuscript ID 98085). We made revisions in the places with light in the revised paper according to the reviewers' suggestions.

Peer-review report(s).

Authors must resolve all issues in the manuscript that are raised in the peer-review report(s) and provide point-by-point responses to each of the issues raised in the peer-review report(s):

Reviewer #1:

Scientific Quality: Grade D (Fair)

Language Quality: Grade C (A great deal of language polishing)

Conclusion: Major revision

Specific Comments to Authors:

Dear Authors, here are my comments related to the submitted version of the manuscript titled: " Association between BMI and lumbar spine volumetric bone mineral density in patients with and without diabetes" (manuscript ID 98085): Overview and general recommendation: I find the topic/scope of the manuscript important and clinically relevant. Also, it is my impression that the topic could be very interesting to the readers of the Journal. On the other hand, the main concerns I have about the submitted version of the article are related to the overstatements in the article and the very broad interpretation of the study results in comparison to current literature. From my point of view, vBMD would be in a very liberating understanding of the parameters of the bone micro-architecture. Further, there are a few downsides to the chosen methodology and manuscript that are not stated in the manuscript (selection bias, effects of different skeletal sites, effects of different stages of obesity, effects of other concomitant diseases, therapy regimens, and lifestyle factors). Moreover, when discussing BMI relation with BMD, it is crucial to distinguish differences in patients with obesity and with overweight. Based on these comments, I could not recommend this version of the manuscript for publication in such a reputable Journal. However, since I recognize the

potential that this manuscript has, I recommend that a major revision is warranted (a detailed explanation can be found below).

Major comments:

- Title: Please be more specific on the type of diabetes. Further maybe the study population and/or type of study should be included in the title.

Response: Thank you for the very important suggestions.

This was a subgroup study of Pinggu Metabolic Disease Study (PMDS), which was carried out in the Pinggu district of Beijing. Types of diabetes were not identified in the Pinggu study.

We changed the title as follows: **“Association between body mass index and lumbar spine volumetric bone mineral density in diabetic and non-diabetic patients: a cross-sectional study”**.

- Abstract: From my point of view, the content of the abstract does not highlight the importance of the topic to the field, nor does it distinguish the novelty, significance, and impact of the results.

Response: Thank you for the very important suggestions.

We rephrased the abstract as follows:

BACKGROUND: The association between body mass index (BMI) and bone mineral density (BMD) has shown inconsistent results, varying by sex and skeletal site. Despite normal or elevated bone mass, individuals with type 2 diabetes have an increased risk of hip and vertebral fractures.

AIM: To assess lumbar spine trabecular volumetric BMD (vBMD) across different BMI categories in individuals with and without diabetes.

METHODS: This cross-sectional study included 966 men over 50 years old and 1001 postmenopausal women from the Pinggu Metabolic Disease Study. Lumbar spine vBMD of lumbar vertebrae 2 through 4 was measured using quantitative computed tomography (QCT). Total adipose tissue (TAT), subcutaneous adipose tissue (SAT), visceral adipose tissue (VAT), and lumbar skeletal muscle area (SMA) were also quantified.

RESULTS: In men with obesity ($P = 0.038$) and overweight ($P = 0.032$), vBMD was significantly higher in the diabetes group compared to non-diabetic men. After adjusting for age and sex, no significant saturation effect between BMI and BMD was found in participants with diabetes or in women without diabetes. However, a BMI threshold of 22.33 kg/m² indicated a saturation point for vBMD in non-diabetic men. Independent predictors of vBMD in men included age ($r=-0.387$, $P<0.001$), BMI ($r=0.130$, $P=0.004$), and VAT ($r=-0.145$, $P=0.001$). For women, significant predictors were age ($r=-0.594$, $P<0.001$), BMI ($r=0.157$, $P=0.004$), VAT ($r=-0.112$, $P=0.001$), and SAT ($r=-0.068$, $P=0.035$).

CONCLUSION: The relationship between BMI and trabecular vBMD differs in individuals with and without diabetes. Overweight and obese men with diabetes exhibited higher vBMD.

- Abstract (line 2): Why did authors focus on bone micro-architecture? There are conflicting data about bone mass, and bone micro-architecture was not investigated in the present study. Please rephrase to avoid misleading statements.

Response: Thank you for the very important suggestions.

We rephrased the sentences in the manuscript to avoid misleading statements.

- Abstract (line 8): Please rephrase to make it easier to understand (L2-L4 level).

Response: Thank you for the very important suggestions.

We rephrased the sentence as follows to avoid misleading statements: “Lumbar spine vBMD of lumbar vertebrae 2 through 4 was measured using quantitative computed tomography (QCT).”

- Introduction (page 4, lines 12-14): This is just one point of view that is highly dependent on the assessed skeletal site (so please indicate the skeletal site in your sentence). Also, some recent studies report that increased BMI is associated with better quality of femoral micro-architecture, while mechanical properties were unaffected in individuals with higher BMI (overweight). This should also be included in the manuscript and discussed adequately to provide a whole story for the readers. It should

also distinguish the difference between individuals with obesity and those who are overweight.

Response: Thank you for the very important suggestions.

We rephrased the sentence as follows to avoid misleading statements: “Higher trunk fat mass assessed by dual-energy X-ray absorptiometry (DXA) and visceral adipose tissue (VAT) assessed by quantitative computed tomography (QCT) correlated with lower trabecular bone volume, reduced stiffness, decreased bone formation, and increased cortical porosity, as revealed by micro-CT of transiliac biopsies[6].”

Some recent studies report that increased BMI is associated with better quality of femoral micro-architecture, while mechanical properties were unaffected in individuals with overweight. We added and discussed in our manuscript as follows.

“Recent findings suggested that overweight men show improved trabecular and cortical microarchitecture in the inferomedial and superolateral regions of the femoral neck compared to controls, indicating better resistance to femoral fractures[33].

- Introduction (page 5, line 1): Please be more specific; which skeletal site is referred to here? Also, this should be a general approach since osteoporosis is not homogeneously affecting all skeletal sites, and we should always have this in mind since it refers to the site-specific fracture risk increase in individuals with obesity.

Response: Thank you for the very important suggestions.

We rephrased the sentence as follows to avoid misleading statements:

“Most studies examining the impact of BMI on bone focus on lumbar spine and hip areal BMD[8].”

We totally agree with your opinion that the fracture risk in obese adults is not the same for all skeletal sites, and we added this in our manuscript.

“Fracture risk also varies by skeletal site in individuals with obesity or overweight. The risk of fractures at non-vertebral sites, such as the proximal humerus, upper leg, and ankle, is higher compared to those with normal weight[19], while the risk at vertebral sites and the proximal femur is lower[20].”

- Methodology (page 6, line 6): Where are these questionnaires described (please add a reference or describe the content)? It should also be stated where the questionnaires were validated, and what was the validation process.

Response: Thank you for the very important suggestions.

We added a reference [Hu P, Li Y, Zhou X, Zhang X, Zhang F, Ji L. Association between physical activity and abnormal glucose metabolism-A population-based cross-sectional study in China. J Diabetes Complications. 2018 Aug;32(8):746-752. doi: 10.1016/j.jdiacomp.2018.05.021. Epub 2018 Jun 1. PMID: 30017433.] which described these questionnaires.

The Long-form International Physical Activity Questionnaire (IPAQ) and a 104-item food frequency questionnaire were completed in a face-to-face interview. Details about the intensity, duration (min/day), and frequency (days/week) of PA undertaken within each of the four domains (work, active transportation, domestic and garden, and leisure-time) were recorded. The domain-specific intensity was quantified in the form of metabolic equivalents of task (METs). The PAEE (MET-min/week) of each domain was calculated and summed to give a total PAEE. The ratios of the PAEE of the work (Rwork), active transportation (Rtransportation), domestic and garden (Rdomestic), and leisure-time (Rleisure) domains to total PAEE were calculated. Sedentary time and sleeping time per day were also recorded. The intake frequency of red meat was obtained by adding the intake frequencies of pork, beef, and lamb.

- Methodology (page 7, line 5): Please add references. Also, it is a general rule that whenever authors refer to data that are not direct results from this study, references should be included to back up these claims.

Response: Thank you for the very important suggestions.

We added a reference.

- Statistical analysis (page 7, line 21): Is study power calculation available? This should be clearly stated in the manuscript.

Response: Thank you for the very important suggestions.

As a cross-sectional study to assess the association between BMI and bone mineral density, we did not calculate study power in this study.

- Discussion (page 12, lines 10-11): From my point of view, vBMD would be a very liberating way to understand the parameters of the bone micro-architecture. This is more of an illustration of bone mass, so I would strongly suggest revising the whole manuscript to avoid overstatements and misunderstandings.

Response: Thank you for the very important suggestions.

We agreed with your opinion that BMI mainly reflected bone mass, and we revised the whole manuscript to avoid overstatements and misunderstandings.

- Discussion (page 14, limitation section): There are a bit more limitations that should be addressed. What about selection bias? Not taking into account the effects of different skeletal sites? Not considering different stages of obesity (class I, class II and class III) and not distinguishing overweight and obesity-associated effects? Did individuals have metabolic-associated fatty liver disease (MAFLD) and could it affect the results? What about variety in smoking, drinking and lifestyle factors (physical activity levels)? What about the differences in the therapy used for treating diabetes? These are all points that are worth discussing.

Response: Thank you for the very important suggestions.

There are some limitations that we addressed and discussed in this manuscript.

Second, although bone quality encompasses bone mass, microarchitecture, and tissue material properties, we focused solely on lumbar spine trabecular vBMD. This limitation restricts our ability to assess how BMI impacts other skeletal sites, highlighting the need for future studies to explore a wider array of bone microarchitecture parameters. Third, the varying stages of obesity (Class I, Class II, and Class III) may differently affect bone mass. However, since only 24 participants in our study had a BMI greater than 35 kg/m², we could not adequately evaluate the influence of these stages on bone mass. Lastly, factors such as metabolic-associated fatty liver disease, smoking, alcohol consumption, lifestyle choices, and hypoglycemic medications may also affect bone mass. Unfortunately, we did not consider these confounding variables in our analysis of vBMD.

We assessed the overweight and obesity -associated effects on vBMD.

We evaluated the influence of BMI on vBMD by classifying participants into three categories: normal weight, overweight, and obese. Analysis revealed no significant differences in vBMD among these groups when stratified by sex and glucose metabolism (Figure 3A).

- Whole manuscript: I recommend using "people-first language," so please consistently correct the term “obese patients” into "patients with obesity".

Response: Thank you for the very important suggestions.

We correct the term “obese patients” into "patients with obesity".

Minor comments:

- Language editing, correcting typos, and consistent formatting are warranted to improve the manuscript's readability (more details in the attached document).

Response: Thank you for the very important suggestions.

We improved the manuscript's readability by language editing, correcting types.

- Please always indicate the type of diabetes and the skeletal site analyzed.

Response: Thank you for the very important suggestions.

We indicated the skeletal site analyzed.

- Please include references whenever not stating the direct results of the present manuscript (more details in the attached document).

Response: Thank you for the very important suggestions.

We included references whenever not stating the direct results of the present manuscript.

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade C (A great deal of language polishing)

Conclusion: Minor revision

Specific Comments to Authors:

I think that you have a good paper. But you can improve this one. Look, some examples of the good references for this theme: A-K. Picke, G. Campbell, N. Napoli, L. C. Hofbauer, and M. Rauner. Update on the impact of type 2 diabetes mellitus on bone metabolism and material properties. *Endocr Connect*. 2019 Mar; 8(3): R55–R70. I. M. Araújo, M. L. M. Moreira, F. J. A.de Paula. Diabetes and bone. *Arch Endocrinol Metab*. 2022;66/5.

Response: Thank you for the very important suggestions.

We carefully read these references and added in the manuscript.

Page 4, line 8: Traditionally, obesity is considered as a protective factor for fractures (??? References?).

Response: Thank you for the very important suggestions.

We added reference to support this sentence [Khosla S., Atkinson E.J., Riggs B.L., Melton L.J. Relationship between body composition and bone mass in women. *J. Bone Miner. Res.* 1996;11:857–863.].

Page 6, line 8-: you wrote: All participants received standardized questionnaires as described previously. Heights were measured to the nearest 0.1 cm without shoes. Weights were measured to the nearest 0.1 kg with wearing light clothing. BMI was calculated as weight (kg) divided by height (m²) (this is better: weight (kg)/[height (m)]²).

Response: Thank you for the very important suggestions.

We rephrased the sentence as follows: “The BMI was calculated using the formula: weight (kg)/[height (m)]².”

Page 9, line 13. The prevalence of osteoporosis was 4.0% at age 50 to 55 years and 36.6% at age 70+ years in men.ii (delete.)

Response: Thank you for the very important suggestions.

We are sorry for this mistake.

Page 11, line 15: The associations between BMI and bone microarchitecture were complex. Some studies found favorable bone microarchitecture parameters in individuals with obesity. References? Is this [13]?

Response: Thank you for the very important suggestions.

References 16 to 20 could support this sentence.

Page 14, line 5, you wrote: Postmenopausal women and men over 50 years were at high risk of fractures (by which factors identified?). It was import to keep the balance between BMI and bone mass. At the first reference. What do think to use et al?! 1. Wang L, Yu W, Yin X, Cui L, Tang S, Jiang N, Cui L, Zhao N, Lin Q, Chen L, Lin H, Jin X, Dong Z, Ren Z, Hou Z, Zhang Y, Zhong J, Cai S, Liu Y, Meng R, Deng Y, Ding X, Ma J, Xie Z, Shen L, Wu W, Zhang M, Ying Q, Zeng Y, Dong J, Cummings SR, Li Z, Xia

W. Prevalence of Osteoporosis and Fracture in China: The China Osteoporosis Prevalence Study. JAMA Netw Open. 2021 Aug 2;4(8):e2121106. doi: 10.1001/jamanetworkopen.2021.21106. PMID: 34398202; PMCID: PMC8369359.

Response: Thank you for the very important suggestions.

We rephrased the sentence as follows: “Postmenopausal women and men over 50 are at a heightened risk of fractures with increasing age[1]. Furthermore, the incidence of clinical fractures in the past five years is significantly higher among individuals with obesity and overweight[1]. Therefore, it is essential to balance BMI and bone mass in this population.”

Once again, thank you very much for your very valuable comments and suggestions. If you have any question, please feel free to contact us.

Best regard,

Fang Lv MD and Linong Ji



**Baishideng
Publishing
Group**

7041 Koll Center Parkway, Suite
160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: office@baishideng.com
https://www.wjgnet.com

Round 2

Dear Authors, thank you for addressing my previous comments. I have no further suggestions to significantly improve scientific merit of the manuscript. Kind regards

Thank you very much for your very valuable comments. If you have any questions, please feel free to contact us.

Best regards,

Fang Lv MD and Linong Ji



**Baishideng
Publishing
Group**

7041 Koll Center Parkway, Suite
160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: office@baishideng.com
<https://www.wjgnet.com>

JOURNAL EDITORIAL BOARD COMMENTS TO AUTHORS

The manuscript should be reassessed by the original reviewers

Thank you very much for your very valuable comments. It has been re-reviewed by the original reviewers.



**Baishideng
Publishing
Group**

7041 Koll Center Parkway, Suite
160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: office@baishideng.com
<https://www.wjgnet.com>

JOURNAL EDITORIAL BOARD'S REVIEW REPORT

JOURNAL EDITORIAL BOARD COMMENTS TO AUTHORS

It is an interesting manuscript. Authors succeed to present their data in a clear way adding information to the existing literature. Therefore, I have no corrections to do and the manuscript can be published unaltered.

Thank you very much for your very valuable comments.