Reviewer's report

Title: Insight in modulation of inflammation by gene, protein and metabolite profiling in mildly obese males: a human intervention study

Version: 1 Date: 28 August 2009

Reviewer: John Fain

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Major compulsory revisions

1. The authors fail to adequately explain why they chose diclofenac treatment at the indicated dosage for only 9 days. This non-steroidal cyclooxygenase inhibitor is associated with significant risks in patients with cardiovascular disease. We ought to be told the rationale for using this drug at the low doses for only 9 days.

2. It is unfortunate that several of the placebo subjects had high CRP levels that went down significantly during the 9 days and this is a confounding effect. I am not completely convinced that the author's treatment of the data from these subjects is the approach to take since the mean values in both controls and treated patients did not change during treatment. In any case diclofenac had no effect on CROP but did reduce PGE2 as expected. In the first paragraph of the results on page 19 the authors essentially conclude that the placebo treatment reduced CRP while the drug had no effect. This makes no sense and the authors should realize that the CRP value in the controls at the end was 2.09 and 2.37 which hardly seems different to me. Thus I question the wisdom of correlating changes in those placebo subjects with a large drop in CRP with other parameters. This may just be noise in the system.

3. The decision to use patients with only mild obesity [BMI of 28.1 ] is concern since the health risks of obesity are primarily associated with BMI values above 38. Please explain.

4. I question the statement that an increase of 60% for annexin means strongly induced as I would call that a borderline effect that is just barely detectable. This is especially so when they cannot detect any change in COX-2 in PBMC cells.

5. I also worry about the fact that the authors have published some of the data in ref. 20 with regard to their doing oral glucose tolerance tests on these subjects and detecting subtle differences. However, those differences are poorly explained in the text.

6. In supplementary table 2 the authors should provide some information as to the extent of the effect of diclofenac for each compound listed [ i. e. was it increased or decreased and by what %]. For example did IL-18 change in the same direction as inflammatory cytokines?

7. The authors provide two summary figures that are difficult to follow. They need
more discussion in the text about why many conventional inflammatory markers did not change after the drug treatment. It should also be made somewhat clearer that it is not established that the inflammatory effects of obesity are mediated through COX-2 and subject to inhibition by diclofenac.

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

**Quality of written English:** Acceptable

**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