Author's response to reviews

Title: Improvements in vascular health by a low-fat diet, but not a high-fat diet, are mediated by changes in adipocyte biology

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Response to referee comments

Referee #1

1. THE PAPER, WHICH IS EXCELLENT OVERALL, HAS A FEW IMPORTANT DEFICIENCIES. WHILE THE DIETARY INTERVENTIONS ARE DESCRIBED WITH REGARD TO MACRONUTRIENT DISTRIBUTION, THEY ARE NOT DESCRIBED IN TERMS OF FOODS. AN ORIENTATION TO WHAT KINDS OF FOODS WERE BEING CONSUMED WOULD BE HELPFUL. RELATED TO THIS IS THE FACT THAT NOT ALL LOW-FAT NOR HIGH-FAT DIETS ARE CREATED EQUAL, AND THUS THE AUTHORS OVERREACH IN SUGGESTING THAT EFFECTS SEEN HERE ARE GENERALIZABLE TO LOW-FAT VS HIGH-FAT. IT MAY BE THAT PARTICULAR APPROACHES TO LOW VS HIGH-FAT ARE GERMANE- THIS WARRANTS DISCUSSION, AND ACKNOWLEDGMENT AS A LIMITATION.

This is an excellent point raised by the reviewer. We have now added a description of the foods consumed by both the high-fat and low-fat diet groups for breakfast, lunch, and dinner to Table 1. We have also discussed how the effects observed in this study may not be generalizable to all high-fat and low-fat diets (lines 343-345).

2. ANOTHER ISSUE IS THE SMALL SAMPLE SIZE, WHICH PROVIDES VERY LIMITED STATISTICAL POWER. THIS IMPOSES A RISK OF TYPE 2 ERROR, AND THUS IS NOT A PROBLEM WITH SIGNIFICANT RESULTS. IT IS A PROBLEM, HOWEVER, FOR NON-SIGNIFICANT RESULTS. AT A GLANCE, ONE SEES DIFFERENCES BETWEEN THE TWO GROUPS AT BASELINE INCLUDING THEIR FMD- WHICH ARE DISMISSED AS 'NON SIGNIFICANT.' THIS LACK OF SIGNIFICANCE MAY MERELY BE A LACK OF STATISTICAL POWER, AND SHOULD BE ACKNOWLEDGED AS SUCH- AND THUS A STUDY LIMITATION. OF NOTE, LOWER FMD IN THE LOW-FAT DIET GROUP AT BASELINE RAISES THE PROSPECT THAT STATISTICAL...
REGRESSION EFFECTS CONTRIBUTED SOMETHING TO THE RESULTS OBSERVED.

This is a valid point. As such, we have included a statement in our discussion indicating that the small sample size employed in this trial imposes the risk of a type 2 error. We have also mentioned that the lack of difference between the two groups at baseline for FMD may be the result of a lack of statistical power (lines 334-339).

3. A FINAL COMMENT HERE: THE ABSTRACT BOLDLY ASSERTS THAT WEIGHT LOSS WITH BOTH LOW-FAT AND HIGH-FAT DIETS IMPROVE ENDOThelial FUNCTION, BUT THE PAPER DOES NOT SUPPORT THIS STATEMENT, SUGGESTING INSTEAD THAT RESULTS IN THIS AREA CONFLICT. THE OPENING LINE OF THE ABSTRACT SHOULD BE REVISED TO CONFORM WITH THE BODY OF THE PAPER.

As suggested, the opening line of the abstract has been revised to conform with the body of the paper (line 22).

4) MINOR TYPOGRAPHICAL ERRORS I DISCERNED:

p. 10, line 195- ‘to’ is missing
p. 15, line 303-304, missing ‘in’
p. 15, line 320, ‘resistin’ is misspelled

These typographical errors have been corrected in the manuscript.

Referee #2

1. P2, L36 - Increased FMD by the LF diet was ‘related to’ increased adiponectin….Would prefer the phrase ‘associated with’ here and throughout manuscript to underscore that this is an association rather than a cause and effect scenario.

This is an important point raised by the reviewer. We have made modifications throughout the manuscript to clarify that increased FMD was “associated with” increased adiponectin (to underscore that this is an association and not a cause-effect scenario) (lines 34, 227, 229, 245, 302).

2. Why was there such a discrepancy between the dietary fiber content between the low and high fat groups? Do the authors believe that this may have contributed to changes in arterial function?

This is an excellent point. It is true that the fiber content of the LF diet (30 g/d) was much greater than that of the HF diet (11 g/d). Recent findings by Rallidis et al. (Am J Clin Nutr. 2009;90:263-8) indicate that increasing fiber consumption may augment FMD in obese volunteers. As such, this discrepancy in dietary fiber content between the two groups may have contributed to the changes in FMD observed. This point has been added to the discussion section of the manuscript.
3. Were the FMD measurements taken on day 1 used as a covariate to examine changes in arterial function at the 6 week period?

As recommend, we have performed additional statistical analyses of week 6 FMD values using baseline FMD values as a covariate. However, the results of this additional statistical test do not impact the results currently presented in the manuscript.

4. Were changes in plasma lipid profile associated with FMD outcomes? This should be addressed within the discussion.

No significant associations were noted between plasma lipids and FMD. This point has been included in the results section of the manuscript (line 236).

Referee #3

1. Diet composition, energy to protein ratio, total cholesterol concentration in diet or its daily intake should be provided.

This is an excellent suggestion. As such, details regarding dietary composition (i.e. specific foods consumed at each meal) have been added to Table 1. In addition, values for protein-energy ratio and cholesterol content have been added to Table 1.

2. The experiment was carried out to compare the treatment effect with its corresponding baseline. Please explain if the effect is solely due to the treatment when no placebo is included.

This is a valid point raised by the reviewer. It is true that the study is limited in that no control group was employed in the experimental design. A discussion of this limitation has been added to the manuscript (lines 339-343).

3. Please justify the reason for choosing time within subjects as a factor, which may make experimental error smaller without a proper rationale.

We agree with the reviewer that using time as the within-subject factor may make the experimental error smaller. We chose to analyze the data in this way (i.e. using a repeated measures ANOVA) due to the small sample size employed. Our limited sample size is an obvious limitation of the trial. A discussion of this apparent limitation, and how it may impact the statistical analysis of the data, has been added to the discussion (lines 334-339).

4. Please also provide the limitation of this study and suggested improvements for future experimental design.

As recommended, a paragraph describing the limitations of the study has been added to the discussion (lines 334-345).