Author's response to reviews

Title: Altered Platelets' Morphological Parameters in Children with Type 1 Diabetes - a Case-Control Study

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

We greatly appreciate the kind reviews and the opportunity to revise and improve our manuscript. Following the recommendations of the Reviewers we made the requested changes to the text. Specific changes are explained below the respective comments.

Reviewer: Dianna Magliano

Reviewer's report:

This is a case- control study of type 1 diabetes in children designed to investigate whether platelet function, morphology or function is related to type 1 diabetes. This is generally a well presented paper but has some errors of expression and spelling. Minor comments below.

1. Abstract: please delete “treated with insulin”, as all type 1 diabetes needs insulin.
   R1: We deleted this phrase.

2. Abstract is long and wordy. Sections can be removed. e.g.: methods of HbA1c can be deleted and the description of statistical tests can be edited down.
   R2: We removed from the abstract sections concerning HbA1c and platelets morphology measurements methods. We feel however that the statistics section should remain within the abstract as stated by the guidelines for authors (http://www.biomedcentral.com/bmcendocrdisord/authors/instructions/researcharticle#formatting-abstract).

3. The description „older patients showed lower platelet counts” is not well expressed. Instead, you could say "Age was inversely associated with platelet count
in both cases and controls”. Also, if age is related to these factors in cases and controls, how and why is that important?

R3: We revised the passage to: “In both cases and controls age was inversely correlated with platelet count”. We would like to state this matter in the abstract to justify the following adjustment.

4." Invitro" should be in italics.

5. Diabetes is spelt incorrectly in line 86 of the introduction

R4-5: Both mistakes were corrected.

6. The aim at the end of the introduction is poorly worded, please re-word.

R6: It was reworded. “Our study was aimed to compare morphological platelet parameters – as the indirect indicators of platelet activity - between children with type 1 DM and their healthy peers. Additionally, we wanted to correlate them with metabolic control parameters.”

7. How were acute complications defined?

R7: There were defined according to ISPAD Guidelines 2014. We added appropriate statement and citations in the article – “Patients with: known monogenic diabetes, acute complications of diabetes (severe hypoglycaemia, diabetic ketoacidosis – defined according to International Society of Pediatric and Adolescent Diabetes Guidelines 2014 [14, 15]), (…)”

8. The wording of the results in the lines 159-161 is confusing. e.g.: "MPW, PDW and P-LCR were significantly associated with duration of diabetes, but the association disappeared after adjustment for age" may be better.

9. Line 161: I would suggest to start a new sentence. Also, adjustment „for” covariates, rather than "to" covariates.
10. Line 166. There is a missing word between "PLT" and "HbA1c" There are more errors in expression to be corrected. This will help the paper flow better.

R8-10: We have substantially revised the manuscript and hope that most of the errors noticed by the Reviewer have been removed.

Reviewer: Neale Cohen

Reviewer's report:

Major revisions:

While this study does show minor platelet changes associated with type 1 diabetes, the discussion is not balanced. The platelet count was independently associated with metabolic control, however there was no difference between platelet count in the controls and diabetic population. This would suggest that glucose control is not a factor. There needs to be a comment on this disparity.

R1. We have looked in depth into this matter and identified a potential source of this disparity – the group of patients with very low HbA1c, presented that in the results of the revised manuscript and elaborated on the matter in the revised discussion.

Discussion of platelet activity seems inappropriate. This study did not measure platelet activity but platelet morphological parameters. There is recent work suggesting platelet 'stickiness', which is unrelated to morphology, is altered in patients with diabetes.

R2. We have an ongoing study on platelet activity, but description of its scope and design within this manuscript would be too exhaustive and we would avoid publishing incomplete data. We were however able to perform an interim analysis for this review purposes to substantiate our claims on platelet activity and morphology.
above mentioned study children treated in our Department (N=652) were screened for MPV and HbA1c level. Patients with the highest and the lowest MPV values (lowest and highest quintile) were selected to the following study. A similar division was performed on the basis of HbA1c levels. This produced four separate groups of highest/lowest-HbA1C/MPV which constituted our study group. During follow-up visits blood samples of at least 800µL volume were collected. Measurements of platelet activity were performed with the INNOVANCE PFA-200 System (Siemens, Germany) with Collagen/ADP (CADP) receptor cartridges. This agonist induce platelet adhesion, activation and aggregation leading to rapid occlusion of the cartridge’s aperture followed by cessation of blood flow called the closure time (CT). The study group was composed of 21 children (47.62% boys) with mean age of 12.78+/−3.96 years and mean diabetes duration of 5.13+/−2.96 years. We found significant negative correlation between CADP and PLT (R= -0.57, p=0.0072) which was shown in Figure below.
Apart from that we have revised the manuscript to underline that we in fact present morphology parameters of the platelets rather than their functional capabilities.

Changes in platelet morphology were small although significant. The increased MPV was of the order of 2%, and the clinical significance of such a small change needs to be discussed.

R3. We have revised the discussion section to underline this fact and elaborated on the clinical significance of MPV changes.

We trust that you will now find our revised manuscript suitable for publication in BMC Endocrine Disorders.
Your sincerely,

Wojciech Fendler MD, PhD, Associate Professor