Reviewer's report

Title: Glucosamine increases hyaluronic acid production in human osteoarthritic synovium explants

Version: 1 Date: 17 February 2008

Reviewer: Gene Homandberg

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Major Compulsory Revisions

The manuscript, Glucosamine increases hyaluronic acid production in human osteoarthritic synovium explants by Uitterlinden et al presents data supporting a hypothesis that glucosamine stimulate synthesis of synovial HA production. However, the studies have been done at much higher concentrations of mM as compared to uM concentrations found in serum of patients or animals receiving oral supplements. This greatly weakens the relevance of the work. Further their data show that glucose at 5 mM enhances HA synthesis by nearly two fold, statistically no different than GlucN at 0.5 or 5 mM. Since glucose metabolism can indirectly affect so many pathways, it argues that there are not specific effects on HA synthesis. Thus it would be difficult to argue that glucosamine provides building blocks. While the authors appear to soften their conclusion in the last sentence, there should be more discussion of this concentration difference so the reader can decide on relevance. Perhaps the conclusion should simply be that GlcN enhances HA synthesis, but because high concentrations are required, further studies should involve testing of other parameters such as kinetics to determine if effects might be observed at lower concentrations over a longer period. The authors should more clearly state the limitation of the study and provide more discussion of this point in order to educate the reader.

The discussion could be shorted with tighter writing. A briefer statement that the difference in activity between Glucose-Ac and Glucosamine might be due to interference by acetyl group would be better.

The last two paragraphs in the discussion could be improved. It is not clear what the authors are suggesting. Their data suggest that GlucN is more effective at lower concentrations than glucose. This point can be stated more simply. The next point is that when GlucN is injected, the synovial fluid concentrations are only micromolar and persist longer than serum levels. As stated earlier, this brings up the question of whether the use of the mM concentrations in this submitted report is relevant, as the authors state in the final sentence. Perhaps lower concentrations would be effective over a longer time period. However, the authors did not vary their experimental conditions to address this possibility. This limitation should be discussed.
Minor Essential Revisions

There is also much missing discussion of the building block hypothesis and of other hypotheses for effects of GlucN. The authors should reference reviews and provide a more complete picture of what is known. There are many hypotheses for beneficial effects of GlcN and some reviews should be cited.

In the background statement the authors allude to pain reduction by GlcN and HA, although the link between HA synthesis and pain alleviation is not reviewed nor discussed. It is not clear why analgesic effects are mentioned since effects on enhancing HA synthesis would not necessarily be the explanation for pain alleviation by either HA or GlcN. The authors should revise relevant sections.

On page 3, it is proposed that if the HAS enzymes are present the synthesis of HA depends on availability of building blocks. This can be true, but this does not necessarily mean that increased substrate increases HA synthesis. The authors should more clearly and accurately explain their implication.

On page 4, bottom, “experimental conditions were added” is clumsy. Perhaps were established. Also, instead of stating “above-mentioned culture medium” several times in Methods, this could be more simply stated with a definition.

Methods are presented present tense. The entire manuscript should have the same tense, typically past tense. Same holds true for Results.

Page 5. Gene expression of HAS is a little too brief for a description. Page 5-6, Tissue processing and gene expression WERE.


Results, first sentence, Increasing significantly with; delete with.

Discussion - First sentence, verb should be led. Change tense to past in next sentence and throughout Discussion.

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article whose findings are important to those with closely related research interests

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.