Author's response to reviews

Title: Age of donor alters the effect of cyclic hydrostatic pressure on production by human macrophages and osteoblasts of sRANKL, OPG and RANK

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Author's response to reviews: see over
Dear Sir/Madam,

Re: Age of donor alters the effect of cyclic hydrostatic pressure on production by human macrophages and osteoblasts of sRANKL, OPG and RANK.

Thank you for the comments by the Reviewer, which we received on the 19th December 2005. We have altered the manuscript in response to these comments.

Wherever possible we have addressed the reviewer’s comments in the text of the revised MS. However, some points have to be addressed in this letter. (Reviewers comments in bold)

General

The suggested reanalysis of the data based on the sOPG:RANKL ratio by the reviewer has significantly changed the authors’ interpretation of their own data and the thrust of the manuscript. It has resulted in many alterations, including several instances of complete turnaround of interpretation. The changes have not been made altogether clearly making the revised manuscript difficult to read. There is almost a whole page of spurious text on page 38 between figure legends and figures. Is this discussion or discarded text? Overall, it seems the modifications have not been applied and blended in well and the paper needs more work to rectify this.
We hope that the changes which have been made will improve the MS to the satisfaction of the Reviewer. The spurious discarded text after page 31 has been removed and we apologise for its inclusion in the previous MS.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1) Results section P10-11: The modifications to this section in the text (p10-11) are overall not well written or organised and as a result are difficult to follow. It would benefit from reorganisation, perhaps to present using appropriate subheadings such as effects on MP alone, OB alone or co-cultures.

   Subheadings have been added as suggested – Page 9, “Effect on co-cultures of macrophages and osteoblasts:”; Page 10, “Effects on monocultures of osteoblasts:” and “Effects on monocultures of macrophages:”

2) Sentence 1 is incomplete (“cocultures of macrophages.”). Table 1 shows the pooled raw data for OPG and sRANKL. Firstly, the title for this table could be more descriptive. Secondly, looking at these data, the reader would not necessarily conclude, as stated in the text, that “pressure did not initially appear to have a consistent effect on secretion ...” This may be a valid comment based on Table 2 the way it is currently presented, however...

   Sentence 1 on page 9 has been altered to clarify the description of the results. The title of Table 1 has been altered to “). The effect of pressure on secretion of sRANKL and OPG by macrophages and osteoblasts cultured alone or in co-culture”

3) The purpose of Table 2 should be to direct attention to age-related effects. Why not rank the donors based on their age? Again, the title for the table should be more descriptive.

   The Table 2 has been altered as the Reviewer suggests and the data has been ranked according to age; the title has been changed to “The effect of pressure on ratio of OPG:
sRANKL is influenced by the age of the donor”. In addition, a further table, 2b, has been added to clarify the effects of age and pressure.

4) In the legend for Table 2, the results are not “+/- SE”, and are they really means of 5 expts? As a minor point here, donor “MMcC” would be better coded as “MM”. The text has been altered as suggested; apologies for a “cut and Paste” error. The initials of the donor have been altered form “MMcC” to “MM”.

5) Sentence 2 is vague and the reference to Table 2 seems misplaced. In the legend of Table 2, the Wilcoxon Signed Ranks Test is cited whereas Mann Whitney and Fishers Exact tests are cited in the text. Make clear whether the data throughout this section refer to mono-cultures (of what) or co-cultures.
Sentence 2 has been rewritten to clarify and better explain the data. The legend for Table 2 has been altered as requested. The addition of subheadings throughout this section should make it clear to the reader which type of culture is being discussed.

6) Page 11: It is not clear whether the text in this section refers to Table 1 as stated or to figure 1, which appears to be otherwise not referred to in the text.
Figure 1 and any reference to it have been removed as it did not add anything to the paper. The other figures have been relabelled accordingly and the text altered appropriately. The new figure files will be resubmitted along with the new text.

7) Fig 4: The labels are misaligned; there are two panels labelled (f). What is the difference between (d) control without pressure and (g) no 1,25D without pressure?
The extra “(f)” has been removed; Control (d) was for cells incubated with 1,25D and control (g) for those incubated without.

8) The conclusion section is messy and seems to lack a ‘take home message’.
We are assuming that the reviewer is referring to the final “Conclusions” section on page 16. This has been rewritten to give a clearer and more concise message.
9) Methods section: Statistical Analysis - Please clarify all statistical tests performed. This has been done throughout the text and legend.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

1) Results P2: change from: sRANKL or OPG to “and”.
   The minor alteration has been made.

We hope that this revised MS will now meet with your approval. Please do not hesitate to contact us again if any points are unclear.

Yours sincerely,

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J.G. Andrew (consultant orthopaedic surgeon)
S. Mylchreest (research assistant)