Author’s response to reviews

Title: Non-invasive detection of microvascular changes in a paediatric and adolescent population with type 1 diabetes: A pilot cross-sectional study.

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Author’s response to reviews: see over
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To: The Editorial Team BMC Endocrine Disorders
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Subject: REPLY TO REVIEWERS COMMENTS WITH MANUSCRIPT CHANGES OUTLINED

Dear Sir/Madam

The time taken by the reviewers to provide advice to refine this article will enhance the final publication, and is greatly appreciated. Please find enclosed amended article (with modifications appearing as “Track Changes”). I will summarise key changes made in response to reviewers’ suggestions below:

**Reviewer 1 (AS-O)**  
• No modifications suggested

**Reviewer 2 (AZ)**

**Comment 1**
“The title ... assessment of microvascular changes by multiple non invasive techniques in a population with type 1 Diabetes : a pilot cross sectional study”
  • Suggested title change: The suggestion more comprehensively captures the breadth of the study - title modified accordingly

**Comment 2**
“Please specify better the purpose of the study” “Was really the ability of nailfold capillaroscopy and the other techniques to detect early microvascular changes or to see if the combination of these techniques could detect better the early microvascular changes”
  • Abstract purpose modified to reflect goal of using combined modality approach to microvascular disease detection

**Comment 3**
“Furthermore I did not like the verb “explore” it is probably appropriate for an invasive procedure and all these techniques are not”
  • The verb "explore" has been replaced with “investigate”

**Comment 4**
“Please also add that you wanted to correlate the results with specific laboratory parameters”
  • The plan to correlate results with specific laboratory parameters is mentioned in “Methods” section of body of article; clarification has been provided that the associations being described refer to all analysed parameters

**Comment 5**
“In methods… please change “the cardiovascular investigations”, capillaroscopy is routinely not used by cardiologist but rheumatologist and immunologist” “Please change the sentence” associations were described… Associations of what??” “In results please put a comma after “recruited”, in the first sentence. Then start with “patients had a mean HbA1c of 8.1%…””

- “Cardiovascular investigations” – as rheumatologists examine vascular changes in nail-bed, “cardiovascular” has been replaced by “cardiac and vascular”
- Syntactical advice on Abstract’s “Results” section noted and adopted

Comment 6
“You should subdivided the results according to the procedures analysed.. then,, please change it as follow. Capillaroscopy showed that avascular areas were present in patients with … the higher number of microhaemorrages was found correlated to … recent HbA1 increase (is this correct?)”

- Subdivision of results according to the procedures analysed appears in body of article
- Please note that abstract modifications have been constrained by word limits
- With regard to reported associations, the study did find that recent HbA1c was positively associated with the number of nailfold microhaemorrhages (p=0.03)

Comment 7
“There is no mention about the length and onset of increased HbA1c”
- Length and onset of increased HbA1c was not analysed in this study

Comment 8
“You should better described and summarize the specific capillaroscopy parameters that were used and how the correlation was done. Although you report this extensively later in the paper, the abstract is really confused and doesn’t provide clear information about the methodology and results.”
- Abstract word limits constrained the ability to list all studied methods, which were expanded upon in body of article
- Correlational analytical methods were also referred to within “Statistics” section due to Abstract word limits

Comment 9
In the conclusion of abstract, what does “moderate” duration mean?? Did you classify the length in moderate, severe, slight??”

- “Moderate” duration term omitted, replaced by “established”

Comment 10
“I would prefer to change the sentence “poor diabetes control” into “with increased level of HbA1c... simply”

- Sentence modified as suggested with poor diabetes control replaced with increased level of HbA1c.

Comment 11
“At the end of the abstract, there are no conclusion of retinal and blood pressure monitoring as the reader is expecting”
- Findings on retinal and Blood pressure monitoring appear in body of text.

Comment 12
“Please erase from the background the paragraph .. We undertook .. etc. it is a repetition ... it was already written in the abstract...” “You should write for example.. Many techniques area currently available to analyze the microvascular involvement.” “Please change the sentence “to explore the use of other more recent investigation techniques..” into .. “to evaluate the use in association of the following non invasive procedures. These procedures are able to assess the morphology and functionality of microvascular network in different anatomic areas. Specifically we use, capillarosocpy etc...”
- Wording within “Background’ modified in light of suggestions

Comment 13
“I am not sure that including 24 blood pressure could add any information to the study and you consider to exclude this technique”
- With regard to the exploration of 24 Blood pressure, this parameter proved to be of limited value; however, as the exploration of this measure represented part of the study’s purpose, it was retained, as it was felt by the authors that the omission of negative results would unnecessarily bias the study’s reporting

Comment 14
“The capillary abnormalities usually analysed should be summarized in a table and not reported in the text (“too long”)”
- Specific capillaroscopic parameters were both tabulated and described in text, for the sake of clarity of presentation

Comment 15
“You should then write ... several capillary changes have been described in diabetes with poor metabolic control, although the results have been debated by other authors”
- Sentence changed according to suggestions

Comment 16
“Clarify that capillaroscopy has many limitations in children (as reported by Zampetti et al 2009)”
- Limitations of capillaroscopy in children are discussed in ”Discussion” section

Comment 17
“You mention the study (Ref 10) please clarify. What does the different reperfusion mean in diabetic paediatric patient??”
- Potential explanations for this study's findings on reperfusion (Ref 10) is presented in the discussion

Comment 18
“Please re-write more clearly the paragraph that mentions ref 11. It is completely confused. Try this was .. With regard to the retinal vessel involvement semiautomated computer-based imaging program have shown that ...”

- The paragraph that mentions ref 11 has been reworded for enhanced clarity.

**Comment 19**

“in the retinal vessel assessment section, you should specify when the images were taken”

- Timing of retinal vessel assessment has been clarified in relevant section within “Methods” section

**Comment 20**

“in the discussion please change the first sentence “this exploratory pilot study demonstrated that results were significantly linked ... I checked the table showing the results and the p was statistically not significant. What do you mean? Is there any trend of association?” “The sentence “this result suggest that changes to the microcirculation in the periphery...” is enigmatic.”

- First sentence in “Discussion” has been retained unchanged, as significant p-values indicating robust associations were found for numerous variables summarised within “Results” section, not appearing in tabular form (e.g. Avascular areas were significantly more common in participants with type 1 diabetes complications (t=-2.33, p=0.03); participants with decreased baseline perfusion had increased capillary density (r=0.63, p=0.001) and were more likely to have microaneurysms (r=0.40, p=0.04))

- For this reason, sentence (“This result suggests that changes to the microcirculation in the periphery”) has been retained

**Comment 21**

“The sentence “both morphological and functional capillary changes were found in the participants” or a similar sentence should be put at the beginning of the discussion.. and the concept should be further discussed”

- The sentence “morphological and functional capillary changes” is discussed, in attempt to limit the length this should not require further discussion.

**Comment 22**

“Please clarify the sentence “this study suggests that these investigations are associated with the traditional markers of poor diabetic control.” you did not discuss this .. no point about the correlation with the laboratory parameters and if glycosilated haemaglobin is a sufficient marker”

- The sentence “This study suggests that these investigations are associated with the traditional markers of poor diabetic control” was also retained, given our demonstration of association between elevated HbA1c and variables such as increased microhaemorrhages, as well as finding of increased avascular areas in individuals with evidence of microvasculopathy (as evidenced by retinopathy and microalbuminuria).

Once again, I express my appreciation for your helpful feedback, and look forward to hearing further news of the article’s progress through the editorial process.

Yours sincerely

Sarah Hosking