Author’s response to reviews

Title: Effect of sitagliptin on blood glucose control in patients with type 2 diabetes mellitus who are treatment naive or poorly responsive to existing antidiabetic drugs: The JAMP Study

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Author’s response to reviews:

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Dear editors and reviewers,

Thank you very much for reviewing our manuscript.

I have revised our manuscript carefully and those changes are as follows.

If you have any questions about our manuscript, please contact JAMP Study office at the address shown below.
I am looking forward to your reply.

Yours sincerely,

JAMP STUDY (On behalf of Dr. Sakura)

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Requests from reviewers

Reviewer#1

Major points;

>1. The treatment protocol is not clear. How were the patients allocated to each drug group? If the treatment was changed before the study, one month of observation period seems too short to stabilize the glycemic marker, HbA1c. This point needs to be clearly described in the methods.

We apologize for the confusion. In this study, subjects were not allocated to groups.

We investigated the glucose lowering effect of sitagliptin when administered in combination with other oral hypoglycemic agents in Japanese patients with type 2 diabetes.

>2. The primary endpoint of this study was change in HbA1c at 3 months. It is assumed that the change in HbA1c at 3 month correlated with that at 12 month. Since it has been reported that the change in HbA1c at 3 month after sitagliptin treatment predicted that at 2 year (Nishimura et al. Intern Med. 2015;54(23):2981-9), this point may be discussed in the manuscript.

Thank you for your suggestions. We have corrected the description as follows:

Nishimura et al. reported that a patient’s HbA1c change at 3 months may be a predictor of their HbA1c change at 24 months. And our study also showed the HbA1c level of 12 month was
similar to 3 month. According to the result of this study, we assume that 3 months of observation period is not too short to evaluate the clinical effects of sitagliptin.

>3. It has also been reported that C-peptide level predicted the efficacy of sitagliptin (Nishimura et al. Diabetes Res Clin Pract. 2015;108(3):441-7). As the authors also speculated that beta cell exhaustion may be the reason of less efficacy of sitagliptin in patients with medium-dose glimepiride, this point should be assessed in more detail in this study and discussed in the manuscript.

Thank you for your suggestions. We have corrected the description as follows:

Although Glimepiride doesn’t beget the secondary failure easily in Sulfonylurea, compared to other drug groups in this study, it is also presumed that in Glimepiride middle-dose group, the pancreas may become exhausted. We can’t identify the cause of it because there were some patients who didn’t laboratory test. However the duration of Glimepiride middle-dose group was 10.2 years, it was longer than overall.

We also have corrected the description as follows:

Patients with type 2 diabetes mellitus have reduced numbers of pancreatic β cells. In an animal experiment, sitagliptin reportedly had pancreatic β cell-protecting and growth-promoting effects , in our present study, the C-peptide reactivity index (CPI) significantly increased at 3 months after starting treatment. It was more likely because of improved beta-cell function rather than increased beta-cell mass because it was just 3 months after the start of sitagliptin, and considering this was an observation in human subjects. However, Nishimura et al. reported that CPI increased from baseline to 3, 6, 12, 18, and 24 months after the start of sitagliptin administration . This indicated the pancreatic β cell-protective effect of sitagliptin in a clinical setting. Nishimura et al. also reported that greater CPI increase after sitagliptin administration were associated with the response to sitagliptin . In our study, the number of patients who test CPI was limited. So we didn’t analysis CPI as the elements of logistic analysis. But CPI may be benchmark of the efficacy of Sitagliptin.

>4. Adherence of sitagliptin administration was checked and evaluated? This point should be mentioned in the manuscript.

Thank you for pointing this out. We have added the adherence of sitagliptin administration as follows:

Talk about adherence, Walker et al. reported 22% of DM patients are defined as poor adherence of medicine, but our study showed only 5.7% of poor adherence of sitagliptin.
>5. The authors should acknowledge and compare with the previous studies evaluating the
efficacy of sitagliptin in clinical settings and discuss in more details. The references are needed
in page 4; line 35, page 9; line 29 and page 11; line 10.

Thank you for your suggestions. We have corrected.

>6. The number of tables and figures are too many. Some of the tables/figures may be considered
as supplementary materials.

We have changed some figures and tables as additional files.

Minor;
>1. This study did not include the patients treated with insulin. This point clearly described in the
abstract and conclusions.

Thank you for your suggestions. We have corrected. (Please see P9, P12)

Reviewer #2
>1. Evaluation of efficacy at 3 months might be too short. Longer period of observation would
have been more interesting. What was the rationale to allow drug modification at 3 months?

Thank you for pointing it out. We have corrected. (Please see P12)

>2. It is common to observe greater HbA1c reduction in patients with higher baseline HbA1c in
many antidiabetic drugs, and DPP-4 inhibitors are not exception (there are a lot of papers,
although high blood sugar decreases incretin signals). The finding is not novel, and figure 6 has
little information and thus can be omitted.

Thank you for your suggestions. We have changed Figure6 as an additional file.

>3. What is the difference between "hypoglycemia" and "hypoglycemic attack" in definition? It
should be defined in method section.
We apologize about this. There is no difference between "hypoglycemia" and "hypoglycemic attack".

We have changed to "hypoglycemia".

>4. Page 10, in Discussion, increased CPI after sitagliptin is discussed in relation with beta-cell protecting and promoting effects of it in animal models. However, observed increase in CPI was just 3 months after the start of sitagliptin, and considering this was an observation in human subjects, it was more likely because of improved beta-cell function rather than increased beta-cell mass. Therefore, the discussion should be reconsidered.

Thank you for your suggestions. We have corrected. (Please see P11)

Reviewer #3

> The inclusion criteria of patients about glucose control are not clear. What does poorly controlled blood glucose' (written in line 12 of page 5) mean?

Is 'poorly controlled' used as the same meaning as inadequate blood glucose?

Judging from figure 5, patients whose blood glucose was not inadequate were included in this study.

We have described about the inclusion criteria in the following sections.

(Study Subjects P.5)

The criterion for inadequate blood glucose control was set at a glycated hemoglobin (HbA1c) level of ≥6.9% (52mmol/mol) or a fasting blood glucose level of 130 mg/dL.

(Evaluation P.6)

At the start of the study in 2011, HbA1c values were expressed in The Japan Diabetes Society levels, the standard system in Japan, but were changed to National Glycohemoglobin Standardization Program (NGSP) system values at the end of the study in accordance with the “Report of the Committee on the Classification and Diagnostic Criteria of Diabetes Mellitus (Revision for International Harmonization),” issued by The Japan Diabetes Society. Pursuant to
the above change, the lower limit of inadequate blood glucose control was also changed. Therefore, patients with an HbA1c level of ≥6.9% (52mmol/mol) were enrolled at the start of the study, but at the data analysis stage, the percentage of patients who achieved the target HbA1c level of ≥7.0% (53mmol/mol) or <7.0% (53mmol/mol) was calculated.

> The adverse events are reported to have occurred in 55 cases. The data whether the patients discontinued sitagliptin due to the adverse events or not are not described. Such information is supposed to be important to evaluate the safety profile of the drug.

Thank you for your suggestions. We have added the description about adverse events as follows:

19 out of 55 patients discontinued administration of sitagliptin because of the adverse event. (Please see P.8)

> Their finding that sitagliptin showed weaker glucose-lowering effects in medium-dose glimepiride considering the baseline HbA1c of this group is interesting.

How about a possibility that this weak effects are derived from inadequate life style regulation of this group?

Thank you for pointing it out. As suggested, we have changed as follows:

Although, smoking and drinking rate are both high in the medium-dose glimepiride group. But we judged it is not significant elements in the multiple regression analysis. (Please see P.10)

Also according to BMC editorial policies and formatting guidelines, we have changed the declaration section.