Would Journal of Diabetes Editorial Team

16 August 2016

Answering Reviewers

Dear Sirs,

Thank you for receiving our manuscript and considering it for review. On behalf of the research group, I would like to express our deep appreciation to reviewers for their prompt and productive reviewing. We have made every effort to revise the manuscript according to reviewer`s comments.

Here we report the following clarifications, corrections and additions in the revised version of manuscript.

1. The db/db mice are commonly used model of type 2 diabetes and non-alcoholic fatty liver disease. Like any experimental model, it is only partially corresponds to metabolic disturbances observed in human diabetes. Although we did not measure the levels of HbA1c in this study, we did not find hypoglycemic effect of linagliptin in db/db mice. The data is in agreement with previous reports of Sharkovska Y. et al. (ref. 27). It has been demonstrated previously that function of the enteroinsular axis is preserved in *db/db* mice and the DPP4 inhibition potentiated it, but the progression of insulin resistance appeared to block the improvement of glucose tolerance through DPP4 inhibition (ref. 28). Our data indicating protective effect of linagliptin on the liver structure give further support to notion that modern hypoglycemic agents, including DPP4 inhibitors, may produce beneficial effects in target organs, regardless of the glucose-lowering activity. The discussion section has been detailed.
2. The declaration of linagliptin effect on the LYVE-1 expression in endothelial cells has been corrected.
3. Figures 7 and 8 are given in compliance with the rules of the journal (Format for Manuscript Revision: Basic Study, pp. 34-35).
4. It is plausible that the lack of significant differences in biochemical parameters between linagliptin and placebo group is explained by the small number of observations. We have attempted to exclude one mouse with near-normal weight from placebo group and recalculate the results of biochemical and morphological investigations. This exclusion

does not lead us to different conclusions. Since the severity of biochemical abnormalities and morphological changes in the liver in this animal was similar to those in other saline-treated mice, we decided to present the results in the initial form.

5. The statements of the glucose-independent effect of linagliptin on the structural parameters of the liver have been corrected according to reviewer`s proposals.
6. The application of yellow filter for assessment of lipid accumulation at some semi-thin sections has produced the differences in color between pictures. To avoid ambiguity, we have replaced some photographs in the revised version of manuscript (Fig. 1a, Fig. 5a, and Fig. 5b). Relevant comments were included in the figure captions.
7. More detailed designations of morphological structures were added in Fig. 1-6.

Yours sincerely,

Dr. Vadim Klimontov