Author's response to reviews

Title: Modulation of obesity-induced inflammation by dietary fats: mechanisms and clinical evidence

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Author's response to reviews: see over
Dear Editorial Team,

Thank you for giving us the opportunity to submit a revised manuscript. We are very grateful for the positive comments from the Reviewers and our responses to the points raised are as follow:

1. The aim of the review is to grasp over a large topic. In this context it would be useful to know what was the major aim major aim of the review? i.e. was it the effect of obesity on inflammation (very large and unspecific topic) or of dietary fatty acids (both quality and quantity?)?

A brief explanation of the mechanisms involved was discussed and followed by the major aim of the review, which is the effect of dietary fats on inflammatory response, based on clinical evidence from both acute and chronic clinical studies in obese and overweight individuals. The manuscript has been revised accordingly as highlighted in yellow.

2. The authors state that one of the aims was to investigate the effect of dietary fatty acids on “obesity-induced inflammatory response”. What is actually meant (or defined) by this and how did it affect the review of the literature and papers discussed? This seems misleading since the studies discussed and presented in the tables also include non-obese subjects, as well as subjects with obesity or undefined anthropometric status.

Revised at lines 1-8, page 3

3. Do the authors have any evidence that the effect of dietary fatty acids on inflammation markers is different depending on body composition, obesity status or metabolic status? If so, this should be taken into account in this review.

Revised at lines 8-13, page 8

4. Also how do the authors define “inflammation” or systemic inflammation?

Refer to lines 2-3, page 4

5. In the authors view, are all inflammation markers equally good biomarkers and should they all be interpreted equally with regard of weighing the evidence? E.g. which markers are better and worse, and how can you interpret the very different and many inflammation markers that are measured in the different studies? If one study shows an effect on CRP, another on IL-6 or IL-1 etc, how are they compared or judged? Did the authors have any a priori thoughts about this?

An array of inflammatory markers participates in different stages of inflammatory process and hence each of the markers plays a pivotal role in low grade inflammation. There are pro-inflammatory and anti-inflammatory markers participated in different stages of the process. The commonly measured inflammatory markers are hsCRP, IL-6, TNF-α, sICAM-1, sVCAM-1 etc. There are varying factors affecting the concentrations of inflammatory markers, i.e. study design (duration, dosage, gender, background diet etc.) may contribute to the different findings. Hence, all these criteria
have been included in the discussion of findings. A section on strengths and limitations has also been included from lines 13, pages 16, until page 17.

6. The limitation with non-systematic reviews is that the quality of the papers is not clearly presented and discussed, and importantly not taken into account in the overall conclusions. For example, using the GRADE system would objectively compare studies not only with regard to study type and intervention, but also quality aspects that are necessary in order to interpret each of the studies and have a overall picture of the evidence. This reviewer understands that using GRADE or other grading tools to systematically evaluate the overall evidence of this topic was not feasible, but this issue should be discussed as a limitation of this review.

Revised at lines 15-19, page 16

7. It should be clearly stated that this review is non-systematic without any specific inclusion criteria, did this reviewer understand this correctly? Also, it is not clear what the inclusion criteria of studies reviewed were; e.g. did they only include obese/overweight subjects, all age groups including children, healthy or patients with diabetes or metabolic disorders, or all diseases included?

Revised at lines 17-26, page 7; and lines 1-4, page 8

8. Sometimes the authors use the term PUFA, although it is more appropriate with e.g. n-3 PUFA (for example The authors often use the terms n-3 PUFA n -6 PUFA, but in most places it might be more useful to be more specific since different PUFAs have different or even opposite effects on inflammation, i.e. more than 90% of dietary PUFA is LA, whereas for example LA and AA are derived from very different dietary sources, and have different functions in the body.

Revised accordingly in the text, pages 8-16

9. The authors have not included any data from prospective or cross-sectional cohort studies, either using fatty acid levels of blood and tissues or by using dietary intake data, these data may provide with important information of these relationships in humans, and the omission and possible implications of doing so should be mentioned and discussed.

Revised at lines 17-21, page 7.

10. In the introductory text and in the context of Fig 3, it should be mentioned that another eicosanoid derived from arachidonic acid, lipoxin A4, is anti-inflammatory (Gewirtz et al., 2002; Levy et al., 2001; Serhan et al., 2003; Vachier et al., 2002).

Revised at line 8-10, page 6 and in Figure 2 (Figure 1 from the previous version has been removed).

11. In recent and updated review by Johnson et al (J Acad Nutr Diet. 2012;112:1029-1041) the authors concluded that; “This review clearly demonstrates that virtually no data are available from randomized, controlled intervention studies among healthy, noninfant human beings to show that the addition of LA to diets increases markers of inflammation” . This review should be commented and cited by the authors in the context of potential proinflammatory effects of LA. How does this conclusion fit with the current results?

Discussed at lines 11-13, page 12
12. It may facilitate for the readers to use more specific sub-headings that divide studies looking at quality versus quantity of fat with regard to inflammation. Perhaps the text and tables could also be structured with regard to comparisons within each study design type (i.e. SFA vs ALA, SFA vs LA, SFA vs EPA and DHA, DHA/EPA vs ALA, ALA vs LA, ALA vs control diet/average duet, TFA vs SFA, etc)

Revised accordingly in Table 1a, 1b, 2a, 2b and 2c. Subheadings were included to vide amount and type of dietary fats

13. Also add subheadings that clearly divide postprandial (acute) studies from chronic studies could be helpful, and differ between iso-caloric and hypercaloric studies as these two situations are difficult to compare with regard to dietary fatty acids and inflammation.

Revised in Table 1a, 1b, 2a, 2b and 2c
Subheadings were included to vide amount and type of dietary fats

14. Line 9, page 17. It should read n-3 PUFA instead of PUFA

The statement was deleted as the present review focuses on obese and overweight individuals but not healthy lean subjects

15. Page 13, bottom end of page it is stated that palm oil contains “substantially amount of MUFA and PUFA”. This statement is exaggerated and can be misleading if it is not clear that it refers to comparison with butter. Compared to butter it does have more PUFA but not much more MUFA, but the PUFA and MUFA levels in palm oil are small as compared with other common vegetable oils.

The statement was deleted as the present review focuses on obese and overweight individuals but not healthy lean subjects

16. Page 14, second line. Please add a reference after the statement that butter is better absorbed due to high proportion of MCT.

Revised at lines 1-2, page 11

17. Page 14, second paragraph, line 6-8. Unclear and difficult sentence, please re-write.

Deleted as not relevant to the current focus

18. Page 16, line 1-11. Some of the studies are partly not correctly cited as the results are not adequately reported. The second summarizing sentence is over-stating the results and should be re-written. On line 9, the authors state that “LA was found to increase the concentrations of sICAM-1 and E-selectin (citing Zhao et al. 2004). This is not true since both ALA and LA reduced these cytokine levels compared with control diet (average American diet), thus there were no evidence of a pro-inflammatory effect on LA in that study. Thus, the term increased is not correct, instead it should be stated that ALA reduced these cytokines more than LA did. Also, why is it not stated that ALA reduced CRP (by 75%) and LA reduced CRP (by 45%) (p=0.08) when the sentence above discuss results on CRP only. Also, including in vitro findings (cell-cultures) may not be relevant in this context of clinical studies.

Deleted as not relevant to the current focus

19. Page 17. It is not very useful to discuss the findings of Mediterranean diets on inflammation markers since many aspects of the diet besides the fatty acid composition has
altered. Thus any interpretation on the role of specific dietary fats mediating effects are speculative. I suggest authors omit interventional studies that have altered other components than fat quality.

**Omitted as not relevant to the current focus**

20. Some other relevant studies I cannot find that the authors should discuss properly; Liou YA, King DJ, Zibrik D, Innis SM. Decreasing linoleic acid with constant alpha-linolenic acid in dietary fats increases (n-3) eicosapentaenoic acid in plasma phospholipids in healthy men. J Nutr. 2007;137:945-952.

**Not included as these studies were conducted in healthy lean subjects**

21. Also see other previous reviews for additional references, eg: Sacks FM, Campos H. Polyunsaturated fatty acids, inflammation, and cardiovascular disease: time to widen our view of the mechanisms. J Clin Endocrinol Metab. 2006;91:398-400

**Cited at line 13, page 12**