Dear Prof Massimiliano Leigheb,
Editor-in-Chief,
World Journal of Orthopedics Date: 15 August 2023

Manuscript ID: 86756
Low weight related to low bone mass in elderly patients with fractures: a case-control study

Dear Prof. Massimiliano Leigheb,

First of all, we would like to thank you and all the reviewers for thoughtful comments and your time for reviewing our manuscript.

We have currently improved the manuscript by addressing all of reviewers' and editors' comments and indicated how their suggestions have been incorporated in the revised manuscript when it is appropriate. A point-by-point response to comments is attached below, and the changes to this revision are uploaded in supplementary files.

We believe the revised version of the manuscript represents a significant improvement, and your favorable consideration would be greatly appreciated.

Sincerely yours,

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Reviewers' comments:

Reviewer: 1 Comments to the Author

Thank you for asking my opinion about the manuscript entitled "Low weight related to low bone mass in elderly patients with fractures: a case-control study". I believe that this manuscript should be major revision.

Reply: We thank reviewer for carefully reading our manuscript and raising recognition. After integrating the opinions of other reviewers, we have addressed all the reviewers' questions and suggestions, and further fully supplemented previous version in revised manuscript. Thanks for the reviewers' continued help and efforts to improve the quality of our manuscript. We believe this revised version represents a significant improvement, and your favorable consideration would also be greatly appreciated.

Q1. It is very important to change and modify the title. the title is not appropriate.

Reply: We thank the reviewer for your kind comment and positive advice. The corresponding amendments in the revised manuscript are as follow. This new title clearly outlines the research context, focusing on the relationship among weight, lipids and bone mass specifically in elderly individuals with fractures. It is informative and provides context for the study's scope.

"Relationships among Body Weight, Lipids and Bone Mass in Elderly Individuals with Fractures: A Case-Control Study"

Q2. Are the objectives and the rationale of the study clearly stated?

Reply: We thank the reviewer for carefully reading our manuscript and raising effective suggestions. We have rewritten the introduction section to make the principles and research objectives clearer.

"The incidence of osteoporosis and low bone mass is progressively rising on an annual basis. Osteoporosis affects over 33% of individuals aged 50 years or older in China [1]. …… This study aimed to examine the interaction between BMI and bone mass, explore the correlation between lipid profiles and bone mass, and further analyze the

interrelationship between lipid metabolism and bone health in individuals experiencing fragility fractures."

Q3. In the abstract, the research gap was not clearly stated. In addition, the authors need to rewrite the study objectives to be more academic writing

Reply: We thank the reviewer for carefully reading our manuscript and raising effective suggestions. We have rewritten the objective section to make the principles and research objectives clearer.

"The prevalence of osteoporosis and low bone mass is steadily rising each year. Low body weight is commonly linked to diminished bone mass and serves as a robust predictor of osteoporosis. Nonetheless, the connection between BMI, BMD, and lipid profiles among the elderly remains elusive. This study aimed to examine the association between BMI and bone mass, explore the correlation between lipid profiles and bone mass, and delve into the interplay between lipid metabolism and bone health."

Q4. In the introduction, include the study's significance and novelty. What makes the study different from the rest and what does it add to the current knowledge?

Reply: We thank the reviewer for carefully reading our manuscript and raising effective suggestions. In the introduction, we have included an overview of the research's significance and novel aspects. Differing from prior investigations, our study centers on elderly individuals with fragility fractures. Considering older adults with bone loss or osteoporosis, the potential of increased BMI for preventing fragility fractures merits thoughtful consideration.

"This study aimed to examine the interaction between BMI and bone mass, explore the correlation between lipid profiles and bone mass, and further analyze the interrelationship between lipid metabolism and bone health in individuals experiencing fragility fractures."

Q5. In the introduction, the authors should have explained the purpose of this study and the existing gaps in this field and explained why this study

was conducted.

Reply: We thank the reviewer for carefully reading our manuscript and raising effective suggestions. The impact of weight gain on enhancing the lipid profile and subsequently mitigating the prevalence of osteoporosis and fragility fractures of the elderly individuals remains uncertain. In line with this objective, we have revised the introduction to elucidate the limitations of previous studies in this domain and to clarify the objectives of our investigation.

"Nevertheless, the relationship among BMI, bone mass, and lipid profiles remains unexplored in populations with osteoporosis and fragility fractures. Fragility fractures frequently occur in elderly patients with severe osteoporosis, exacerbating the prognosis [21]. The impact of weight gain on enhancing the lipid profile and subsequently mitigating the prevalence of osteoporosis and fragility fractures remains uncertain. This study aimed to examine the interaction between BMI and bone mass, explore the correlation between lipid profiles and bone mass, and further analyze the interrelationship between lipid metabolism and bone health in individuals experiencing fragility fractures."

Q6. Are the methods clear and replicable? Do all the results presented to match the methods described?

Reply: We thank the reviewer for carefully reading our manuscript and raising effective suggestions. The methods section has been revised to enhance the clarity of the inclusion and exclusion criteria for this study. Furthermore, we have explicitly stated that the laboratory test results used in the study were derived from the initial blood test conducted upon the patient's admission to the hospital. This adjustment aims to improve the congruence of our results with the methodology and enhance the overall reproducibility.

"This retrospective study was conducted at a singular orthopaedic trauma centre during the time span of January 2017 to December 2020. The study meticulously applied specific inclusion and exclusion criteria as delineated below:

……

All laboratory data used in this study were obtained from blood samples collected during the initial admission."

Q7. If relevant are the results novel? Does the study provide an advance in the field? Is the data plausible?

Reply: We thank the reviewer for carefully reading our manuscript and raising effective suggestions. Our findings indicate a strong correlation between BMI and lipid metabolism markers in the population with fragility fractures, and this association remains consistent even in more detailed stratified analyses. These results imply the potential for mitigating the prevalence of osteoporosis and fragility fractures through weight increase and lipid profile enhancement. In terms of data reliability, the original data can be made available by the first author.

Q8. References are relevant, correct, and not recent. The number of references should be increased. please add some references. since this is a scientific review, all the sentences need to be supported with references. This study is very beautiful. I liked the sequence and enjoyed reading. Please add more references on similar studies.

Reply: We thank the reviewer for carefully reading our manuscript and raising effective suggestions. Accordingly, we have refreshed the references in this study to enhance its overall novelty.

"Reference:

21. Migliorini F, Giorgino R, Hildebrand F, Spiezia F, Peretti GM, Alessandri-Bonetti M, Eschweiler J, Maffulli N. Fragility fractures: Risk factors and management in the elderly. Medicina (Kaunas) 2021; 57: [PMID: PMC8538459 DOI: 10.3390/medicina57101119]

22. Pouresmaeili F, Kamalidehghan B, Kamarehei M, Goh YM. A comprehensive overview on osteoporosis and its risk factors. Ther Clin Risk Manag 2018; 14: 2029-

2049 [PMID: PMC6225907 DOI: 10.2147/TCRM.S138000]

26. Ma M, Feng Z, Liu X, Jia G, Geng B, Xia Y. The saturation effect of body mass index on bone mineral density for people over 50 years old: A cross-sectional study of the us population. Front Nutr 2021; 8: 763677 [PMID: PMC8554069 DOI: 10.3389/fnut.2021.763677]

34. Alfahal AO, Ali AE, Modawe GO, Doush WM. Association between serum lipid profile, body mass index and osteoporosis in postmenopausal sudanese women. Afr Health Sci 2022; 22: 399-406 [PMID: PMC9993279 DOI: 10.4314/ahs.v22i3.43]"

Q9. There are a lot of grammatical errors. This must be taken care of and addressed.

Reply: We thank the reviewer for carefully reading our manuscript and raising effective suggestions. A professional was engaged to refine the revised manuscript, and we have included Editing Certificate.

Q10. What are the limitations of the study? A description of limitations is missing at the end of the discussion section.

Reply: We thank the reviewer for carefully reading our manuscript and raising effective suggestions. A dedicated section highlighting the strengths and limitations has been incorporated into the discussion, under the premise that this revised segment will furnish more comprehensive insights.

"This study investigated the interplay between BMI, lipid profile, and bone mass within a population vulnerable to brittle fractures.

……

Additionally, we intend to investigate the nexus between BMI, lipid profile, and bone mass via prospective studies involving nutritional interventions in patients."

Reviewer: 2 Comments to the Author

The presented retrospective study added the knowledge about relationship between body weight and bone mineral density. The study contains some limitations that should be added at the end of the manuscript. In the title of the article, it is worth indicating that the study was carried out in China in connection with the population characteristics of the development of osteoporosis in residents of different countries of the world. The conclusions are consistent with the goal. The limitations include the following.

Reply: We thank reviewer for carefully reading our manuscript and raising recognition. After integrating the opinions of other reviewers, we have addressed all the reviewers' questions and suggestions, and further fully supplemented previous version in revised manuscript. Thanks for the reviewers' continued help and efforts to improve the quality of our manuscript. We believe this revised version represents a significant improvement, and your favorable consideration would also be greatly appreciated.

1. Collection of blood samples immediately after the fracture. As described in the methods: "Serum samples were collected immediately after the patients were admitted" at the Trauma Center with hip, vertebral, distal radius and proximal humerus fractures. Can the authors explain whether such a serious injury as a hip fracture affected the studied parameters? Is it possible to compare the biochemical parameters of patients with distal radius and hip fractures and combine them into the same group?

Reply: We thank the reviewer for carefully reading our manuscript and raising effective suggestions. Fragility fractures encompass both hip and distal radius fractures. This study investigates the potential correlation between low body weight, lipid metabolism, and bone mass, irrespective of trauma severity or location. We greatly appreciate the reviewer's insightful feedback, which prompted us to revise the references in the introduction and methods sections. This adjustment has significantly enhanced the logical coherence of our study's framework.

2. Assessment of low/normal bone mass from proximal femur based on bone mineral density alone. Probably, if you did not also use the second part of the skeleton for assessing bone mass, then it is worth indicating this in the limitations.

Reply: We thank the reviewer for carefully reading our manuscript and raising effective suggestions. We have elaborated on this aspect in the discussion section dedicated to limitations.

"Among patients undergoing DXA assessments, the T-value of the proximal femur was the only site measurement employed for standardization, with lumbar and radius measurements being omitted."

Furthermore, I have the following questions to the authors: 1. According to the average BMI given in the tables, all the patients in the study appear to be of normal weight. It is probably worth mentioning this in the description of the results and in the limitations of the study. If this is not the case, could you supplement the information on the distribution of patients with normal weight/obesity in groups in the results.

Reply: We thank the reviewer for carefully reading our manuscript and raising effective suggestions. In Table 1, we employed the mean value to characterize BMI. Figure 3 illustrates the BMI distribution, encompassing individuals across the spectrum from obese to thin. As suggested, we have revised the BMI stratification analysis in the table. As our study delved into the correlation between BMI as a continuous variable and lipid metabolism and bone mass, we maintained the analysis of BMI as a continuous variable in subsequent investigations.

"Table 1

	Univariate analysis				Multivariate analysis		
	Normal (n=85)	Osteopenia (n=184)	Oeteoporosis (n=251)	P-value	OR	95%CI	P-value
Age (years old)	75.54±8.22	76.31±8.00	79.72±7.62	P<0.001	-0.040	0.016-0.064	0.001
Gender (N)				P<0.001	1.34	0.968-1.720	P<0.001
Male	48	81	49				
Female	37	103	202				
BMI (Kg/m²)	25.46±3.32	23.43±3.32	21.83±3.10	P<0.001	-0.018	-0.245-0.128	P<0.001
≤18.5 (n)	1 (1.18)	9 (4.89)	38 (15.14)	P<0.001			
18.5-24 (n)	27 (31.76)	92 (50.00)	148 (58.96)				
≥24 (n)	57 (67.06)	83 (45.11)	65 (25.90)				

"

2. Could the authors add the exact value of the BMD scores to their statistical analysis, since the T-score is itself a standard deviation from the normal BMD reference value. Moreover, you are writing "However, the relationship among BMI, BMD, and lipid profiles remains unclear".

Reply: We thank the reviewer for carefully reading our manuscript and raising effective suggestions. Due to substantial variations in BMD values across diverse age and gender categories, analyzing the BMD T-value as a continuous variable is deemed impractical. In light of this, we contemplate amending "BMD" to "bone mass".

“Nevertheless, the relationship among BMI, bone mass, and lipid profiles remains unexplored in populations with osteoporosis and fragility fractures.”

3. Page 7. Add appropriate references after the sentence "Previous studies have reported that many factors contribute to osteoporosis."

Reply: We thank the reviewer for carefully reading our manuscript and raising effective suggestions. In order to substantiate our argument with existing research, we incorporated relevant references into this sentence.

“Previous studies have reported that many factors contribute to osteoporosis [3, 22].”