Author's response to reviews

Title: Effectiveness of Chinese herbal medicine for impaired glucose tolerance

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Author's response to reviews: see over
Re: BMC Manuscript 1150750098749884 - Effectiveness of Chinese herbal medicine for impaired glucose tolerance

Dear Carmela Quidoles

Thank you for your reviewers’ comments. We greatly appreciated the reviewers’ constructive comments and have implemented their recommendations. We believe the manuscript has been strengthened as a result of these changes.

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Reviewer 1

1. The Abstract should include more information about the trial, such as outcomes, trial design including blinding and significant results.

   Thank you. We have amended the Abstract as suggested.

2. There are 3 primary outcomes in this trial (Methods: Outcome Measures). Thus, there would be a multiple testing problem. Correction for the multiple comparisons must be considered. Otherwise, clarify the primary end point.

   Thank you for your suggestion. We have amended the paper and noted that as all three tests (FBG, 2hr OGTT and HbA1c) are highly correlated to each other, the impact of multiple testing issues on the p value is much reduced. See the 3rd sentence under Outcome Measures.

Minor Essential Revisions

Methods

A. Patient and Recruitment

1. The second line of ‘Patient and Recruitment’ in Methods section, the definition of mild type 2 diabetes is confusing (i.e. 2 hr plasma glucose load level # 7.8 < 11.1).

   We have made amendments to the second sentence under ‘Patient and Recruitment’ to clarify this definition.
2. For randomization, what is the exact meaning of ‘simple block’? Please describe the exact block size and the randomization methods such as computer generated or envelope method.

Thank you we have now described exactly how randomisation was generated, please see the first sentence in the third paragraph under ‘Patient and Recruitment’.

3. Describe the allocation ratio planned and who were blinded.

These details are now provided, please see the first sentence in the third paragraph under ‘Patient and Recruitment’.

4. Selection criteria should be explained in detail.

These are now explained, please see the third sentence under ‘Patient and Recruitment’.

B. Herbal Intervention and Treatment Schedules

1. How many capsules were instructed to be administered?

Amended in the 3rd paragraph under “Herbal Intervention and Treatment Schedules’ to include the dosage of 3 capsules 3 times a day.

C. Outcome Measures

1. Obesity itself is a vague parameter for the outcome measurement. Please clarify the endpoint ‘obesity’, such as weight and BMI.

Endpoint now clarified as BMI, see the last sentence of the 1st paragraph under ‘Outcome Measures’.

D. Statistical Analyses

1. At statistical analyses section, the follow up period is describe as 8 weeks, however, it needs to be expressed in advance in ‘Methods’ section.

This statement is now included under the “Herbal Intervention and Treatment Schedules” heading within the Methods section.

Results

A. Fasting blood glucose

1. Explain what variables were adjusted for the analysis.

Please see amendment to the 1st sentence under the ‘Results’ section.

2. The values of fasting blood glucose in two groups do not match with the numbers in Table 3.

Figures in text amended to reflect the correct figures from Table 3.

3. For the paragraph, that describes for the 2hr post prandial blood glucose levels, ‘Table 2’ should be ‘Table 3’.

Amended.
B. Insulin

1. In the abstract conclusions, it is explained that the insulin measures were improved, however, in Table 3, only ‘insulin’ and index for insulin resistance (HOMA-IR) differences are statistically significant. The detail of the result will be helpful to understand while reading the abstract.

   It is only serum insulin that showed statistical significance, I have amended the ‘Results’ section of the Abstract to make this clearer.

2. It is expressed that ‘shown in Table 2’, but, in Table 2, there are no figures of 22.1±25.9 and 11.6±5.5 for mean levels of insulin item.

   The table reference should have been Table 3, now corrected.

C. Cholesterol

1. The p-value of between groups might be only the one, however, two p-values are shown in the manuscript. etc.

   Thank you we have made some amendments and hopefully clarified the meaning.

Reviewer’s report: Gurjeet Birdee

Major Compulsory Revisions:

1. Methods: First paragraph, defining “mild” diabetes. Recognizing that the authors have defined mild diabetes for the purposes of the study, it would be helpful to state what “controlled” diabetes was defined as. I do not think the temporal description “early” is appropriate (appears in abstract and conclusion), as diabetes for 5 years is significant (especially since many people are diabetic for several years prior to diagnosis).

   Thank you for your suggestion. We agree, and have now made amendments and changed “mild” to “controlled” throughout the manuscript.

2. Methods: 4th paragraph, Herbal intervention: More information should be given regarding the herb. Where was this herb produced? If by a company, which company? How was it manufactured, and how was quality assured?

   The following information has been incorporated into the second paragraph under ‘Herbal Intervention and Treatment Schedules’:

   Both the Jiangtang Xiaozhi Capsule and the placebo were manufactured in China by Tianjin Zhongxin Pharmaceutical Group Corporation Ltd, a pharmaceutical manufacturer in China with an Australian Good Manufacturing Practice (GMP) license issued by the Therapeutic Goods Administration (TGA). Specnuezhenide from Nu Zhen Zhi (Ligustrum lucidum Ait.), a key herb in the formula has been selected as the biomaker of the formula for the quality assurance purpose (as required in China). Specnuezhenide was quantified (>4.77 mg per capsule) using HPLC method according to 2010 Edition of the Chinese Pharmacopeia. In addition, fingerprinting of the formula was conducted using thin layer chromatography (TLC) to ensure batch-to-batch consistency.
3. Methods: 4th paragraph: Patients were asked not to alter their diet or exercise and this was monitored. Since this was monitored, and this is an important confounder to a diabetes study, please report this data if available in results section.

Results can now be found in the “Results” section under “Other Measures”. We do have statistical data on this but given the limited word count we chose not to include this level of detail, but can be made available on request.

4. Methods, statistical analysis: Glycemic control can be measured by fasting blood glucose or hemoglobin A1c. It is not stated in the methods if one measure was decided as the primary outcome of the study, or both.

We have amended the paper and noted that as all three tests (FBG, 2hr OGTT and HbA1c) are highly correlated to each other, the impact of multiple testing issues on the p value is much reduced. See the 3rd sentence under Outcome Measures.

5. Results: Please include differences in BMI and HOMA in table 1. These appear to be different between treatment groups.

BMI is included and a reference made to the difference in Paragraph 2 of the Results section. A sentence has also been added on HOMA.

6. Discussion: Please not the large difference in standard deviation for insulin levels in the placebo group. Discuss why the variance. How will this affect your interpretation of the results in your conclusion?

Thank you for the suggestion. We have included a paragraph within the results section explaining how the standard deviation was examined.

Minor Essential Revisions:

1. Abstract: Methods section: second sentence incomplete, “At baseline and outcome a well being…. Amended.

2. Abstract: Results, 2nd sentence with two periods. Amended.

3. Abstract: Results, put in insulin resistance data if room. Amended

Discretionary Revisions

1. Introduction, 2nd paragraph: Authors use the term, “strong anecdotal”. I have never found anecdotal evidence to be strong. That is why we do clinical trials. Amended

2. Introduction, 2nd paragraph: It would be helpful to state if the meta-analysis included or did not include the Chinese herb Jiangtang Xiaozhi. Thank for the suggestion. The meta-analysis did not include Jiangtang Xiaozhi (only Chinese herbal medicine trials for impaired glucose tolerance or impaired fasting blood glucose as opposed to diabetes were included in the meta-analysis).