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Name of Journal: *World Journal of Diabetes*

ESPS Manuscript NO: 24407

Manuscript Type: Clinical Trials Study

REVIEWER -1

Name of journal: World Journal of Diabetes
ESPS manuscript NO: 24407
Title: Prediction of the Effect on Antihyperglycaemic Action of Sitagliptin by Plasma Active Form GLP-1
Reviewer's code: 00009616

COMMENTS TO AUTHORS

Well conducted study that has clinical implications.

Answer to Reviewer 1

N/A

REVIEWER -2

Name of journal: World Journal of Diabetes
ESPS manuscript NO: 24407
Title: Prediction of the Effect on Antihyperglycaemic Action of Sitagliptin by Plasma Active Form GLP-1
Reviewer's code: 00505681

COMMENTS TO AUTHORS

We need to know more about the use of active Glucagon like peptide-1 in daily clinical practice.

Answer to Reviewer 2

We add information about active GLP-1 measuring for use of in daily practice in DISCUSSION section as below.

P.18

Measuring active GLP-1 in fasting plasma can give another evaluation of the characteristics of patients with type 2 diabetes, independent of insulin secretion and insulin resistance. For daily

practical use, the examination costs were rather expensive and health insurance does not apply to this in Japan, and a standard test should be confirmed as a worldwide standard.

REVIEWER -3

Name of journal: World Journal of Diabetes
ESPS manuscript NO: 24407
Title: Prediction of the Effect on Antihyperglycaemic Action of Sitagliptin by Plasma Active Form GLP-1
Reviewer's code: 03490189

COMMENTS TO AUTHORS

Overall, this study makes an important observation regarding the prediction of the efficacy of DPP-4 inhibitor-therapy based on a baseline clinical parameter. In order to make the document stronger, please consider the following: 1) Making the manuscript easy to read by collaborating with a professional editor or writer. 2) In the limitations, please acknowledge the fact that this was an open label, single-arm study. 3) The discussion needs to be more cogent. 4) The reason why the group with his baseline active GLP-1 had the least response needs to be elaborated.

Answer to Reviewer 3

We thank your comments.
1) Language polishing is performed again. We added a certification file.
2)We added the sentence as below. P17
"Other limitations are the design, the study of an open-label, single arm trial and the somewhat small spectrum of subjects, and it being a single-ethnicity study, performed in a single health center."
3) and 4) We modified DISCUSSION section to a large extent, and mainly to include reference to the reason why the group with high baseline active GLP-1 had the least response and to improve logicality of discussion. For example(P14-);

The factors defining plasma active GLP-1 level have not been reported, but are easily speculated as the balance between GLP-1 secretion and inactivation/degradation by DPP-4. If DPP-4 activity is low in insulin sensitive, non-obese subjects, low active GLP-1 level is probably derived from low GLP-1 secretion. In contrast, insulin resistant patients indicated relatively high GLP-1 level in spite of presumably high DPP-4 activity[19]. Therefore, the reason the high baseline active GLP-1 group had the smallest response is probably due to the low contribution of the GLP-1 - DPP-4 system on their insufficient glycemic control or insulin action. The causes of this low contribution of GLP-1 – DPP-4 system should be focused on the fact that sitagliptin cannot raise GLP-1 level in the baseline high active GLP-1 group. One possible speculation is the insufficient inhibition of high DPP-4 activity by sitgliptin. In which case, GLP-1 overcomes or evades high DPP-4 activity in insulin resistant subject. Activity of plasma DPP-4 correlates with insulin resistance and predicts sitagliptin efficacy [19], however this was not measured. Another speculative cause is the unknown feedback regulation of active GLP-1

level other than DPP-4 activity, such as incretion from L cells. Injection of excessive GLP-1 can cause nausea or vomiting more frequently than administration of DPP-4 inhibitors [28]. Therefore there might be a physiological cap of GLP-1 level caused by unknown factors other than DPP-4, thus avoiding the imbalance of gastrointestinal homeostasis or other catastrophe.

Aside from the result of examination of multiple regression, it is clearly demonstrated that active GLP-1 is statistically independent of other factors, such as HbA1c, disease history, use of medications, the specific hormonal parameters for insulin, glucagon, low-grade inflammation, and HOMA indicators. Active GLP-1 level correlated with insulin resistance but predicts HbA1c improvement independently to insulin resistance. The high active GLP-1 and high DPP-4 activity from insulin resistance might have an additive effect on resistance to sitagliptin treatment.