Reviewer's report

Title: Hyperadiponectinemia enhances osteogenesis through osteoblast formation in mice

Version: 2 Date: 15 July 2010

Reviewer: Lilian I Plotkin

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Comments to the authors:

This manuscript describes partially the bone phenotype of male mice overexpressing human adiponectin in liver. The authors propose that increase adiponectin results in enhanced osteogenesis due to increase osteoblast differentiation, without affecting osteoclasts. This is an interesting possibility; however, it is not supported by the data presented. In addition, the methods are incomplete, and there are contradictions and substantial mistakes throughout the manuscript. Specific comments are indicated below:

Major Compulsory Revisions:

1. Abstract, Results section: it is not clear the relationship between increased bone mass and osteoclast formation. Why the authors expected a change in osteoclast formation resulting from increased bone mass?

2. Introduction, third paragraph: the authors indicate that …serum adiponectin levels positively correlated with bone density… (lines 8-9 from the bottom) and that …the circulating level of adiponectin negatively correlated with bone density… (lines 5-6 from the bottom). Please, clarify.

3. Materials and methods: this section is incomplete and lacks sufficient information to evaluate the data presented. For example, no information is provided on fluorochrome injections (timing, number of doses, etc), required to perform dynamic histomorphometry. In addition, they do not indicate where the quantification of osteocalcin and cathepsin K positive cells was done (is it cancellous bone or cortical; if cortical, is it endosteal or periosteal surface?).

4. Figure 1: it is indicated that transgenic expression of adiponectin results in hyperadiponectinemia. However, only human adiponectin was measured and, as expected, the levels of this protein are undetectable in control mice. The authors should provide the circulating levels of murine adiponectin (or at least the normal levels found in this strain of mice) in order to determine whether indeed there is hyperadiponectinemia.

5. Tables 1 and 2 should be cited at the end of the first sentence in which they are described (page 8, line 5 for Table 1 and line 17 for Table 2). In addition, the units for MAR are incorrect in Table 2.

6. Page 8, second paragraph: osteoblast number and osteoid surface are not parameters of bone formation. Please, change the text accordingly.
7. Page 9, end of first paragraph and second paragraph, line 2: no evidence is presented of increased osteoblastogenesis. Increased osteoblast number could not only result from increase osteoblast differentiation, but also from prolonged osteoblast lifespan.

8. Figure 5: it is not clear what additional evidence is provided in this figure. The authors already showed increased osteoblast surface without change in osteoclast numbers or surface in Table 2. Moreover, number of cells without correcting by bone area does not provide useful information, as changes in cell number might be the reflection of more extensive bone surfaces. Therefore, Figure 5 should be deleted.

9. Page 10, line 2 from the bottom: please clarify what trabecular bone number is.

10. There are several mistakes and typos throughout the manuscript.

**Level of interest:** An article of limited interest

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests