

## PEER-REVIEW REPORT

**Name of journal:** *World Journal of Diabetes*

**Manuscript NO:** 75795

**Title:** Factors associated with trabecular bone score in postmenopausal women with type 2 diabetes and normal bone mineral density

**Provenance and peer review:** Invited Manuscript; Externally peer reviewed

**Peer-review model:** Single blind

**Reviewer's code:** 00659462

**Position:** Peer Reviewer

**Academic degree:** MD

**Professional title:** Doctor

**Reviewer's Country/Territory:** Taiwan

**Author's Country/Territory:** Russia

**Manuscript submission date:** 2022-02-15

**Reviewer chosen by:** AI Technique

**Reviewer accepted review:** 2022-02-16 00:28

**Reviewer performed review:** 2022-02-22 02:15

**Review time:** 6 Days and 1 Hour

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input checked="" type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

<b>Peer-reviewer statements</b>	Peer-Review: [ <input checked="" type="checkbox"/> ] Anonymous [ <input type="checkbox"/> ] Onymous Conflicts-of-Interest: [ <input type="checkbox"/> ] Yes [ <input checked="" type="checkbox"/> ] No
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## SPECIFIC COMMENTS TO AUTHORS

The manuscript reported the findings from a cross-sectional study exploring the independent factors associated with lower trabecular bone score in postmenopausal women with type 2 diabetes and normal bone mineral density. A main issues of the manuscript is the presentation of the results. As multiple linear regression, logistics regression, and ROC analysis were used, different sets of results were obtained. The authors need to focus, with explanation, which is the main finding of the study. 1.

Title: As the study design is cross-sectional and therefore not able to establish causality, the authors should consider changing the word “affecting” to “associated with”. i.e., Factors Associated with Trabecular Bone Score in Postmenopausal Women with Type 2 Diabetes and Normal Bone Mineral Density 2. Abstract, Methods: The words “POC curves” should be “ROC curves”. 3. Abstract, Results: Numerical results, such as odds ratio and p values, should be provided. 4. Abstract, Conclusion: The conclusion should not merely a repeat of the sentences in the Results section. The authors may want to use what they have indicated in the Core tip section. 5. Methods: As a longer duration of type 2 diabetes is generally associated with increased fracture risk, is it possible to include and adjust for the potentially confounding effect of duration of type 2 diabetes? 6. Methods: Were the chronic diseases listed in the exclusion criteria ascertained from diagnosis on the medical record of eligible participants? For example, for the criteria “any kind of malignancy”, is there a specific period or just “ever diagnosed with any kind of malignancy”? 7. Statistical Analysis (page 8): “Statistics 13.0” should be indicated as “Dell Statistica 13.0 (Dell Software, Aliso Viejo, CA, USA)” 8. Statistical Analysis (page 8): More details should be provided for the sample size calculation,

including the choice of effect size. 9. Statistical Analysis (page 8): IBM SPSS should be cited as “IBM SPSS Statistics for Windows, Version 26.0 (Armonk, NY: IBM Corp.)”. 10. Results: The description of the variables in Table 1, 2, and 3 should include p values (if significant). 11. Results: The description of the regression models should include p values and odds ratios, as appropriate. 12. Results: The authors should consider adding a new table to show the results of the multivariate stepwise regression analysis. Only variables that were significantly associated with a decreased TBS should be retained in the final model and shown in the table. 13. Results: Please explain why the multiple logistic regression analysis was not performed with a variable selection procedure, such as backward elimination. 14. Discussion: TBS was analyzed as both a continuous and binary variable using linear regression and logistic regression, respectively. In the Discussion and conclusion, the authors mixed the findings from both analyses as if they were from a single regression analysis. The two results should be explained separately because they are based on different outcome. The authors should explain the advantage and limitation of treating TBS as a continuous and binary variable. For example, the choice of cut-off for TBS value was chosen according to the results of a meta-analysis. However, the 95% CI for it was 1.21–1.42. A different set of significant variables might emerged with a slight change in the cut-off value. 15. Discussion: “HU Moon et al. have shown that TBS increase as visceral fat mass decrease in men and women with T2D [24]” should be “Moon et al. have shown that ...” 16. Conclusion: It is mentioned that “older age, greater height and lower body weight, as well as central adiposity” were the significant predictors. However, only BMI was identified as the risk factors of decreased TBS based on ROC analysis. It is not clear why lower body weight was mentioned. 17. Table 1, 2 & 3: Please add a new column showing the exact p values, regardless whether it is significant, for all variables. 18. Table 1, 2 & 3: The footnote “TBS <1.31, group of individuals with TBS <1.31” should be “TBS 1.31, group



**Baishideng  
Publishing  
Group**

7041 Koll Center Parkway, Suite  
160, Pleasanton, CA 94566, USA  
**Telephone:** +1-925-399-1568  
**E-mail:** [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)  
**https://**[www.wjgnet.com](http://www.wjgnet.com)

of individuals with TBS 1.31''

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**Reviewer's code:** 05420967

**Position:** Peer Reviewer

**Academic degree:** FACE, MD

**Professional title:** Doctor

**Reviewer's Country/Territory:** India

**Author's Country/Territory:** Russia

**Manuscript submission date:** 2022-02-15

**Reviewer chosen by:** AI Technique

**Reviewer accepted review:** 2022-02-16 03:47

**Reviewer performed review:** 2022-02-26 04:42

**Review time:** 10 Days

<b>Scientific quality</b>	<input checked="" type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous
	Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

## SPECIFIC COMMENTS TO AUTHORS

The study by Fazullina et al aims to analyse the factors affecting trabecular bone score in postmenopausal women with type 2 diabetes and normal BMD. The title, abstract, keywords, methodology, results, statistics and ethical issues are appropriate. The background of the study needs further elaboration including a brief mention about pathophysiology. The meta-analysis by Ho-Pham (10.1007/s00198-019-05053-z) assessed the association between trabecular bone score and type 2 diabetes. A comparison of the study with previous ones will be prudent and a mention of whether any unique aspects are being addressed in the current research can be considered. Some specific comments related to the manuscript are listed below.

1. Introduction section - "Recent data from the Continuous National Health and Nutrition Examination Survey (NHANES) indicate an increasing prevalence of osteoporosis and osteopenia in the US among T2D patients and non-diabetic subjects aged 40 years and older". - Please clarify. Did the data show increase in osteoporosis trend among non-diabetic subjects above 40 years.
2. Introduction section - "In addition, the TBS decrease in subjects with pre-diabetes was demonstrated." Reframe and elaborate.
3. Methodology section - The cut off for TBS was taken as 1.31 The more widely used cut offs are as follows TBS > 1.350 is considered to be normal; TBS between 1.200 and 1.350 is considered to be consistent with partially degraded microarchitecture; and TBS <1.200 defines degraded microarchitecture Silva BC, Leslie WD, Resch H, Lamy O, Lesnyak O, Binkley N, McCloskey EV, Kanis JA, Bilezikian JP. Trabecular bone score: a noninvasive analytical method based upon the DXA image. Journal of Bone and Mineral Research. 2014 Mar;29(3):518-30. Please clarify in the discuss section.
4. Methodology section - Was country specific FRAX calculator

used? 5. Methodology section - The BMI ranged from 19.1 to 50.2 kg/m<sup>2</sup> (median 33.6 kg/m<sup>2</sup>). Increasing soft-tissue thickness can artifactually decrease TBS values due to degradation in DXA image quality. The manufacturers recommend including patients in the BMI range of 15-37 kg/m<sup>2</sup>. Could this be a potential confounder at extremes of BMI >37 kg/m<sup>2</sup>? Does the TBS iNsight software (version 3.0.2.0, GE, USA) correct for extremes of BMI? 6. Methodology section - Six women with TBS >1.31 and 14 women with TBS <1.31 had at least one fracture in their medical history ( $\chi^2=5.64$ ,  $p=0.02$ ). In these groups, low-energy fractures were documented in 2 and 9 women respectively. Were the fractures documented by X-Ray? At what sites were these fractures found? Were lumbar vertebrae with fractures excluded from TBS measurement? 7. Methodology section - Were patients on pioglitazone/rosiglitazone excluded from the analysis? 8. Results - Page 10 - In a model of multivariate stepwise regression .. correct grammar 9. Discussion - HBA1C was not identified as a risk factor for low TBS scores which is in contrast to the established fact that hyperglycemia adversely affects bone health. What could be the possible explanation?

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**Peer-review model:** Single blind

**Reviewer's code:** 05489430

**Position:** Peer Reviewer

**Academic degree:** MD

**Professional title:** Doctor

**Reviewer's Country/Territory:** Australia

**Author's Country/Territory:** Russia

**Manuscript submission date:** 2022-02-15

**Reviewer chosen by:** AI Technique

**Reviewer accepted review:** 2022-02-21 02:11

**Reviewer performed review:** 2022-03-06 03:15

**Review time:** 13 Days and 1 Hour

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
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## SPECIFIC COMMENTS TO AUTHORS

This is a useful observational study examining factors affecting TBS in women with type 2 diabetes. Osteoporosis and type 2 diabetes are important global health concerns, and with an increasing incidence worldwide, studies in this area are crucial. Overall the study is well-written. I have several comments to the authors, listed below.

**Methods** 1. The authors state a power calculation was done, however the minimum sample size determined using the power calculation is not stated.

**Results:** 1. Paragraph 4, please include the types of fractures. It would be useful to add fractures into Table 1. 2. It would be useful to include a table for the results of the stepwise multivariate linear regression analysis, as well as the logistic regression analysis. 3. In the model of multivariate stepwise regression analysis, the authors state that age, age since menopause, gynoid fat mass and eGFR were significant predictors of TBS (results paragraph 7). However, the ROC analysis included height, BMI and the android / gynoid fat mass ratio. What was the reasoning for choosing these parameters for ROC analysis, when they were not found to be significantly associated with TBS in multivariate stepwise regression analysis? 4. Regarding logistic regression analysis, were all factors included in the initial stepwise logistic regression analysis, or only those listed in Table 5? If all factors were included, then these should be included in Table 5 (either in the footnotes, or in the table itself). If not, what is the reasoning for including only certain factors in the logistic regression analysis?

**Discussion** 1. First paragraph, the authors state that 'older age, height, lower BMI and gynoid fat mass, higher android fat mass and greater android / gynoid fat mass ratio' contribute to TBS decrease. However, when adjusted by multivariate linear regression, only age, age since

menopause, gynoid fat mass and eGFR were associated with TBS. Different factors were found in logistic regression analysis. Given adjusted analyses were done, it is inaccurate to state as a summary the univariate analysis results, as these are likely to be confounded by other factors. 2. Paragraph 3, the authors state 'We identified older age and younger age at menopause as factors associated with lower TBS values, although we were unable to establish cut-off points for these parameters'. Did the authors attempt to determine a cut-off value, if so why could a cut-off not be established? 3. Paragraph 5, authors state 'At the same time, it is believed that vitamin D deficiency can be a causative factor for insulin resistance and associated disorders.' The data linking vitamin D deficiency to insulin resistance is still inconclusive and causation has not been established. I think the authors should include comments regarding the uncertainty here, or else leave this line out. 4. Paragraph 6, the authors state that 'we were unable to identify HbA1c as a risk factor for a decrease TBS, we cannot exclude the role of hyperglycemia in the deterioration of bone microarchitecture'. Can the authors include some comments about why this might be? For example, could the association be U-shaped, might glycaemic variability rather than HbA1c be associated with bone? A number of studies have been published on this issue, and would be important to include here. 5. Paragraph 7, authors could reference studies using TBS adjusted FRAX in diabetes, as it appears that the adjusted FRAX still under-estimates fractures in these patients (Eg article by Leslie, 2018). 6. Limitations: The obvious major limitation of this study is the observational nature, and single centre site. The authors state theirs is the first study investigating risk factors for impaired bone microarchitecture in post-menopausal women with type 2 diabetes and normal bone mineral density. I think it is important to mention 'microarchitecture by TBS' here (see point below). 7. Throughout the paper, no mention is made of HRpQCT. HRpQCT is considered the gold standard for non-invasive assessment of bone microarchitecture. While TBS is more available and less expensive, I

think it is important for authors to acknowledge this technology. Studies have been done examining HRpQCT in diabetes. Conclusion: 1. Again, authors have included factors not significant on multivariate analysis in the conclusions.