Reviewer’s report

Title: Genistein Treatment Improves Fracture Resistance in Obese Diabetic Mice

Version: 0 Date: 07 Aug 2016

Reviewer: Erica Homan

Reviewer’s report:

Summary: Odle et al explored whether the increased risk of fracture in type 2 diabetics would benefit from genistein supplementation by treating Ob/Ob and control mice for 4 weeks and assessing the bone by histomorphometry and 3 point bending. The authors found that although there was an increase in B.Ar and T.Ar in Ob/Ob mice, the B.Ar/T.Ar was the same when compared to control mice. They found that Genistein decreased Tt.Ar and increased ultimate force in both the Ob/Ob and control mice and attribute these alterations to changes in bone quality. Although it is important to assess potential treatments in type 2 diabetics, I have concerns over statistical power and in the types of assessments utilized to assess the bone parameters.

Are the methods appropriate and well described?

* It may be better to perform a volumetric assessment of bone using a method such as uCT to assess both cortical and trabecular bone parameters in all treatment groups. By assessing volumetric parameters of trabecular bone and cortical bone, you may better observe differences in bone parameters.

Are the conclusions drawn adequately supported by the data shown?

* Histomorphometric assessments typically require a large sample number (10-12) in order to have adequate statistical power. I am concerned that the analysis is not powered appropriately to observe a difference. This is important given that you suggest the treatment may affect overall bone structure since you don't observe differences in the histomorphometry. Please do a power analysis to show that your study has sufficient power to detect a difference. Otherwise, please increase the sample numbers to boost your power.

Other comments:

* Is treatment with Genistein for 4 weeks enough time to observe differences in the bone?

* As genistein has been shown to have effects on both the osteoblast and osteoclast, a histomorphometric assessment of bone turnover (toluidine blue and TRAP stained sections) and analysis of bone mineralization (von kossa staining) would add to the bone analysis.
* If you think the treatment alters bone quality, you could look at the intrinsic biomechanical properties from the 3-point bending analysis (cross-sectional moment of inertia and elastic modulus for example) to look at intrinsic material properties.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

No

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Yes

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

No

**Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?**
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I recommend additional statistical review

**Quality of written English**
Please indicate the quality of language in the manuscript:

Acceptable

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