Author’s response to reviews

Title: Switching from glargine+insulin aspart to glargine+insulin aspart 30 before breakfast combined with exercise after dinner and dividing meals for the treatment of type 2 diabetes patients with poor glucose control - A prospective cohort study

Authors:
Jing Li (627168316@qq.com)
Liming Wang (wlmyjw@163.com)
Fen Chen (chenfen-03@163.com)
Dongxia Xia (xia-1216@163.com)
Lingling Miao (27790351@QQ.COM)

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Title: Replacing the regimen of glargine+insulin aspart with glargine+premixed insulin for treatment of type 2 diabetes patients with poor glucose control- A prospective cohort study

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Response to Reviewers’ comments

Dear Dr. Muscogiuri,

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,

Reviewer #1

The Authors aim at comparing an insulin regimen with glargine + premixed insulin (before breakfast) with a "basal-plus" regimen (glargine + once daily insulin aspart) in patients with T2DM and poorly controlled blood glucose levels. The main limit of the article is that it is an observational prospective single-arm cohort study without either a control group or a cross-over design: therefore, it is not possible to state if the regimen proposed is better than others. Furthermore, no conclusion about patients satisfaction and compliance can be drawn, since these aspects have not been presented or discussed in the paper. Lastly, the article needs to be revised by an English native medical translator.

Response: We thank the Reviewer for the comments. The manuscript was edited accordingly. The limits raised by the Reviewers have already been presented in the manuscript.

Specific issues

1) The paper needs a revision as there are some orthographical and typographical mistakes in the text. I think it should be better if the paper was revised by an English native speaker, since it is often hard to read and understand.
Response: The manuscript was proofread.

2) This was an observational, prospective, single-arm study, without a cross-over design and with the limitation of an 'intervention bias': therefore, it is not possible to state if the insulin regimen proposed is better than others. As stated by the Authors in the discussion, "No control group was neither included, nor other types of insulin regimen." It is impossible to say how many patients would have achieved a better HbA1c level replacing glargine+ premixed with glagine+once daily aspart.

Response: We agree with the Reviewer. We can only observe the improvement in the control of glucose parameters after the switch.

3) Many kinds of premixed insulin exists, but the article took into consideration only a specific type (Insulin Aspart 30). The article should specify just from the title that this specific type of premixed insulin has been tested, instead of "glargine+premixed insulin"

Response: We agree with the Reviewer. It has been clarified in the manuscript.

4) the follow-up was very short (4+12 weeks) to draw any conclusion about the efficacy of this regimen

Response: We agree with the Reviewer. Nevertheless, the results suggest that the switch could lead to better glycemic control. The manuscript was edited accordingly.

5) Abstract: "Blood glucose levels were well controlled and 58.7% of the patients achieved the HbA1c targets compared to 33.1% before switching." This pertains more to the section results than to the section Methods. Furthermore, in the section Results, no information about insulin doses, BMI, 2h-PG, hypoglycemia events, and patients' satisfaction is given.
Response: We agree with the Reviewer. The abstract was edited accordingly.

6) Methods: Were the 185 patients (fulfilling inclusion criteria) screened for participation consecutively seen? Why the age range of 50-82 years has been chosen as an inclusion criteria? (this limitation is admitted in the discussion)

Response: We thank the Reviewer for the comment. Indeed, the patients were consecutive. We selected patients of >50 years of age because they were retired or nearly retired and they could more easily keep up with the 30-min of exercise compared with younger working people, probably with children at home, and with less available time.

7) Melbine: do you mean metformin?

Response: We are sorry for this. It was corrected.

8) Results: The Authors state that "Switching to glargine+premixed insulin before breakfast resulted in lower breakfast, lunch, and dinner 2hPG and HbA1c, as well as a higher proportion of patients reaching the HbA1c target". However: "1) the initial dose of premixed insulin analogues was set as 1.5 times of the dose of breakfast insulin aspart in the original "1+1" mode; 2) furthermore, the insulin aspart 30 was gradually adjusted until at least one of the 2hPG levels after breakfast or lunch met the standard level"; 3) "For patients with 2hPG failing to meet the requirement after one meal or two meals (except for patients with 2hPG failing to meet the requirement at both breakfast and lunch), they had to select smaller servings; 4) Thirdly, "30min exercise after dinner and/or reduced servings were adopted". Therefore, a real comparison between the same insulin doses of the two regimens has not been performed.

Response: We agree with the Reviewer. The patients reported lower breakfast, lunch, and dinner 2h PG after switching to glargine + premixed insulin 30/70 before breakfast, oral hypoglycemic drugs, and lifestyle intervention. More patients reached HbA1c target compared with before the switch. A meta-analysis indicated that lifestyle interventions lower HbA1c by
about 0.5% [1]. In the present study, patients’ HbA1c levels decreased by a mean of 1.1%, suggesting the effectiveness of glargine + premixed insulin 30/70. Nevertheless, we agree that additional studies are still necessary.

9) Was the rate of hypoglycemia higher, equal, or lower vs the previous insulin regimen? Not stated in the text

Response: We thank the Reviewer for the comment. Since it was an observational study, a run-in period was not included and we could not reliably record the hypoglycemic events before switching. Additional studies are necessary to examine this point.

10) What was the effect on weight/BMI? Not stated in the text

Response: We thank the Reviewer for the comment. As shown in Table 3, the patients lost weight after switching. It was added to the manuscript.

11) Discussion: "Results showed that blood glucose levels were well controlled and 58.7% of the patients achieved the HbA1c targets compared to 33.1% before switching [1]. Therefore, for patients with T2DM that is poorly controlled under the 1+1 regimen, switching to glargine+premixed insulin analogues after breakfast showed promising benefits": see major issues #2

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

12) "glargine could steadily play its fundamental role at dinner, since it is an α-glucosidase inhibitor playing a synergistic hypoglycemic effect." Not clear to me: glargine is an α-glucosidase inhibitor?!

Response: We are sorry for this. Acarbose is an α-glucosidase inhibitor. It was corrected.
13) Conclusions: "In conclusion, for patients with T2DM that is poorly controlled under the 1+1 regimen, switching to glargine+premixed insulin analogues after breakfast showed promising benefits, as well as good satisfaction and compliance". Satisfaction and compliance results have not been presented or discussed in the paper, even if they represent two outcomes of the study, according to the abstract.

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

Minor issues:

1) Glycated hemoglobin sometimes written as HbA1c, sometimes as HbA1C. Please, unify

Response: It was corrected.

2) "What is GAUC"??

Response: We meant "area under the glucose curve". It was corrected.

3) "especially for patients with seriously impaired insulin metabolism who had been diagnosed with diabetes for >5 years". Do you mean glucose metabolism?

Response: It was corrected.

Reviewer #2

1. Although an appreciable effort made in assessing a method aimed at reducing the need of multiple insulin injections throughout the day, a control group would have been needed in the study.
Response: We agree with the Reviewer. Nevertheless, the objective of the study was to examine the effect of the switch on glycemic control. A control group will be included in our future studies comparing different insulin regimens.

2. There is not a direct comparison between a control group and alternative treatment. A post hoc test would be appropriate in this case in order to assess a direct comparison between the control and the study group. Therefore, either examination of two parallel groups or examination of the same group before and after treatment would have been acceptable controls.

Response: We thank the Reviewer for the comment. It was added in Tables 2 and 3.

3. Although conclusions have been drawn correctly based on the outcomes of the study, parameters varied a lot throughout the study. Therefore an homogeneous group could not be detected in comparison to the beginning of the study, likewise adjustments made during the study should not be accepted if you want to compare the beneficial effects of a new treatment versus the standard.

Response: We agree with the Reviewer that we cannot examine only the effect of switching to a new insulin regimen. Nevertheless, the aim of the present study was to examine the effect of switching to a multi-modality approach. The manuscript was edited accordingly.

4. Raw data are necessary and the exact number of screened people, withdrawals and primary and secondary outcomes need to be defined prior to the beginning of the study.

Response: We agree with the Reviewer. They were added.

5. Legends under graphs and tables should include statistical analysis performed post hoc test and n numbers.
Response: We agree with the Reviewer. The legends and table footnotes were edited.

References