

REVIEWER #1

The manuscript submitted by Silvia Costantini, Caterina Conte is an interesting and well written review about bone health and the mechanisms responsible for increased susceptibility to fracture across the spectrum of glycaemic status, spanning from insulin resistance to overt forms of diabetes. The textual content and the citations presented in this article are written accordingly. The latest important references were cited accordingly and the language in article clearly and concisely express the information. The review can be published in WJD.

We thank the reviewer for her/his comments.

REVIEWER #2

The manuscript is devoted to the actual clinical problem of osteoporosis and fractures in patients with diabetes and prediabetes. In general, authors comprehensively review the clinical and pathophysiological aspects of the topic. The manuscript is written clearly. It will undoubtedly be interesting to the audience of the journal. Unfortunately, the authors failed to avoid some unfounded allegations. Besides, some clinically important aspects of the problem are omitted. To improve the quality of the article, I recommend some major revisions.

We thank the reviewer for her/his constructive comments. The manuscript has been extensively revised to include important aspects of the relationship between diabetes, prediabetes and bone that had been omitted in the first version of the manuscript. We believe that our work has greatly improved, and hope that it will be deemed suitable for publication in the World Journal of Diabetes.

1. The authors indicate that fracture risk appears to be greater in men than in women with T2D. This is a false statement and incorrect citation.

We thank the reviewer for pointing out this oversight. We have now modified the text to acknowledge that fracture risk does not significantly differ by gender.

2. Another wrong generalization: “Bone turnover markers are reduced in patients with T2D”. Not all markers of bone remodeling are reduced in patients with diabetes. It is necessary to specify which of the markers of bone formation or bone resorption in question. We thank the reviewer for this comment, which allowed us to improve the manuscript. We now state that “Bone turnover markers are generally reduced in patients with T2D”, and specify which markers are reduced or elevated (page 10 of the revised manuscript). Furthermore, a table with the effect of prediabetes/insulin resistance and T2D on bone turnover markers has been added (Table 1).

3. It is in the Conclusions: “Caution should be used with antidiabetic drugs known to negatively affect bone health, such as insulin and TZDs”. Is it too bold conclusion about insulin? The negative effect of insulin on the bone health has not been shown, especially in those with type 1 diabetes.

We agree that an association between insulin therapy and increased fracture risk has been shown in patients with T2D, whereas intensive insulin therapy has even been reported to favorably affect bone in those with T1D. Accordingly, we modified the text to clarify that “Drugs shown to be associated with increased fracture risk in T2D, such as insulin and TZDs should be avoided, when possible” (page 19 of the revised manuscript) and that “Caution should be used with antidiabetic drugs known to negatively affect bone health, such as TZDs and insulin in patients with T2D” (page 23 of the revised manuscript). Furthermore, the relationship between insulin use and fracture risk is now explored in a new section on “*pharmacological treatments for diabetes*” (pages 16-18 of the revised manuscript).

4. The article does not cover the role of obesity and body composition in the shifts of BMD and bone microstructure in subjects with type 2 diabetes and prediabetes.

We thank the reviewer for this suggestion. The text has been expanded to include information on the role of obesity and body composition (sections “*BMD in T2D and prediabetes*” and “*Bone geometry and microarchitecture in T2D and prediabetes*”, pages 9-10 and

14-15 of the revised manuscript, respectively).

5. The impact of glucose-lowering modalities on the bone health is not mentioned.

Two sections have been added to illustrate the effect of glucose-lowering modalities on bone health. In particular, we added a section on "*pharmacological treatments for diabetes*" (pages 16-18 of the revised manuscript), where the main glucose-lowering drugs used for the management of diabetes are dealt with. Given the increasing role of bariatric-metabolic surgery for the treatment of type 2 diabetes and the possible role of pancreas transplantation in improving bone health in type 1 diabetes, we also added a section on "*surgical treatments for diabetes*" (pages 18-19 of the revised manuscript). Accordingly, in the conclusions we now mention that healthcare professionals involved in the management of T2D patients undergoing bariatric surgery should be aware of the possible detrimental effects on bone health, and implement appropriate nutritional strategies.