Reviewer's report

Title: Obesity-induced inflammation: the link to insulin resistance and modulation by dietary fats

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Reviewer: Ulf Riserus

Reviewer's report:

The authors have aimed to review an interesting and large topic, both aiming at discussing the underlying obesity-modulated inflammatory pathways and their impact on insulin signaling, as well as aiming at discussing the effect of dietary fatty acids on the obesity-induced inflammatory response, based on clinical evidence from both acute and chronic clinical studies. The authors conclusions on dietary fat are overall inconclusive, which may be justified by the data, but there are several important points that need to be addressed by the authors in order to improve the paper.

Major Compulsory Revisions:

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?)?

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.

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.

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

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?

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.

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?

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.

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.

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).

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?

Minor Essential Revisions:
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)
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.

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

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.

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

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

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.

Page 17. It is not very useful to discuss the findings of Mediterranean diets on inflammation marekrs 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.

Some other relevant studies I cannot find that the authors should discuss properly;
Freese R, Vaarala O, Turpeinen AM, Mutanen M. No difference in platelet activation or inflammation markers after diets rich or poor in vegetables, berries


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

**Quality of written English:** Not suitable for publication unless extensively edited

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

**Declaration of competing interests:**

I have no competing interests