Author’s response to reviews

Title: Effects of lifestyle changes including physical activity and specific dietary intervention in the management of patients with chronic hepatitis C

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Author's response to reviews: see over
Effects of lifestyle changes including physical activity and specific dietary intervention in the management of patients with chronic hepatitis C

Reviewer: Dungeng Peng

1. It seems that the major purpose was to compare the effect of these two diets according to the title. But in the context, overall, most of the comparisons were only done within the group with the same diet. In other words, I wonder if the authors had no intention to compare the effects between the two diets. Otherwise, they may need change the title to avoid confusion.

The aim of the study was to evaluate the two diets (prudent diet versus low-fat diet) in patients with CHC in terms of reducing insulin resistance, obesity, hepatic steatosis and fibrosis. We have added in the text and tables differences between the two diets.

We have added a paragraph comparing the diets on page 5.

2. Some part of the manuscript need to be checked carefully and rewritten. For example, starting from the third paragraph on page 8, the authors define the group A as the subgroup with weight gain at the beginning. And then, the authors suddenly chose the subgroup with weight loss less than 5% as group A to describe the details; and so on.

We have read over and corrected the article; we have rewritten the paragraph related to weight loss (page 7).

3. The authors should point out what the exact comparison is, when they marked out the significance with symbols. Some of them were not well defined in the table and it is even harder to find them in the context. For instance, in table 1, the authors showed the significance between the groups, which the reviewer assumed that between the genders in the same diet group, but nowhere had mentioned this information in the context.

We have added to Table 1 statistical significance between the two groups
In Table 2 we have noted abbreviations and statistical significance between the 2 diets at 12 months
In Table 3 we have noted Abbreviations and statistical significance between the 2 diets in terms of lipid profile changes
In Table 4 and 5 we have presented Abbreviations
In table 6, 7 we have written abbreviations and number of patients in each subgroup

4. an independent expert should check the statistics.

In this short time we have found no another statistician to verify data but this can be done.
Reviewer: Amedeo Lonardo

MAJOR
1. Title – I feel the definition “Prudent diet” should be replaced in the title and throughout the manuscript by something much more specific. I note the Authors use “normoglucidic diet” in the Discussion. Could prudent diet become a low-calorie normoglucidic diet? Moreover, I note the title fails to name physical activity and it should. Both these changes would make the title mirror more accurately the content of the study making its reading more attractive to those potentially interested in going beyond the title alone.

   We have changed the title „Effects of lifestyle changes including physical activity and specific dietary intervention in the management of patients with chronic hepatitis C”. We have defined on page 5 prudent diet as hypocaloric normoglucidic, normolipidic, normoproteic diet.

Summary – It quite unclear whether the aim of the study was weight control alone as opposed to liver histology outcome (fibrosis) given that both aims are named in different sections of the summary though histological analysis was seemingly not included in the study design. I suggest to be more consistent with the statement contained in the manuscript “reducing insulin resistance and hepatic steatosis and fibrosis by nutritional intervention”.

The aim of the study was to evaluate the two diets (prudent diet versus low-fat diet) in patients with CHC in terms of reducing insulin resistance, obesity, hepatic steatosis and fibrosis. Histological examination obtained by liver biopsy (PBH) is the gold standard for the diagnosis of hepatic steatosis and fibrosis. PBH has been performed in 49 patients who were to receive treatment with interferon and ribavirin, but in Romania approval for interferon file lasts very long so (this time) these patients have been followed, applying the lifestyle improvement through diet (PD or LFD) and physical activity; the time the file has been approved and treatment has begun patients have been excluded from follow-up because interferon and ribavirin therapy is associated with metabolic changes (glucoregulation disorders, hypertriglyceridemia), reduced appetite, anorexia.

Since we had PBH results only from 49 patients and at baseline we have not included the data in the article.

3. The conclusion “Nutritional therapy should be an essential component of care for people infected with hepatitis C because this medical condition through its associated entities should be considered as a metabolic disease” sounds more like the background than the conclusion and should be deleted. “Present study establishes the positive impact of an educational program in management of patients with hepatitis C.”

   This conclusion has been erased

4. Do the Authors really believe that HCV infection should be managed by lifestyle changes alone without administering antiviral schedules?

   Lifestyle improvement should be an integral part of the treatment of patients with chronic hepatitis C and does not exclude antiviral therapy.

5. Highlight that compliance was significantly different between the 2 diets.

   We have added to the Discussions differences in patient’s adherence to the 2 diets.
6. Introduction – The concept of HCV infection as a metabolic disorder may be supported better by quoting specific references, including; (Lonardo A, et al. Hepatitis C and cardiovascular risk: facts and controversies Hot Topics In Viral Hepatitis, Issue 24, 2012, ISSN 1973-9648.)
We have added references

7. Study design – It is unclear to this Reviewer whether the Authors are proposing lifestyle changes as the only treatment option in those with HCV infection. Please address the issue that lifestyle changes are deemed to additive to proper antiviral treatment schedules which remain the standard of care (Adinolfi LE, et al. Expert Opin Pharmacother. 2011;12:2215-34.)
We have added to the Discussions that antiviral treatment is the standard of care and have added references (Adinolfi LE, et al. Expert Opin Pharmacother. 2011;12:2215-34).

8. It is critical to describe accurately criteria for inclusion and exclusion.
Inclusion and exclusion criteria have been detailed on page 3

9. Moreover, the technique followed to randomize patients (e.g. sealed envelopes; randomization list; telephone call to a randomization center) should be described.
For randomization we used a computer software - added on page 5

10. It would be of interest if the Authors might be willing to discuss better why the wanted to compare these 2 diets and, shortly, what they differ in.
We have added to the Material and methods (paragraph) a comment on diets and how they are different.

11 “The serum concentrations of adiponectin, leptin, resistin, TNF alpha, IL6 were measured by enzyme-linked immunosorbent assay (ELISA). Samples were prepared at the appropriate dilutions and paired samples were assayed together according to the instructions of the manufacturers. The intra- and inter-assay coefficients of variation for resistin, leptin, and adiponectin were: <4% and <7%, <8% and <10%, <5% and <7%, respectively. Insulin, peptide C and citokines as adiponectin, leptin, resistin, interleukin-6 (IL-6), tumor necrosis factor (TNF-alpha) were measured at baseline and 12 months.”
Have been erased/deleted

12. Hepatic steatosis (HS) was evaluated using ultrasonographic criteria –Please quote recent semiquantitative indices used to assess steatosis which have been validated against histology (Ballestri S, Liver Int. 2012;32:1242-52.) and proven useful in the specific settings of lifestyle interventions (Scaglioni F, Clin Res Hepatol Gastroenterol. 2012 Dec 26. ).
We have added these data to the Material and methods (paragraph) (pages 4-5)

13. Discussion - The Authors might be willing to discuss that the prevalence of the Metabolic syndrome in their study appears to be higher than reported in previous european studies (reviewed in Adinolfi LE, et al. Expert Opin Pharmacother. 2011;12:2215-34.). Moreover, at variance with data from the feneral population, the prevalence of MetS appears to be more elevated in men. Does this imply a particular selection of cases?
We have added to the Discussions; indeed inclusion of patients with BMI over 25 kg/m2
have resulted in a higher prevalence of metabolic syndrome; we have added that the
prevalence of MetS at the end of follow-up decreased in both groups.

English – The study has several spelling and grammar mistakes and definitely
needs editing by a native English.
Article has been read and corrected by a person with language skills;

MINOR
were associated with improvement of ALT levels[,] and steatosis [(Ueno,
Andersen)].--> Add the references were missing; use consecutive numbers
rather than the Authors’ names
We have corrected

Tables 5. and 6. “Hepatic function”--- Liver tests
We have corrected

Tables 6. And 7. These tables are quite difficult to follow. Would it be possible to
improve/delete them ? Consider putting them as an appendix.
We have added the number of people for each group; it can be moved to appendix

Reviewer: Prachi Sharma
We have corrected the highlighted mistakes.