Author's response to reviews

Title: Variation of C peptide decay rate in diabetic patients with positive glutamic acid decarboxylase antibody: better discrimination with initial fasting C peptide

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Author's response to reviews: see over
Dear Editor,

Thank you very much for your advice on our manuscript. The responses to each point raised by the referees are listed as following.

Referee 1:
1. Inclusion criteria of this study should be mentioned in more detail. Ex., sampling strategy, period of sampling, sampling size, etc. These are not described. The disease duration at the point of enrollment is quite important point in this paper, but it is difficult to know how authors define or speculate it.

Response: Thanks for the advice. We have added more information on the sampling strategy, period of sampling, sampling size and definition of disease duration to the “Methods” (see in the “Inclusion of subjects and data collection” part).

2. Information on the treatment during 48 month follow up period is lacking.

Response: Thanks for the advice. The information on the treatment during the follow-up period was added to the “Methods” (see in the “Inclusion of subjects and data collection” part).

3. During 48 months of observation period, the decreasing rate of serum C peptide level seems to be similar in both groups (Fig.1). Patients with preserved beta cell function at 48 months seem to develop beta cell failure next 48 to 96 months. Could that mean the different clinical course of these two groups just come from the time-lag of the diagnosis of their diabetes and enrollment?

Response: Thanks for the advice. The decreasing rate of C peptide is not linear. As shown in Figure 1, the decreasing rate of serum C peptide level was much slower in “Group 3” during the 36 months follow-up. Indeed, Patients with preserved beta cell function at 48 months seem to develop beta cell failure next 48 to 96 months, this may need longer follow-up. As we enrolled newly diagnosed patients, we think the different clinical course of these two groups did not come just from the time-lag. On the other hand, in this article, we are focusing on the actual ending of beta cell function, that is, the absolute levels of C peptide at the end of the follow-up and there was dramatic difference between two groups.

4. Other factors which could influence the decline of beta cell function should also be analyzed (ideally, with multivariate analysis) to emphasize the importance of initial serum C peptide level.

Response: Thanks for the advice. We have added the above results in the “Results” (see in the “Factors which influence the decline of beta cell function” part).

5. Condition of postprandial C-peptide sampling is missing (ex., amount of meal, and timing of sampling).
Response: Thanks for the advice. The information of postprandial C-peptide sampling had been added in the “Methods” (see in the “Measurement of beta cell function” part).

Referee 2:
1. The criteria used to categorize patients into T1D and LADA are unusual and need to be explained. Ketosis is usually not used for the classification as not every patient with T1D experienced ketoacidosis at clinical onset. Inclusion of only GADA for classification of autoimmune diabetes is not sufficient. Especially young T1D patients may be GADA negative, but positive for IAA and/or IA-2Ab.

Response: Thanks for the advice. Yes, ketosis is usually not used for the classification as not every patient with T1D experienced ketoacidosis at clinical onset. We defined T1D by the criteria as “Requirement of insulin therapy since diagnosis”, ketosis was used just as another evidence of insulin insufficiency. To avoid the misunderstanding, we had omitted the “ketosis” part.

Yes, inclusion of only GADA for classification of autoimmune diabetes is not sufficient. So we had changed our title to “Variation of C peptide decay rate in diabetic patients with positive glutamic acid decarboxylase antibody: better discrimination with initial fasting C peptide”. Thanks again.

2. The statement that GADA are the most widely used and valuable markers for autoimmune diabetes needs to be rephrased. Positivity for GADA or any of the other islet cell autoantibodies alone is not used as autoimmune markers for prediction or diagnosis of T1D. In T1D other autoantibodies (IAA and IA-2Ab) are in fact often more prevalent as they correlated inversely with age at onset, while GADA correlate directly with age at onset. Positivity for GADA is used as a predictor only in LADA.


3. The authors argue that the initial FCP level may be a predictor of beta cell function failure. Judging from the presented figure, it would be important to calculate the loss of c-peptide level over time. Both cohorts appear to loose c-peptide over time.

Response: Thanks for the advice. Yes, it would be more informative to calculate the loss of c-peptide level over time. But as our enrolled subjects had a relatively low C peptide, during the follow-up, some C peptide levels were under the minimum detectable range. So larger sampling is
needed. Thanks for the advice.

4. The argument that the authors make when comparing decline in beta cell function in group 1 and 2 is not clear. The authors state that patients in group 2 (longitudinal loss of FCP) had higher FCP at onset. However, this is evident by their own categorization of group 1 of being FCP negative at onset and therefore does not need to be stated.

Response: Thanks for the advice. Group 1—3 was divided according to the C peptide levels at the end of follow-up (whether they had developed beta cell failure), and not according to the initial C peptide levels.

5. It would be of interest to know what is the percentage of T1D and LADA in Groups 1-3. The similar age in groups 1 and 2 suggests that the traditional T1D and LADA forms of autoimmune diabetes overlap in this cohort.

Response: Thanks for the advice. We had added the results in Table 1.

6. The authors refer to a paper by Maldonado, using autoantibody positivity and beta cell functions to differentiate four forms of ketosis-prone diabetes. It needs to be emphasized that the Maldonado paper refers only to patients with ketosis-prone diabetes.

Response: Thanks for the advice. We had emphasized this point in the Discussion part.

7. Some published work was not cited. Other publications already show that FCP at onset predict loss of beta cell function in T1D (Jensen RA et al 2007), the authors site only some of the publications on prediction of beta cell loss in autoimmune diabetes.

Response: Thanks for the advice. We had added the above articles as our reference.

If there is any other information is needed, please do not hesitate to contact me at hellolxwj@yahoo.com.cn.

Best wishes,

Yours sincerely,

Xia LI