November 3, 2020

Prof. Timothy Koch, Editor in Chief

World Journal of Diabetes

Dear Editor,

Re: Manuscript ID: 59358 revision

Title: **"Factors associated with dyslipidemia in patients with type 1 diabetes: a single-center experience"**

We greatly appreciate the time and effort spent by you and the reviewers and are grateful for the opportunity to revise the manuscript. Our point-by-point response to the reviewers appears below. We trust that in its present form this manuscript will be considered suitable for publication in the *World Journal of Diabetes*.

We thank you for your consideration and look forward to your reply.

Sincerely,

Prof. Shlomit Shalitin on behalf of co-authors

The Jesse Z. and Sara Lea Shafer Institute for Endocrinology and Diabetes, National Center for Childhood Diabetes, Schneider Children's Medical Center of Israel, 14 Kaplan St., Petah Tikva 49202-35, Israel [shlomits2@clalit.org.il and shalitin@netvision.net.il]

Reviewer #1 :
Scientific Quality: Grade C (Good)
Language Quality: Grade C (A great deal of language polishing)
Conclusion: Major revision
Specific Comments to Authors: This is a comprehensive analysis of a wide range of CVD risk factors and dyslipidemia in type 1 DM (T1D) patients.

We greatly appreciate the time and effort spent on review of our submission and are grateful for the opportunity to revise the manuscript.

 I have some comments about the MS. #Title of the paper: I admit that the association between CVD risk factors and dyslipidemia shown in Table 3, which is considered to correspond to the title of this paper, is an important finding of this paper. But this is one of them. Interpreting other tables and figures (Tables 1&2, Figures 1&2), the CVD risk factors analyzed PER SE (i.e., regardless of its association with dyslipidemia) are also important. I would recommend the following title (as in the running title): 'Dyslipidemia and cardiovascular disease risk factors in patients with type 1 diabetes: a single-center experience'

Indeed the title you suggested is more representative of the data presented. We have changed the title of the manuscript accordingly.

#This comment is also related to the above one. Reading the abstract, especially its 'Results', it is about 'the association between dyslipidemia and CVD risk factors' all over. But this paper also has the results shown in Tables 1&2/Figures 1&2, which are not necessarily about 'the association'. Please incorporate all the results shown in tables and figures into the abstract with easy-to-understand expressions.

Thank you for this comment. We have added these results to the revised abstract.

 #Table 1, 'lipid profile': In this line, it says, 'n=144, n=77, n=73' but not 'n=170, n=86, n=84'. These are the subject numbers where lipid data are available? An appropriate explanation needs to be described in the table caption. #Table 2, 'Cardiovascular disease risk factors in patient (>I think 'patients' is better here)': This is also the same as the above. In this line, it says, 'All n=149, n=74, n=75' but not 'n=170, n=86, n=84'. These are the subject numbers where risk factor data are available? An appropriate explanation needs to be described in the table caption.

Thank you for this comment. We have clarified the subject numbers in the table captions and have replaced the term 'patient' with 'patients'.

#Figure 1 and 2: In each of these figures, the 'CVD risk factors' analyzed in this paper need to be listed in the figure legend (by making it).

Thank you for this comment. Please note that the legends for the figures appear after the references in the original version of the manuscript. We have added the 'CVD risk factors' analyzed in this paper to the revised figure legends.

#Some of the readers (including this reviewer) must be unfamiliar with this kind of statistical analyses. Please make sure of the correctness of the statistical methods of this MS with professionals of statistics.

A professional statistician reviewed the statistical analyses. The accuracy and rigor of the statistical methods were carefully reviewed and confirmed.

#There are a number of grammatical errors throughout the MS. Ex. -Abstract, conclusion, line 1: elevated lipid profile is >>> elevated lipid profiles are -Introduction, 2nd paragraph: 1st line: Study >>> Studies; Last line: the excess CVD risk >>> the excess of CVD risks -etc, etc, etc…

The revised manuscript has been reviewed and grammatical errors have been corrected.

Reviewer #2 :
Scientific Quality: Grade D (Fair)
Language Quality: Grade A (Priority publishing)
Conclusion: Major revision

We greatly appreciate the time and effort spent on review of our submission and are grateful for the opportunity to revise the manuscript.

Specific Comments to Authors: This retrospective study suggests a very high prevalence of dyslipidemia in people with type 1 diabetes. I am curious why young people with type 1 diabetes are associated tripled comorbidity of dyslipidemia in the study population?

As mentioned in the discussion section of the manuscript: "Previous studies have reported a high frequency of dyslipidemia among pediatric and young adult patients with T1D [19,50,51], with a prevalence rate between 26-72% and the highest prevalence (72%) in a Brazilian study [52]. Similarly, we found a relatively high prevalence of dyslipidemia already during childhood in a little over one-third of our study population, rising to about 60% at adulthood." Of note, these studies represent a variety of countries including the United States, Lithuania, Turkey and Brazil. In our studied cohort, it is plausible that the increase in the rate of dyslipidemia from 37.5% to 60.8% mirrors the increase in overweight/obesity from 16.5% to 39.9%, as our patients progressed from childhood/adolescence to young adulthood.

1. It is interesting that either age or sex is the risk factor for dyslipidemia in this study. The univariate comparisons between participants with and without dyslipidemia as well as its specific type (such as elevated LDL-C) is necessary to present.
We carefully considered this suggestion. The academic statistician working on this research project performed univariate analyses. We believe that it would be quite cumbersome for the readers if these analyses were presented in the manuscript.

2. Please indicate the regression model the authors used to predict the dyslipidemia.

The regression model used for the prediction of each of the four lipid-profile outcomes [TC, triglycerides, LDL-c, and HDL-c] was a stepwise linear regression model. The independent variables which were included in each model were: sex, age at diagnosis, ethnicity, positive family history of CVD risk factors [type 2 diabetes, cardiovascular disease, dyslipidemia and hypertension], the patient's clinical characteristics in 1998 [BMI-SDS, Tanner pubertal stage, diastolic and systolic blood pressure categories according to percentiles, duration of diabetes] and cumulative mean of

all HbA1c values (from 1998 until the last visit). We have clarified this in the statistical methods in the revised manuscript.

3. It is also critical to suggest how many people used statins or other lipid-lowering drugs.

Thank you for raising this important issue. In 1998, only 1 female patient used statins. In the last visit, 18 males and 11 females used statins. We have added this data to the revised tables 1 and 2.

4. The flow diagram of patient recruitment is also necessary.
The study is a longitudinal and cross-sectional retrospective study. Therefore, patients were not recruited to the study; rather, the medical files of type 1 diabetes patients followed in our tertiary diabetes center were reviewed and all cases meeting inclusion/exclusion criteria were included.

5. It is also critical to show the remission rate of dyslipidemia in this population.
Thank you for this comment. Spontaneous remission of dyslipidemia in subjects with type 1 diabetes was not reported.

4 LANGUAGE QUALITY
Please resolve all language issues in the manuscript based on the peer review report. Please be sure to have a native-English speaker edit the manuscript for grammar, sentence structure, word usage, spelling, capitalization, punctuation, format, and general readability, so that the manuscript's language will meet our direct publishing needs.
We have resolved all language issues.

5 EDITORIAL OFFICE'S COMMENTS
Authors must revise the manuscript according to the Editorial Office's comments and suggestions, which are listed below:
 (1)Science editor: 1 Scientific quality: The manuscript describes a retrospective study of the dyslipidemia and CVD risk factors in T1D. The topic is within the scope of the WJD. (1) Classification: Grade C and Grade D; (2) Summary of the Peer-Review Report: This is a comprehensive analysis of a wide range of CVD risk factors and dyslipidemia in T1DM patients. This is an interesting study, and the manuscript is well written. However, there are some issues should be addressed. The authors need to add more details in the "method" section. It is also critical to suggest how many people used statins or other lipid-lowering drugs. The flow diagram of patient recruitment is also necessary. It is also critical to show the remission rate of dyslipidemia in this population. The questions raised by the reviewers should be answered; and (3) Format: There are 3 tables and 2 figures. A total of 53 references are cited, including 12 references published in the last 3 years. There are no self-citations. 2 Language evaluation: Classification: Grade A and Grade C. 3 Academic norms and rules: The authors provided the Biostatistics Review Certificate and the Institutional Review Board Approval Form. The authors need to provide the signed Conflict-of-Interest Disclosure Form and Copyright License Agreement. Written informed consent was waived. No academic misconduct was found in the CrossCheck detection and Bing search. 4 Supplementary comments: This is an unsolicited manuscript. The topic has not previously been published in the WJD. The corresponding author has not published articles in the BPG. 5 Issues raised: (1) I found the language classification was grade C. Please visit the following website for the professional English language editing companies we recommend: https://www.wjgnet.com/bpg/gerinfo/240; (2) I found the authors did not provide the original figures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the

editor; (3) I found the authors did not add the PMID and DOI in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout; and (4) I found the authors did not write the "article highlight" section. Please write the "article highlights" section at the end of the main text. 6 Re-Review: Required. 7 Recommendation: Conditionally accepted.

 (2)Editorial office director: I have checked the comments written by the science editor.

(3) Company editor-in-chief: Manuscript under further review

Thank you for the time spent on review of our submission. We have addressed all the reviewers and editorial comments. We hope that you will endorse publication of the revised manuscript.