Author’s response to reviews

Title: Single-dose acarbose decreased glucose-dependent insulinotropic peptide and glucagon levels in Chinese patients with newly diagnosed type 2 diabetes mellitus after a mixed meal

Authors:

Zhong Chen (rose@medmail.com.cn)
Xiaoying Fu (fuxy126@163.com)
Jian Kuang (jkuang780@sina.com)
Ju Chen (chenjunew@163.com)
Hongmei Chen (ch_may@163.com)
Jianhao Pei (jianhaopei@163.com)
Huazhang Yang (yanggdph@hotmail.com)

Version: 1 Date: 08 Jul 2016

Author’s response to reviews:

Manuscript ID: BEND-D-16-00013

Title: Single-dose acarbose influences incretin levels in Chinese patients with newly diagnosed type 2 diabetes mellitus

Journal: BMC Endocrine Disorders

Response to Reviewers’ comments

Dear Dr. Papatheodorou,

We thank you for your careful consideration of our manuscript. We appreciate your response and overall positive initial feedback, and made modifications to improve the manuscript. After carefully reviewing the comments made by the Reviewers, we have modified the manuscript to improve the presentation of our results and their discussion, therefore providing a more complete context for the research that may be of interest to your readers.

We hope that you will find the revised paper suitable for publication, and we look forward to contributing to your journal. Please do not hesitate to contact us with other questions or concerns regarding the manuscript.
Best regards,

Jian Kuang

Department of Endocrinology, Guangdong General Hospital/Guangdong Academy of Medical Sciences, Guangzhou 510080, Guangdong, China
Tel: +86-13802511168
Fax: +86-21-64085875
E-mail: jkuang780@sina.com

Reviewer #1

Good Review of Literature.

Response: We thank the Reviewer for taking the time to review our manuscript and for his comment.

No Additional comments. Can discuss limitation of your small sized study and possible reason of differences in a little more detail.

Response: We expanded the discussion about the limitations.

Reviewer #2

This very interesting work describes the difference in the influence of acarbose on the metabolic response to carbohydrate ingestion in patients with newly diagnosed type 2 diabetes who had either a standard oral glucose tolerance test or an equivalent carbohydrate intake in a mixed meal. The results are fascinating. Acarbose had an effect after a mixed meal, but not after an OGTT.

Overall the paper is carefully laid out and the authors have clearly done a great deal of important work, but the description of that work needs to be refined in places to make the paper and the specific hypothesis in hand easier for readers to understand. I found the paper very confusing and hard to follow in its current form. I would have the following specific suggestions.

Response: We thank the Reviewer for taking the time to review our manuscript and for his comment. The manuscript was edited according to the suggestions.

In the methods section, the study is referred to as a trial, but it isn't really (at least in its current design). To that end, it is not at all clear why the "control" group are included or necessary. The paper needs to be revised with the control group removed. Controls in a trial are from the same population as the participants who go in to the intervention - whereas the "controls" here are a different population! This suggests a lack of understanding of what a trial actually is, and
suggests that the methodological approach is weak (which it is). The authors need to focus on the population of interest, which is patients with type 2 diabetes, and how their response to MMT was different to their response to OGTT after acarbose. That is not a trial with a control group. The authors should speak with a trialist in their institution to guide the necessary amendments. On the issue of trial methodology, a random number table is a wholly inadequate randomisation procedure.

Response: This preliminary study focused on the study of the potential mechanisms of acarbose in patients with T2DM. Previous studies did not study the effects of acarbose on intestinal hormones (GLP-1 and GIP) and this is why we included controls in the present study. We agree with the reviewer that the present study is not a strict clinical trial, but it is the policy at our hospital that all studies involving a drug or compound have to be formally registered.

About the controls, we agree that they are dissimilar to the patients. Indeed, the age of onset of T2DM is relatively old. These patients were randomly divided into the two groups and these two groups are similar. We selected treatment-naive patients to remove the confounding effects of medication of incretins. Of course, we agree that it would have been better if the controls would have been exactly matched to the patients, but we fear that if we remove them, we will not be able to reflect the effects of acarbose on the patients. As for randomization, we think that a random number table method is enough for a preliminary small sample size study.

We edited the manuscript to take these elements into account.

The rationale for giving acarbose only at the time of the ingestion of the second OGTT/ MMT is not adequately described. Should participants have started it in the period before the repeat test? How quickly does acarbose work? Did they get it before or during the test? This is important information for those seeking to replicate these important studies.

Response: The mechanism of acarbose is that its molecular structure allows it to bind to the α-glycosidase and thus inhibiting food polysaccharides or disaccharides from being decomposed into simple sugars and subsequently absorbed into the bloodstream. Therefore, acarbose can decrease postprandial blood glucose from increasing through decreased intestinal absorption. Since acarbose do not bind covalently to α-glycosidase but competitively, it has to be consumed at the same time as the meal.

Acarbose is seldom absorbed into the bloodstream (<5%), and there is no pharmacokinetic issues such as effective drug concentration in the blood. Acarbose is excreted through the feces.

In this study, healthy control OGTT and MMT did not take acarbose. In diabetic patients, they did not take acarbose during the first OGTT and MMT, but they took it (100 mg) during the second OGTT and MMT. Between the two tests, they did not take acarbose.

This information was added to the manuscript.
Aside from the study design per se being very poor, so is the description of endpoints, which are far too vague. You can only have a specific "primary" endpoint, not several. These considerations don't take away from the undoubted merit and importance of the authors' work, but they do diminish its credibility by giving the impression that they didn't apply methodological rigor.

Response: The main objective of this study was to examine the effect of a single dose of acarbose on intestinal hormones (GLP-1 and GIP) under different types of energy loading (glucose or mixed meal). We edited the endpoints accordingly.

In sections of the discussion, it seems the results are being presented again. Also, the authors haven't focussed adequately on the relevance and significance of their specific findings and this section needs to be more focussed. Why do the authors think that there was a differential ("better") response to acarbose in MMT versus OGTT, when the opposite might have been expected? This needs to be explored further.

Response: We agree with the Reviewer. We added some discussion about this point. It must be noted that our results do not allow reaching other conclusions than the ones we only had, and that further study is necessary. Nevertheless, as discussed in the manuscript, OGTT is a load of pure glucose. Since acarbose delays the hydrolysis of polysaccharides and disaccharides but has no effect on the direct absorption of glucose [DeLeon et al., Diabetes Res Clin Pract 2002], acarbose had no effect on the OGTT parameters. On the other hand, since the mixed meal contained polysaccharides and disaccharides, acarbose delayed their hydrolysis, resulting in changes in incretins. We focused the discussion a little more on this point.

Smaller points are as follows: The first reference in the introduction is weak. Otherwise this section is okay.

Response: We added references to back up this point.

Refer to glucose as glucose, not "PG".

Response: This was corrected.

The figures in figure 2 need to be much more clearly labelled.

Response: We agree with the Reviewer. It was improved.

I found it hard to follow table 2 - it is not well laid out.

Response: We agree with the Reviewer. It was improved.

The conclusions do not adequately describe the overall findings in the paper.

Response: We agree with the Reviewer. The conclusions were toned down.
The paper's title is also vague and misses the point of the specific hypothesis the authors are addressing.

Response: We agree with the Reviewer. It was improved.

Reviewer #3

1. Since incretin and glucagon immunoassays have been an issue of debate (J Diabetes Complications. 2015 Apr;29(3):445-50; Endocr Connect. 2015 Mar;4(1):50-7), the authors should describe cross-reactivity of each assay kit, or cite appropriate references for each kit.

Response: We now provide some references for each kit.

2. The authors should provide reasonable discussions why glucagon secretions were suppressed by acarbose in the MTT group. Normally, glucagon secretion is enhanced by amino acids and fatty acids while it is suppressed by glucose. In this context, glucagon secretion might be enhanced by acarbose after meal ingestions.

Response: Under normal glucose metabolism, glucagon is negatively regulated by glucose. On the other hand, under hypoglycemia, the body secretes glucagon to increase the blood glucose levels to ensure an appropriate energy supply. Because of insulin resistance and pancreas islet dysfunction in T2DM, the high levels of glucose are not properly used by the cells. Therefore, as a protection mechanism, the body will secrete more glucagon. About GLP-1, we think that the possible reason is that postprandial glucose decreased the stimulation of insulin, and the insulin level is a well known modulation mechanism of glucagon secretion. When the glucose levels didnot reach the threshold condition of hypoglycemia, the relative decrease of insulin secretion led to decrease of glucagon. Another possible mechanism is that the regulation of glucose by GIP and GLP-1 include the stimulation of the secretion of insulin and the inhibition of the secretion of glucagon, and is glucose-dependent. The insulin secretion stimulation is increased following increased glucose levels. Therefore, a single dose of acarbose could delay the postprandial glucose increase, and decrease the secretion of GIP and insulin. Nevertheless, these possible mechanisms are speculative and additional studies are necessary to address this issue.

3. The authors should compare the current findings with the previous Caucasian data in the context of ethnic differences. As widely accepted, pathophysiology of East Asian type 2 diabetes is different from that of Caucasian (Curr Diab Rep. 2015 Jun;15(6):602).

Response: We added some discussion about this previous study, but we limited this discussion because it was not the objective of the study and we did not want to burden the manuscript.

Editorial Requests

Ethics:
If your study involves humans, human data or animals, then your article should contain an ethics statement which includes the name of the committee that approved your study.

If ethics was not required for your study, then this should be clearly stated and a rationale provided.

Response: The study was approved by the local medical ethics committee. All participants provided a written informed consent. This study was registered with the Chinese Clinical Trial Registry (ChiCTR-TRC-14004260, http://www.chictr.org.cn).

Consent:

If your article is a prospective study involving human participants then your article should include a statement detailing consent for participation.

If individual clinical data is presented in your article, then you must clarify whether consent for publication of these data was obtained.

Response: The study was approved by the local medical ethics committee. All participants provided a written informed consent. This study was registered with the Chinese Clinical Trial Registry (ChiCTR-TRC-14004260, http://www.chictr.org.cn).

Availability of supporting data:

BioMed Central strongly encourages all data sets on which the conclusions of the paper rely be either deposited in publicly available repositories (where available and appropriate) or presented in the main papers or additional supporting files, in machine-readable format whenever possible. Authors must include an Availability of Data and Materials section in their article detailing where the data supporting their findings can be found. The Accession Numbers of any nucleic acid sequences, protein sequences or atomic coordinates cited in the manuscript must be provided and include the corresponding database name.

Response: Supporting data are available upon request to the corresponding author.

Authors Contributions:

Your 'Authors Contributions' section must detail the individual contribution for each individual author listed on your manuscript.

Response: The authors' contributions are listed at the end of the manuscript.