JG|U UNIVERSITÄTSmedizin. MAINZ

JOHANNES GUTENBERG UNIVERSITY MEDICAL CENTER

Professor George J. Kahaly

George.kahaly@unimedizin-mainz.de

Department of Medicine I
Bldg. 303, Mainz 55101, Germany
Fax (phone) +49–6131-17-3460 (17-2290)

Dr. LIAN-SHENG MA
Chief Executive Officer
World Journal of Diabetes

08.27.2020

Dear Dr. MA,

Thank you for accepting our invited manuscript subsequent to a revision according to the comments of the three below reviewers. We are relying on your letter dated August 22, 2020. Therefore and enclosed, please find our invited and revised research article ***# 57663*** **(**with two tables, four figures, one supplemental table and one suppl. figure) entitled "TYPE 1 DIABETES AND ASSOCIATED AUTOIMMUNE DISEASES", authors Frommer L and Kahaly GJ, which has been submitted for publication in the *World Journal of Diabetes*.
The invited original manuscript has been revised in accordance with the Editor's and Reviewer's comments. In detail, we have tried to comply with all requests and most constructive recommendations of the reviewers and have stated all replies in **bold** and *italics*, enumerating the specific comments of the reviewers and explaining point-by-point how each has been addressed. Please see our responses as follows:

REVIEWER #1:
This article provided detailed demographical and serological comparisons between T1D patients and those with associated autoimmune diseases (AID). The authors conducted long-term, longitudinal observational study on those patients and their first-degree relatives. While the association of glandular and non-glandular AID in T1D patients has already been well characterized; this study provided useful information on gender-specific and late onset characteristics with T1D-associated AID. The major shortcoming of this article was some data described not being displayed quantitatively. This study was well designed, with clear definition for the diagnosis of different AID. However, a few minor modifications would make this article of better quality:

1. In comparing the demographic data, the authors stated the average time interval between the onset of T1D and glandular AID was much shorter than that between T1D and non-glandular AID. It would be more convincing to provide the quantitative figures. The same apply more T1D+AID relatives were affected by AID when compared to T1D relatives.

   Authors' reply: We concur with the reviewer and have added these quantitative data (please refer to page 7 lines 192 -195 and 198-199).

2. In the clinical and serological data of relatives, it would be advisable to display the relationship between prevalence of autoantibodies and occurrence of AID. Currently, only the former information was provided.

   Authors' reply: Again, we concur with the reviewer and have edited the text accordingly. Please refer to page 8 lines 208-213 and 227-236).

3. Could the authors provide an explanation of the prevalence of most autoantibodies assayed in T1D relatives being higher than that in T1D+AID relatives? The trend was completely opposite as observed in T1D and T1D+AID patients.

   Authors' reply: Most probably, this interesting finding might be due to the large number of relatives followed at our referral center for autoimmune endocrine and orphan diseases. These results might indeed differ in other centers.

4. Please provide the normal range of all autoantibodies assayed in this study. Currently, only parts of them were provided in Table 1.

   Authors' reply: As requested, the normal range of all autoantibodies assayed in this study is now provided (please refer to table one).

REVIEWER #2:
This study examines the clinical factors associated with multiple autoimmunity in people with T1DM. The results appear valid I have several suggestions:

1. INTRODUCTION - it is too long and meandering. The first paragraph can be removed. Simply state that T1DM is associated with other AI disorders and you are reporting your own experience. Indeed the authors do not mention the purpose of the study in the INTRO.

   Authors' reply: We concur with the reviewer and have followed her/his recommendations. The introduction has been shortened and the objective of the study clearly stated (please refer to page 5 lines 110-113)

2. METHODS - refer the reader to the table of the autoimmune conditions and the immune markers. There is no point in listing them in the text.

   Authors' reply: We apologize for having missed this relevant point and have edited the text accordingly (please refer to page 7).

3. You can take some of the information in the INTRO and put in the DISC section.

   Authors' reply: Again, we concur with the reviewer and have followed the well-taken proposal. Please refer to page 9 lines 247-252.

4. RESULTS "...AID. In average, we did observe 1.88 associated AID. More patients with AID were followed than patients with T1D only; hence." What is 1.88? Something is missing... More patients with AID were followed than T1D alone - please explain this. Not clear as written.

   Authors' reply: We apologize for this unclear statement. In average TWO AID were observed with a maximum of five. This has been edited accordingly. Further, being a referral center for autoimmune and orphan disorders, we do

follow a very large number of patients with various endocrine autoimmune diseases and their relatives.

5. DISC - "screening for 21 hydroxylase deficiency should be done" This is too strong a statement. The disease is rare. Perhaps "should be considered".

   Authors' reply: Done (see page 10 lines 275-278).

REVIEWER #3:
This is a good study. However, few minor modifications are required in the manuscript:

1. Core tip needs modification. The second sentence is too long.

   Authors' reply: We concur with Reviewer #3 and have edited the text accordingly (see page 3 lines 71-75).

2. The information related to prevalence of autoimmune diseases and antibodies among relatives are not matching in abstract/results and figure 4.

   Authors' reply: We apologize for this error, which has been corrected on page 2 lines 49-52).

3. Few mistakes are there in figures 3 & 4 e.g. DNS.

   Authors' reply: Done.

Looking forward to a positive evaluation and acceptance of our extensively revised invited manuscript,

Best regards,

George J Kahaly,
Corresponding author