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23 September 2019  

Regarding: Resubmission of manuscript with revisions  
Manuscript Number: IJMS-572791  
Manuscript Title: Impact of Diabetes Mellitus on Bone Health  

Dear Kaitlyn Wu,  

Thank you for giving us the opportunity to revise our submitted article. The authors are very grateful for the comments made by the reviewers and have made every effort to address all of the points raised.  

Both Reviewer 1 and Reviewer 2 have requested the addition of a section addressing the impact of glucose lowering agents on bone health. Therefore, a new section has been added on page 9 and 10 of the revised submission to discuss the use of metformin, insulin therapy, GLP-1 agonists and SGLT inhibitors clinically and their impact on osteopathy.  

The foremost concern of Reviewer 1 was the inclusion of the hyperglycaemic memory in diabetes mellitus. To address Reviewer 1’s concerns, a new section has been included on page 5 specifically addressing this topic.  

The foremost concern of Reviewer 2 was how DM-induced epigenetic changes may be involved in high fracture risk among diabetic patients. To address Reviewer 2’s concerns, the text has been modified to include a section on the epigenetic impact of DM with respect to bone health (page 6).  

We thank Reviewer 3 for their time in considering our submission and for their positive comments.  

Attached please find a point-by-point response to the comments raised by reviewer’s 1 and 2. Furthermore, we are also attaching a manuscript with the changes highlighted.  

If you have any further questions or queries, please do not hesitate to get in touch with me.  

Sincerely,  

Cliodhna Murray
Reviewer 1:
The manuscript by Murray and Coleman examines an extremely important subject. The risk of fracture in patients with diabetes is, among the many diabetic complications, often underestimated by clinicians.

We thank reviewer 1 for their time considering our manuscript. We agree that more emphasis needs to be placed on the relationship between DM and osteopathy and hope that this review might reach an audience of health care providers, thereby influencing their provision of care.

The review is well written and I have few suggestions to improve the clarity of the text and its scientific impact:

The difference between bone mineral density in T1DM and T2DM should be moved in a dedicated paragraph and not in the introduction.

As per Reviewer 1’s suggestion, a new section to highlight this discrepancy has now been added on page 2 of the manuscript.

Here [in the introduction] authors should just describe the clinical/scientific impact of their topic and provide a short overview of the review structure.

The introduction (page 1 and 2) has been re-arranged to highlight the impact of DM on bone health, provide an outline of the review to follow and to describe the methodology used to identify resources as per Reviewer 2’s request.

The figure1 as presented is pointless. The description in the legend is too brief and unclear. Each reported element and its interaction should be described in details, especially if reported throughout the text.

A very detailed legend for Figure 1 has now been provided (page 3) as requested by Reviewer 1. Additionally, further references to Figure 1 have been added to the review narrative when relevant.

To improve the quality of the manuscript, author should provide a concise overview about the effects of glucose lowering agents, especially with regards to those of the new generation such as GLP-1 agonists and SGLT inhibitors, on bone health.

We thank Reviewer 1 for this excellent suggestion. A new section has now been added on pages 9 and 10 describing the effects of glucose lowering agents on bone health. GLP-1 agonists, DPP-4 inhibitors and SGLT-2 inhibitors are specifically discussed, along with metformin and insulin per Reviewer 2’s suggestion.

Moreover, is there evidence of hyperglycemic memory in bone tissue?

We sincerely thank Reviewer 1 for the idea of adding in a section discussing hyperglycemic memory in bone tissue. This had not occurred to us, but does significantly enhance the quality of the manuscript. We have inserted two sections addressing this topic on pages 5 and 6.
Reviewer 2:
This is a well written paper aiming to explain molecular events associated with high risk of fracture among diabetic patients. The subject of work is very timely, since both incidence of fracture and diabetes constantly increases.
We thank Reviewer 2 for their kind words and for acknowledging the timeliness of the manuscript.

I think that following issues can be interested to the readers and increase the quality of paper:
There is no methodology section. Please provide the criteria of references selection.
We apologize for this oversight and have addressed this omission in a new paragraph on page 2 of the revised manuscript.

Please add a paragraph or section presenting information how epigenetic mechanisms - induced by diabetes mellitus may be involved in high fracture risk among diabetic patients.
We thank Reviewer 2 for this excellent idea as it will enhance the quality of the manuscript. A new paragraph addressing the epigenetic impact of DM has now been included on page 5 and 6 of the revised submission.

It is also very interesting how different hypoglycemic drugs affect fracture risk, metformin and insulin therapy are of special importance, since they are the most frequently used hypoglycemic drugs.
To address both reviewer’s concerns, a new section has been added on pages 9 and 10 of the revised submission discussing the impact of metformin, insulin therapy, GLP-1 agonists and SGLT inhibitors.