PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Low Glycemic Index Diet to improve Glycemic Control and Cardiovascular Disease in Type 2 Diabetes: design and methods for a randomized controlled clinical trial
AUTHORS	Chiavaroli, Laura; Mirrahimi, Arash; Ireland, Christopher; Mitchell, Sandra; Sahye-Pudaruth, Sandhya; Coveney, Judy; Olowoyeye, Omodele; Maraj, Tishan; Patel, Darshna; de Souza, Russell; Augustin, Livia; Bashyam, Balachandran; Blanco Mejia, Sonia; Nishi, Stephanie; Leiter, Lawrence; Josse, Robert; McKeown-Eyssen, Gail; Moody, Alan; Berger, Alan; Kendall, Cyril; Sievenpiper, John; Jenkins, David

VERSION 1 - REVIEW

REVIEWER	Honghui Guo Department of Nutrition, Henry Fok School of Food Science and Engineering, Shaoguan University, Daxue Road 288, Shaoguan, 512005, Guangdong Province, China.
REVIEW RETURNED	25-Apr-2016

GENERAL COMMENTS	The manuscript offers a comprehensive listing of study design and data analyses. It can be accepted for publication in this journal as it is.

REVIEWER	Mirela Jobim de Azevedo Universidade Federal do Rio Grande do Sul (UFRGS) Porto Alegre, RS Brazil
REVIEW RETURNED	01-May-2016

GENERAL COMMENTS	The study protocol entitled “Low Glycemic Index Diet to improve Glycemic Control and Cardiovascular Disease in Type 2 Diabetes: design and methods for a randomized controlled clinical trial” is an original, well written and detailed manuscript. Its design is robust and certainly the main objectives of this study will be accomplished. However, some aspects could be clear. The following comments did not reduce the relevance of this project but are aimed to improve its results, and possible, its external validity. 1. Inclusion criteria: A baseline BMI was not an inclusion criteria, and could be an important aspect in this trial count. First, in general there is a limit for weigh when using the Philips 3-Tesla whole body scanner, even tough it is a high limit (550 lbs). Moreover, patients who have more than 40 mg/Kg can have specific metabolic

	abnormalities that could constitute a confusion factor. 2. Exercise should be evaluated not only at baseline. Exercise can change insulin resistance and body weight. Furthermore, what tool will be used to evaluate exercise? 3. Anti-diabetic oral agents: during a long-term follow up study the need for using new anti-diabetic agents will certainly occur. How the researchers intend to deal with the introduction of agents that can increase (sulphonilureas) or reduce (GLP1 agonists, SGLT2 inhibitors) body weight? 4. Anti-hypertensive medications: considering that more than 80% of type 2 diabetic patients are hypertensive and that a strict blood pressure control can prevent and delay both, micro and macrovascular, chronic diabetic complications, blood pressure values during the study should be discussed in more detail (as well as the use of anti-hipertensive medication). A goal for blood pressure could be determined (as a cutoff for HbA1c was adopted) in order to maintain the blood pressure similar between the two intervention groups. 5. According recent recommendations, the goals for glucose control should be individualized. Therefore, its not clear why only when the HbA1c exceeds 8.5% participants will be referred to the family physician. 6. Appendix on Dietary Instruction -Sheet intervention diets, describes specific foods in both High Cereal Fiber Diet and Low GI diet. However, it would be important to to know the macronutrient composition of these diets, in terms of protein, carbohydrates, and lipids. More important, would be knowing the fiber content of both diets (total and soluble fiber) because in general foods rich in fibers also have a low GI (confusion factor). Describing these characteristics using an hypothetical diet, for example a 2000 kcal/day, for a High Cereal Fiber Diet and for a Low GI diet, would allow to the reader a more complete comparison comparison between intervention diets. Additionally the glycemic load could be described.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

The manuscript offers a comprehensive listing of study design and data analyses. It can be accepted for publication in this journal as it is.

Thank you.

Reviewer: 2

The study protocol entitled “Low Glycemic Index Diet to improve Glycemic Control and Cardiovascular Disease in Type 2 Diabetes: design and methods for a randomized controlled clinical trial” is an original, well written and detailed manuscript. Its design is robust and certainly the main objectives of this study will be accomplished.

However, some aspects could be clear. The following comments did not reduce the relevance of this

project but are aimed to improve its results, and possible, its external validity.

1. Inclusion criteria: A baseline BMI was not an inclusion criteria, and could be an important aspect in this trial count. First, in general there is a limit for weigh when using the Philips 3-Tesla whole body scanner, even tough it is a high limit (550 lbs). Moreover, patients who have more than 40 mg/Kg can have specific metabolic abnormalities that could constitute a confusion factor.

Thank you. Body size will be included in sensitivity analyses as a covariate expressed as waist circumference (please see page 14 of resubmission with track changes).

2. Exercise should be evaluated not only at baseline. Exercise can change insulin resistance and body weight. Furthermore, what tool will be used to evaluate exercise?

Thank you. Participants are encouraged to maintain their exercise habits consistent throughout the study, at the same level as they had at entry. At each clinic visit, they are asked about their exercise habits and if these have changed. At a later stage we will attempt to translate this leisure exercise into METs since as you say, exercise can influence insulin resistance. However, from past studies, we anticipate no significant change in exercise habits. We have added “The consistency of exercise is checked at each clinic visit and any deviations recorded.” (please see page 12 of resubmission with track changes).

3. Anti-diabetic oral agents: during a long-term follow up study the need for using new anti-diabetic agents will certainly occur. How the researchers intend to deal with the introduction of agents that can increase (sulphonilureas) or reduce (GLP1 agonists, SGLT2 inhibitors) body weight?

Thank you. We are obtaining detailed record at each visit of the participant’s medications, noting any changes. A sentence to highlight collection of these has been added on page 8 of the resubmission. These data will be analyzed in exploratory analyses to assess treatment differences in medication use over all post-treatment values (please see page 15 of resubmission with track changes). We anticipate that introduction of new medications will occur equally on both treatments.

4. Anti-hypertensive medications: considering that more than 80% of type 2 diabetic patients are hypertensive and that a strict blood pressure control can prevent and delay both, micro and macrovascular, chronic diabetic complications, blood pressure values during the study should be discussed in more detail (as well as the use of anti-hipertensive medication). A goal for blood pressure could be determined (as a cutoff for HbA1c was adopted) in order to maintain the blood pressure similar between the two intervention groups.

Thank you for highlighting this. As mentioned in the manuscript, blood pressure must be below 145/90mmHg at screening in order for participants to be eligible (as outlined in Table 1). As outlined in the protocol, blood glucose and blood pressure were reviewed by study safety committee as necessary, thus we have added a line highlighting this in the manuscript (please see page 16 of the resubmission with track changes). Our experience from past studies is that blood pressure falls on both arms of the study. Additionally, blood pressure changes between treatments will be analyzed as a secondary outcome (as outlined on page 11 of the resubmission with track changes).

5. According recent recommendations, the goals for glucose control should be individualized. Therefore, its not clear why only when the HbA1c exceeds 8.5% participants will be referred to the family physician.

Thank you. 8.5% is considered the upper threshold of recommended target for glycemic control according to various diabetes guidelines. We have included a sentence to highlight this (please see

page 16 in resubmission with track changes). We have not attempted to individualize patient cut-points for HbA1c, although we acknowledge that accounting for these differences, with differences in treatment strategies, is good clinical practice. However, we have noted in previous studies that the participants who volunteer for our trials are usually remarkably well controlled in terms of blood pressure and blood lipids. Hence, for simplicity we have maintained uniform cut-points for all. The participant's physician is free to change medications as they deem best, however it is only when we observe 2 consecutive clinic visits with levels above 8.5% that we contact the participant's physician.

6. Appendix on Dietary Instruction -Sheet intervention diets, describes specific foods in both High Cereal Fiber Diet and Low GI diet. However, it would be important to to know the macronutrient composition of these diets, in terms of protein, carbohydrates, and lipids. More important, would be knowing the fiber content of both diets (total and soluble fiber) because in general foods rich in fibers also have a low GI (confusion factor). Describing these characteristics using an hypothetical diet, for example a 2000 kcal/day, for a High Cereal Fiber Diet and for a Low GI diet, would allow to the reader a more complete comparison comparison between intervention diets. Additionally the glycemic load could be described.

Thank you. We have added as supplemental material (Appendix Table 3) a sample of the nutritional profile for each diet based on our previous 6-month trial with similar interventions, and included this in the text on page 13 of the resubmission with track changes.