Reviewers report

Title: Increased skin autofluorescence of children and adolescents with type 1 diabetes despite a well-controlled HbA1c: results from a cohort study

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Reviewer: Baqiyah Conway

Reviewers report:

Summary

Van der Heyden and colleagues investigated the relationship between skin autofluorescence in adolescents with Type 1 diabetes and HbA1c in adolescents with Type 1 diabetes. In both diabetic patients and non-diabetic controls, SAF increased with age. SAF was also increased across all age groups of adolescents with Type 1 diabetes compared to non-diabetic controls. SAF was associated with both current and average cumulative HbA1c values in univariate analyses but only with current HbA1c in multivariable analyses. When current HbA1c was dichotomized into <8.5%, 8.5%, and non-diabetic controls, those with and HbA1c 8.5% appeared to have the highest SAF values in all but the highest age group (17-19 year olds). The authors also stated that there were subgroups that had high HbA1c and low SAF or low HbA1c and high SAF, but the data presented did not seem to support this. The authors concluded that in general SAF does not appear to provide information beyond that of HbA1c in adolescents with Type 1 diabetes.

Strengths:

1. In general, this is a well written and easy to read manuscript.

2. Multiple measures of HbA1c from which to determine cumulative average HbA1c.

Concerns

Abstract. P. 3, lines 44-48. In the results section of the abstract it is not clear if the univariate and multivariable results presented are specific to the diabetic population. With the exception of the first results sentence, it appears that the remainder of the results are specific for the diabetic population. However, upon reading the actual manuscript, at least some of these results have the non-diabetic controls as the comparison group.

Methods
p. 6. The age range of the controls should be stated in the methods section. If the age range was 11-19 years, what type of school was this that included such a wide age range of children and adolescents?

p. 7, lines 111-113. Please clarify that this data is for the diabetic patient population only. In general it should be stated more clearly what anthropometric and laboratory data were collected in diabetic patients only. If not anthropometric or laboratory data were collected in the healthy controls, that should be stated.

p. 8, line 144. What was the study period?

Results.

1. A traditional participant characteristics table, with data stratified by Type 1 diabetes/healthy control status, would make it easier for the reader to get a picture of the study population. In lines 178-182 it cannot be determined whether the blood pressure and BMI data presented are for the diabetic population only, the healthy controls only, or for both.

p. 10, lines 194-196. Why was the Pearson correlation used for historical HbA1c, but he Spearman for current HbA1c?

p. 10, lines 196-198. The authors state: "Figure 3 shows that in a subgroup of patients, a low HbA1c is associated with a high SAF, whereas in another subgroup of patients, a high HbA1c is associated with a low SAF." However, this is not discernable from the Figure.

p. 11, lines 212-216. Is this data referring to current or to historical HbA1c. According to Figure 2, it is for current HbA1c. If so, please state this in the text.

Discussion

In general the authors over-emphasize subgroup differences in the relationship between glycemic control and SAF when the data as presented do not seem to support this.

p. 12, lines 234-246. If it is true that the study results show subgroup differences in the relationship between glycemic control and SAF (this reviewer would like to see stronger data demonstrating this) another possible explanation might be hypoglycemia induced oxidative stress.

p. 12, lines 248-249. Exclusion of non-Caucasians from the study and thus the non-necessity of adjustment for skin color was not a strength of this study; it was actually a weakness of the study due to the limited ability of autofluorescence readers to measure glycation induced fluorescence in non-fairskinned persons. This should be stated.

Table and figures
p. 20, lines 380-381. The table title should be more descriptive and be able to stand alone, separate from the main manuscript. What is the table showing univariate and multivariable linear regression analyses of? Also it is not necessary to state that significant p-values are indicated in bold.

p. 22, lines 393-395. It is not clear what the reference group is. The concept of compared (compared, vs.) is used twice.

Figure 3. What do the p-values represent. Who are being compared? Or is this a test for global differences?

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

No

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

Quality of written English
Please indicate the quality of language in the manuscript:

Acceptable

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If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

I am a co-inventor of a patent using the SCOUT, a skin intrinsic fluorescence reader, to assess coronary artery calcification. I have also received a travel award in the amount of $1500 from VeraLight the inventor of the SCOUT skin intrinsic fluorescence reader. However, the VeraLight was dissolved and thus is no longer in existence.

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