

Format for ANSWERING REVIEWERS



April 23, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 2429-review.doc). We would like to thank the referees for their careful reading of our manuscript and especially for the helpful comments for improvements in our manuscript. In this revision, every attempt has been made to retain the positive features and improve presentation in terms of experimental design, statistical methodology, and interpretation. On behalf of my colleagues, I would like to respond to them. Responses are illustrated by **bold** text below.

Title: Diabetes-related impairment in bone strength is established early in the life course

Author: Krista Casazza, Lynae J. Hanks, Gregory A. Clines, Hubert M. Tse, Alan W. Eberhardt

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 2657

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

This paper compares bone properties in NOD and NOD.scid mice (that do not develop diabetes). The conclusions are interesting but the paper is difficult to follow. This is largely because the authors have not included figure legends that allow the reader to follow exactly what is shown in the figures.

We thank the reviewer for identifying this. Indeed, the figure legend was overlooked when the tables and figures were incorporated into the text of the manuscript. Not only has the legend been added, but in accordance with your suggestions, additional clarifications have been included.

In figure 1 it should be stated if bars represent mean \pm SD (or is it SEM?). **The bars represent SEM and this information has been added to the figure legend.**

In figure 2 the legend states that the figures represent "Body composition differences". At week 5 all values are 0. It is not clear why - since the text states that body weight at week 5 between NOD and NOD.scid mice is significantly different. The data has clearly been standardised in some way. All of this should be clarified in a figure legend. **Understandable, without a figure legend, this was not clear; however, the figure represents changes in body composition between the two strains. This has been clarified in the figure legend.**

Figure 3 has no units on either axis and no indication if the bars represent mean and SD (or n numbers). Does the figure represent maximum load?

Tibia strength by 3-point breakage analysis using the NTS 85MTS Minibionix8 with a 100N load cell. The span was 9mm and the bones were loaded with a rate of 0.1mm/s to evaluate maximum load to failure in five and eight weeks in NOD (dark gray bars) and NOD.scid (light gray bars). Error bars represent SEM.

It would be helpful if the authors made the difference between table 1 and table 2 clearer. I believe that table 1 represents the pooled data from five and eight week old mice. However, it is not clear in this

case why the body weight value for NOD mice in this table is greater than the body weight for 8 week old NOD mice in table 2 (bearing in mind that the value in table 1 should be averaged across both 8 week old mice and 5 week old mice which table 2 shows are noticeably lighter). **We again thank the Reviewer for recognizing the importance in clarification. Table 1 is the pooled data from all mice from five to fifteen weeks.**

The text states that the NOD mice at week 5 have significantly less body weight than the NOD.scid (first paragraph of results) however this comparison is not marked as being significant in table 2. **We thank the reviewer for pointing this out. This demarcation has been added.**

It would be interesting for the authors to comment on why they think that the increased Ct.MTV and ct.TMD in NOD mice at week 8 does not translate into increased mechanical strength. Have the authors looked at intrinsic bone properties in the two strains?

We agree that the increased Ct.MTV and ct.TMD in NOD mice at week 8 which does not translate into increased mechanical strength is an interesting finding of this study. The following text has been added to the discussion. "The increased Ct.MTV and Ct.TMD in NOD mice at week 8 which did not translate into increased mechanical strength was surprising. Speculatively, a compensatory increase in insulin early in T1D prior to insulinitis may enhance anabolic properties at the outer surface. However, assessment of the strength-structure relationship requires evaluation of both outer and inner surfaces as well as the intrinsic properties within the bone (Ego Seeman, personal communication)."

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

A handwritten signature in black ink, appearing to read 'Krista Casazza', with a stylized, cursive script.

Krista Casazza