Author's response to reviews

Title: Protein-Enriched Meal Replacements Do Not Adversely Affect Liver, Kidney or Bone Density: an Outpatient Randomized Controlled Trial

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Author's response to reviews: see over
Dear Sirs:

Please find enclosed our revised manuscript which has undergone significant revision in response to Dr. Ganji’s comments. These changes are detailed below:

The title has been changed from “Effects of Protein-Enriched Meal in a Weight Loss Program on Liver, Kidney or Bone: a Randomized Controlled Trial” to “Protein-Enriched Meal Replacements Do Not Adversely Affect Bone Density, Liver or Renal Function: An Outpatient Clinical Trial”.

In addition, the following specific revisions were made:

1) Although they mentioned the procedures for compliance, they failed to mention the level of compliance that the investigators are looking for. Was it 70%, or 80% or 90% compliance with the MR? If they did not measure that should be mentioned the limitation section.

Response to 1): The purpose of the study is now clearly delineated as an examination of the effects of recommending a protein-enriched meal replacement in the setting of weight management. Since the two groups both consumed meal replacements with either a protein supplement or placebo supplement, the degree of compliance would be similar in both groups. Nonetheless, the lack of measuring compliance is now mentioned as a limitation in the discussion as requested (lines 193 to 198).

2) I see they have included the drop out data in the revised manuscript. It was not clear, whether the data associated with the drop out subjects were eliminated in the final analysis? This needs to mentioned in the "statistical analysis" section.

Response to 2): Table 1 now reflects the actual sample size without including the subjects whose data were not included in the analysis.

3) On page 11 (line # 197-200), they is a mention of increased protein excretion SP but no in the HP group. I wish they had commented about this in the discussion. This definitely may not be due to the MR administration. This is an odd observation. Any mix up of samples or mislabeling of specimen? If there is more protein catabolism, protein gets excreted from the kidney? I doubt it. If at all if there is a more protein excretion it has to be in those subjects with high protein intake. Did they assess serum creatinine (or any other marker of renal function) to investigate whether subjects had any kidney dysfunction? Without this, this a major limitation and this should be explicitly indicated. Nonetheless this observation is very odd.
**Response to 3):** No significant differences were found when comparing 12 month mean concentration of serum creatinine, urea nitrogen and urine nitrogen and creatinine clearance within the groups and between the groups. Therefore, we agree that the within group changes observed are a statistical anomaly and not likely a physiologically important observation. The data were provided for completeness since the examination of all the data were performed within as well as between groups. However, we do not think this is a major point of difference between the groups.

4) I am little confused with "weight loss". On page 14, line #261-262 you said "the expected effects of increased weight loss resulting from a high protein diet were not seen in this study". At the bottom of the same page, under conclusion you said ".....HP and Sp diets resulted in the expected weight loss typical of an MR diet plan at 12 months". Can make these 2 statements a bit more clearer. It appears those two statements contradict. Not sure how those two sentences are complimentary.

**Response to 4):** In previous studies from our group and others high protein diets lead to increased weight loss over one year by comparison to usual protein intake. These diets went to special lengths to increase total protein intake. In the present study, we measured the impact of recommending a protein-enriched shake in a practical application of a weight management strategy. We did not include a control group, because many previous studies have demonstrated that meal replacements lead to weight loss compared to a control diet recommending reduced intake of favorite foods. The two test diet plans here including either a protein-enriched shake or a placebo-enriched shake with carbohydrate that were isocaloric showed the same amount of weight loss. We believe this is clearly expressed in the revised manuscript.

5) It is interesting to see there is some beneficial effects with the MR in lipid profile at 3 or 6 month level depending on the type of lipid. Authors should comment on this. Perhaps it may be due to the fact that participants did not adhere to the diet plan after first 3 or 6 months. Studies have shown after 3 to 6 months the compliance with the study procedures goes down. This is a possibility but not sure how likely in your study. This may also likely explanation for lack of effect on other biochemical parameters. This should be mentioned in the discussion and put under limitation

**Response to 5):** The following limitation statement was added to the discussion on lines 195 to 198: “Compliance with diets is known to decrease on an outpatient basis and is an unmeasured effect that may account for the lack of findings of adverse events in our study. Nonetheless, this was a practical applied test of the issue as it would be encountered in people undertaking a weight management regimen.”

6) What is the grams of protein per kg of body weight. This should also be given in addition to the intake per kg of lean body mass. I would expect the protein in MR per kg body weight would be much less. My guess is that the protein content in the HP group would be around 1.6-1.8 g/kg body weight. If this is correct and this is not a
very high protein diet by any means. Then the the biochemical markers would not be affected that much because our body can easily adjust to fluctuations in macronutrient intake on a daily basis.

Previously we said: "Our MR treatment consisted of administering protein according to Kg of lean body mass (HP: 2.2 grams protein per Kg; SP: 1.1 gms per Kg of lean body mass). We did not consider total weight because of variation in body fat mass. Our population was obese by definition and most likely the protein administered per Kg would be low because of excess body fat in our population."

Reviewer's comment: I see the rational but the protein recommendations are based on body weight as per the Institute of Medicine (0.8 g/kg body weight). My interpretation is that the amount of protein given in these two treatments is not that much based on the per kg body weight. If they do not want to give protein amount per kg body weight then they have to give a justification that the protein amount given is really high in protein for those participants. There is so much not so sound information is floating around, people might interpret this as a green signal to go and indulge in high protein diet.

We have now added a significant discussion of this issue as follows (line 270-285):

"The Institute of Medicine (IOM) of the National Academy of Sciences (27) has set acceptable macronutrient distribution ranges for carbohydrate (45%-65% of energy), protein (10%-35% of energy), and fat (20%-35% of energy; limit saturated and trans fats). These proportions provide a range broad enough to cover the macronutrient needs of most active individuals, but specific carbohydrate and protein recommendations are also typically made based on a g/kg body weight formula. These ranges are 5 to 12 g of carbohydrate/kg body weight and 1.2 to 1.8 g/kg body weight for protein depending on the level of physical activity. Clearly both the HP and SP group dietary intakes of protein were within this recommended range for protein intake. Therefore, our research can only be applied to structured meal plans using protein-enriched shakes for their ability to increase satiety and should not be interpreted as a blanket endorsement of very high protein diets popular with some athletes exceeding the IOM recommendations by including pure protein supplements, high fat animal meats or other sources of organic acids and hidden fat which could adversely affect liver function, renal function, or bone density."

Reviewer's Comment: Overall, the explanation was inadequate. There were several limitations in this study and they need to be explicitly explained. Given the limitations of the study, the conclusions were very strong.

Overall Response: We have significantly changed our paper and hope that these changes meet with approval from the reviewer.