

July 10, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name:11890-review.doc).

Title: Impact of enteral nutrition on energy metabolism in patients with Crohn's disease

Author: Jie Zhao, Jian-Ning Dong, Jian-Feng Gong, Hong-Gang Wang, Yi Li, Liang Zhang, Lu-Gen Zuo, Yun Feng, Li-Li Gu, Ning Li, Jie-Shou Li, Wei-Ming Zhu

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The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer.

Reviewer by 02530212

Reviewer: I think this article is good study about Enteral nutritin is effective in remission induction of active Crohn's disease, and also in impact of EN on the body metabolism and composition of CD patients.

Response: Thank you very much for your remarks! We really appreciate your recognition of our manuscript.

Reviewer by 02531403

Reviewer: I read with interest the manuscript "The impact of enteral nutrition on body composition and energy metabolism in patients with Crohn's disease" written by

Zhao and coworkers. It is an interesting study, although the number of the patients enrolled is small, as stated by the authors. However, I have some major remarks:

Major remarks - it could be useful to know how the ileal involvement was distributed along the three groups, to better understand how the disease extension could influence the outcome - it could be also useful to know the duration of the disease, to better understand how the long duration of the disease could influence again the outcome.

Response: Thank you very much for your recognition of our manuscript and your constructive suggestions which could improve the quality of this manuscript! We have supplemented the ileal involvement distribution and duration of the disease of the three groups in the Results section of the manuscript (table 1). There were no significant differences in ileal involvement distribution and duration of the disease among the three groups ($P > 0.05$).

Reviewer: Why further parameters with a leading role in the onset of malnutrition in IBD patients, as vitamins and minerals, were not considered baseline and after EN?

Response: Thank you very much for your good suggestions! The reason why further parameters with a leading role in the onset of malnutrition in CD patients, such as vitamins and minerals, were not considered as a baseline and after EN was because this article was aimed at observing the changes in energy metabolism of the same CD patient, the changes in body composition was secondary compared with metabolism. And we have supplemented the vitamins (VitD, evaluated by 25(OH)D₃) and minerals as you proposed.

Reviewer: Minor remarks-which was the steroid-free (and eventually the immunosuppressant/biologic-free) period before the inclusion of the patients in the study?

Response: Thank you again for your good questions! The steroid-free (and eventually the immunosuppressant/biologic-free) period before the inclusion of the patients in the study meant that the patients were free from steroid, immunosuppressant/biologics for one month before EN support. This was done to

exclude the influence of these drugs on the study results; and in particular, to exclude the impact of steroids on metabolism.

Reviewer by 00036961

1. There are numerous grammatical errors throughout the manuscript. It needs to be very thoroughly proof (copy) read to be considered for publication. I have included a few specific ones within this review but there are many more.

Response: Thank you very much for your professional and constructive suggestions! We have submitted our manuscript to a professional English language editing company to make use of a copyediting service. The grammatical errors in this article have been corrected.

2. Were these at home or in-patients for the duration of the study? What evidence can be provided that subjects were compliant with the treatment and received exclusive enteral nutrition? Were there any complications related to 4 weeks of naso-gastric tube feeding? It must be very difficult indeed to only have NG feeding (and no food) for 4 weeks when you have inactive disease!

Response: Thank you for your good questions! The patients included were all in-patients for the duration of the study. We could not provide direct evidence to prove that the subjects were compliant with the treatment and received exclusive enteral nutrition. However, the articles about EN in the treatment of CD that we have previously published (i.e., Feng Y, Li Y, Mei S, et al. Exclusive enteral nutrition ameliorates mesenteric adipose tissue alterations in patients with active Crohn's disease. Clin Nutr, 2013; Guo Z, Wu R, Zhu W, et al. Effect of exclusive enteral nutrition on health-related quality of life for adults with active Crohn's disease. Nutr Clin Pract, 2013,28(4):499-505.) could prove this. During the 4 weeks of nasogastric tube feeding, some patients had symptoms of abdominal distention, diarrhea and throat discomfort.

We overcame these difficulties by appropriately adjusting the quantity, using the infusing pump to warm up the nutrient fluid, taking some oral throat tablets, changing the feeding tube into another nasal cavity and offering psychological comfort. Yes, it was very difficult to only have NG feeding (and no food) for 4 weeks for the CD patients in remission. We supported and encouraged their involvement in the study by telling them that EN through nasogastric tubes could not only improve their nutritional status but also maintain their remission.

3. Reference for 15 is for anorexia nervosa which is a different entity to anorexia from other physical (inflammatory / malignant etc) conditions.

Response: We had not realized the mistake of anorexia nervosa with anorexia from other physical (inflammatory/malignant etc) conditions until you pointed it out. We have deleted the sentence as same as the reference that had little relation to the article. Thank you very much!

4. What was the target study size (ie how many patients to recruit) and why?

Response: Thank you for your questions! The target study size of patients in this study was approximately 20 per group because the inclusion criteria of this study were relatively strict. The time length of 4 weeks, the same enteral nutrition formula, nasogastric tube, no other drugs or operation all contributed to the smaller sample size.

5. I assume the REE in figure 1 is calculated by the 'Schofield equation'? Its not at all from the results (or indeed methodology) that this was used. The legend from this figure mentions how a p value was calculated but its result is not included.

Response: Thank you for your suggestions! We are sorry that we have not made it clear. The REE in Figure 1 was the measured REE, not the predicted REE by the 'Schofield equation'. And we have added explanations to make it clear in the manuscript. Compared to the H-B equation (variables: age, weight, height and gender), the accuracy of the Schofield equation (variables: age, weight and gender) was relatively lower. So we used the H-B equation instead of the Schofield equation as the predicted REE to compare

with the measured REE. We have supplemented the P value into the figures.

6. I don't understand what 'experiential 25cal/Kg/day' means - it needs to be explained early on in the paper.

Response: We are sorry that we did not use the appropriate word and that it was confusing. We have changed the word 'experiential' to 'experimental' according to your suggestion and added explanations early in the 'assessment' part of the manuscript. Thank you for your good suggestions!

7. Were none of these 61 patients on any treatment for their Crohn's? I would find this highly unlikely.

Response: Thank you for your doubt and questions! Yes, none of these 61 patients were on any treatment for their Crohn's. We had an IBD center at the Jingling hospital, and we could treat approximately 600 to 800 CD patients during one year. We collected sixty-one patients for our study according to the strict criteria. Most of the CD patients included early on were eventually excluded because they could not tolerate the enteral nutrition, EN could not relieve the symptoms or the symptoms became worse. The remaining sixty-one patients were just twenty percent of all the patients enrolled early and they indeed had no other treatments.

8. What are 'basic diseases' (inclusion criteria)? What does 'TPF' stand for (treatment section)?

Response: We are sorry that we did not explain 'basic diseases' and 'TPF' (inclusion criteria). We have changed 'basic diseases' to 'systemic diseases' (such as hypertension, diabetes or cancer, etc). The word 'TPF' meant one type of intact-protein nutrition (bottled preparations; net content of a 500 mL bottle included 20 g of proteins, 19.5 g of fat, 61.5 g of carbohydrate, etc. 1 mL TPF provides 1 kcal of energy). We have added these explanations to the 'inclusion criteria'.

9. How can the BMI of all patients have increased significantly ($p = 0.017$) where

there is virtually no difference in the 3 groups for this entity in table 1?

Response: We are sorry that we made a mistake when analyzing the BMI data before and after EN support in group A. We incorrectly used the unpaired-samples *t* test instead of the paired-samples *t* test. We have corrected the mistake in the article, and we apologize again for our mistake. We are so sorry for this mistake!

10. Why is some of the analysis (ie CRP, ESR and CDAI) presented with groups A and B combined where they are separated in table 1? This produces confusion - the authors should present all data the same (could be by adding an extra column for A+ B into table 1 and separating the others out later on. Table 1 also needs some explanation within the legend as to what 'Group A, etc are.

Response: Thank you very much for your suggestions. We have made the change by adding the data of CRP, ESR and CDAI of patients in group A and group B into table 3 according to your suggestions. We have added some explanations about group A, group B and group C in the legend.

11. Did the EN make may difference? Couldn't it be said that the 50% of those with initially active disease just settled during the study independently of the NG tube? Is it the fact that the disease settled rather than the EN working that made the changes that have been documented?

Response: Thank you very much for your excellent comment and question! We could not prove the fact that EN, rather than the disease, made the documented changes. We could not use active CD patients without EN or any other drug treatment as a control group because of ethical concerns. Many studies have indicated that EN is effective at inducing remission of CD. Studies have shown that EN had similar efficacy as corticosteroids in children with CD (Yamamoto T. Nutrition and diet in inflammatory bowel disease. Curr Opin Gastroenterol. 2013. 29(2): 216-21.).

12. The words 'body mass increased overall fat mass' in the 'Body composition' section just re-iterate the earlier part of the sentence and don't seem to be needed.

Response: Thanks for your good suggestions. We have deleted the sentence 'body mass increased overall fat mass' which was not needed in the article.

13. The discussion is conventionally started with an overview of the study and the key findings rather than discussing any potential short falling of the work. Likewise the concluding sentence is not formatted in the conventional way ie outlining the key aspect(s) of the work and proposing the way forward.

Response: Thank you again for your excellent suggestions and advice. We have deleted the content discussing any potential shortcomings of the work and made the discussion conventional by starting with an overview of the study and briefly discussing the key findings. We have also adjusted the concluding sentence to outline the key aspects of the work.

14. Discussion - 'But unlike from traditional researches' and 'Increased REE increases yet' within the discussion are examples of grammatical problems. I assume 'experiential 25cal...' should be 'experimental'. Also, my interpretation of the data is that there is no significant effect on BMI (see above). Finally, I do not understand the last sentence - what is 'dynamic monitoring REE'? and it is not this that will satisfy the nutritional requirements it may assess / measure them but not provide the calories.

Response: We are sorry that we had multiple grammatical errors that made the manuscript confusing. We have submitted our manuscript to an English editing service to correct these mistakes. We have changed the word 'experiential' to 'experimental' according to your suggestions. We changed the unsuited word 'dynamic monitoring REE' into 'timing detection of the REE'. We have also changed the inappropriate phrase 'satisfy the nutritional requirements' into 'assess the nutritional requirements' to make the sentence more specific.

Thank you again for all of your professional comment and suggestions.

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

Weiming Zhu, PhD

Department of General Surgery, Jinling Hospital

Medical School of Nanjing University

NO.305 East Zhongshan Rd, Nanjing 210002, People's Republic of China.

Fax:+008680863736

E-mail:zhuweimingtg@163.com