PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	FACTORS ASSOCIATED WITH HIGH LEVELS OF GLYCATED HEMOGLOBIN IN PATIENTS WITH TYPE 1 DIABETES: A MULTICENTER STUDY IN BRAZIL
AUTHORS	ANDRADE, CARINE; RIBEIRO, GUILHERME; SANTOS, CARLOS ANTONIO; NEVES, RAIMUNDO CELESTINO; MOREIRA JR, EDSON

VERSION 1 – REVIEW

REVIEWER	Yoshifumi Saisho Keio University School of Medicine, Tokyo, Japan
REVIEW RETURNED	20-Jun-2017

GENERAL COMMENTS	In this study, Andrade et al. investigated the role of sociodemographic, behavioral and clinical factors on HbA1c levels of type 1 diabetes (DM1) patients. This was a cross-sectional study enrolling a total of 979 DM1 patients aged >=18 years from 10 major Brazilian cities. Sociodemographic, behavioral and clinical data were obtained through interviews. HbA1c, the main outcome measure, was measured by standardized liquid chromatography. Hierarchical multiple variable linear regression models were used to identify factors correlated with high HbA1c levels. The mean HbA1c levels were 9.4% and 89.6% of the patients had HbA1c >=7%. Factors independently associated with increased HbA1c levels were lower education, non-participation in diabetes classes/lecture, having a self-perception of poor adherence to diet and insulin, not having private medical care and not measuring HbA1c levels in the prior year. Among them, poor adherence to diet and insulin were the factors most strongly associated with high levels of HbA1c. Based on these results, the authors concluded that specific actions, particularly those targeting improving adherence to diet and insulin, may contribute to successful management of DM1 patients. Overall, the study was conducted properly and the results were clearly presented. Although the major limitation was that the information was obtained by interview, the relatively large sample size seems to overcome this limitation. The conclusion was straightforward and supported by the data presented. The message of the study to readers is clinically important to improve HbA1c levels in DM1 patients in Brazil. There are some comments. 1. Introduction. Page 5, line 16. “, a country where >31,000 persons <15 years of age have DM1”. Since this study included only the patients aged >=18 years, this sentence should be revised to the content more relevant to this study population.

	2. It would be better if BMI was included as clinical factors in the analysis. 3. In Table 2, number insulin doses per day. No patients used insulin pump? 4. As the questionnaire regarding self-monitoring glucose (SMBG) seemed too rough and not quantitative, this might be the reason why they failed to find the association between the frequency of SMBG and HbA1c levels. This point should be discussed in the manuscript. 5. Although the conclusion of the authors was straightforward, this was a cross-sectional study and causal relationships remain unclear. The authors should appreciate this limitation and discuss this point more clearly.

REVIEWER	Piotr Ladyzynski, Ph.D., D.Sc. Nalecz Institute of Biocybernetics and Biomedical Engineering of the Polish Academy of Sciences, Warsaw, Poland
REVIEW RETURNED	25-Jun-2017

GENERAL COMMENTS	The manuscript under review concerns factors associated with high levels of glycated hemoglobin A1c (HbA1c) in patients with type 1 diabetes. Authors considers three groups of factors associated with socioeconomic / sociodemographic, behavioral and clinical variables. Values of these variables for particular study participants were estimated based on results of a review / questionnaire. Authors performed the bivariate and multiple variable linear regression analysis to estimate the effect of the independent variables on the level of HbA1c. Variables with the most significant associations were then included in the robust, hierarchical, multiple variable models. The study is summarized with the general conclusion that poor glycemic control is associated with sociodemographic, behavioral and clinical factors. It is also suggested that actions targeting improving adherence to diet and insulin, may contribute to successful management of patient with type 1 diabetes. Below particular comments and questions related to the manuscript have been listed. • No randomization was used in the study. According to information provided in the manuscript it can be concluded that the medical centers taking part in the study were selected arbitrary. This rise doubts regarding the representativeness of the results. • These doubts are even stronger after considering that 63.8% of the participants are female and 62.4% of the participants lives in the Southeast region of Brazil. Authors are advised to provide justification that the study group was representative for the population of patients with type 1 diabetes aged 18 years or higher in Brazil. • All the analyzed data are based on results obtained from questioning participants. This means that authors' statement (page 5) that they "investigated the role of sociodemographic, behavioral and clinical characteristics in the levels of HbA1c" is not fully justified.

	In fact, authors studied an association of patients' perception of their own sociodemographic, behavioral and clinical characteristics with the level of HbA1c. The study would gain in objectivity if the data from a medical registry / record were used instead of the subjective patients' reported data. For example, in the current study authors assess not the number of patients with diagnosed retinopathy but the number of patients who think they have been diagnosed with retinopathy. • In page 6 it is mentioned that the study participants had been reviewed in years 2006-2007. This reviewer wonders why authors have waited for 10 years before they decided to publish their results. • In page 8 the Akaike Information Criterion (AIC) is mentioned. However, values of AIC for the models considered in the manuscript are not reported and they are not used to select the most appropriate model. • The way in which the hierarchical models are used is not convincingly justified. It seems that the AIC should be used to select the most appropriate model and then this model should be used to interpret the results. It is not clearly clarified, e.g. why authors consider on Model C variables which are not statistically significant (i.e. "Education – primary care or less"). • The conclusion in abstract is too general. It should be modified to be more specific. • Discussion is very general. In its current form it does not contribute much to what has been discovered an reported earlier by other researches. Thus, authors are advice to modify the Discussion stressing their original contribution. • This reviewer suggests to replace a word "multicentric" in the title of the manuscript to more commonly used word "multicenter".

REVIEWER	Adam J. Streeter Plymouth University Peninsula Schools of Medicine and Dentistry, Plymouth, United Kingdom
REVIEW RETURNED	31-Jul-2017

GENERAL COMMENTS	Major comments: Please could you clarify how you selected the categorical variables or factors for your multivariable models: You have stipulated a significance level of 5% ($p<=0.05$) for inclusion of candidate variables. However, in the tables and in the results and discussion, you have only referred to the p-values pertaining to the comparator levels of each factor. In this case, these p-values represent the significance test of whether a certain level is different from the reference level. This may be useful and interesting in understanding where the differences exist between levels of a significant factor, but where any factors have more than two levels, then selection should be based on a global test of significance of each non-binary factor, not on whether any particular level of a factor is different from the reference level.

	Please avoid contradictions in terms: There are two: page 18 line 16 “independently associated”, and page 19 line 19 “independent correlation”. If you are suggesting that there was an association between two variables, having adjusted for possible confounders then please state this. If you are suggesting there was no association or correlation, then write there was no association or correlation, preferably reflecting statistical uncertainty in the detection of effects (e.g: “no evidence of association”, “no correlation was detected”, “small non-significant effect size”, etc). Page 6, line 33: a pre-tested questionnaire is mentioned, but what is this? Was it a validated questionnaire? How was it pre-tested and on whom? Please either provide the reference to the relevant study, or briefly describe how the questionnaire was tested, including a copy of the questionnaire in an appendix. Page 8 lines 4-9: a “previously defined conceptual framework” is mentioned. You will either have to insert a reference to this or briefly describe what you mean. It sounds like you are using a mixed-effects approach to allow for clustering around cities. You also mentioned “distal determinants”, but this definition that attributes direction to the spatiotemporal scale is not universally acknowledged and may confuse a large section of your potential readership (Krieger N. Proximal, Distal, and the Politics of Causation: What’s Level Got to Do With It? American Journal of Public Health. 2008;98(2):221-230. doi:10.2105/AJPH.2007.111278.). I would advise re-writing this section using less obscure terms. Building the regression model through backward elimination using successive blocks of variables was clearly described, but no justification was presented for following this method, as opposed to, say, eliminating variables from a saturated model or forwards building from a null model. Could you include a brief justification for this approach please? The reduction in the effect of education with the subsequent introduction of further variables from blocks 2 and 3 should be mentioned in the final paragraph of the results section on page 14. This forms the basis for the discussion of mediation in the final section of the paper. The presence of mediation is first mentioned, out of the blue, in the first paragraph of the discussion on page 16, without justification. Only later in the third paragraph on page 17 does further discussion follow, and the basis for this conclusion become clear. Currently this is too disjointed. Please discuss mediation in a single paragraph, having highlighted the associated change in the coefficients of the affected variables in the results. Page 17, line 2: The text states “ . . patients with primary school or less had a mean level of HbA1c nearly 1% greater greater than patients with at least some college level education.” The distribution of HbA1c levels are not on a scale that justifies rounding the effect estimate up to the nearest integer. On that basis, all the other estimates are either 0 or 1%. Please revise to at least 1 decimal place. Also the text “ . . patients with primary school or less . .” does not make sense. If you were referring to patients, whose highest level of educational attainment was primary school, then please write something to that effect. Minor comments: The journal may accept mathematical inequality signs instead of full English text (e.g: “less than or equal to”), but at times these are confusing. Better communication may be served by replacing these with their text equivalents. Regardless of the journal policy, I would recommend this for line 16 on page 5. Page 4, line 28 – . . aiming for glycated . . .

	Page 9, line 19 – . . . self-referred were white . . Page 14, line 7: . . . HbA1c levels were, on average, reduced by . . . Page 15, table 3: Caption reads “The Model shows . . . “. Writing “Model A shows . . . “ would be clearer. Page 18, line 30: “evidence” is singular. Page 19, line19: Any correlation would be between the factor describing measurement in the last year and HbA1c, rather than one level of that factor (i.e: no measurement in the previous year). A level of a factor cannot itself correlate with anything. Really you ought to either describe the correlation between the factor and the outcome, or more simply, you should be describing how measuring HbA1c is associated with lower levels of HbA1c, which is arguably a clear statement. That result itself is interesting and is consistent with historical and sustained monitoring being better for controlling HbA1c levels, which makes sense. Page 19, line 26: Your message may be clearer if you define who the “counterparts” are (patients exclusively receiving publicly funded healthcare?), and to talk about the effect on HbA1c in comparison to private services. Page 20, line5: I think interviews may be widely used, rather than “interviewers”.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Yoshifumi Saisho
Institution and Country: Keio University, School of Medicine, Tokyo, Japan
Competing Interests: None declared

The authors mostly, but not sufficiently, responded to the comments.

1. If there are no data available regarding the prevalence of T1DM in Brazil, the authors should comment this in the manuscript for international readers.

2. If the authors included BMI in Table 2, Methods section and Table 1 should also be revised accordingly.

3. It is a surprise that there are no patients with T1DM treated with insulin pump in Brazil. Since the use of insulin pump would affect glycemic control, the authors should state this point clearly in the manuscript.

4. If this study uses a part of the cohort previously published, this point should be clearly described in the manuscript.

Reviewer: 2
Reviewer Name: Piotr Ladyzynski
Institution and Country: Nalecz Institute of Biocybernetics and Biomedical Engineering of the Polish Academy of Sciences, Warsaw, Poland
Competing Interests: None declared

The authors adequately discussed the comments and persuasively answered the questions contained in the review of the original manuscript. This reviewer has no additional comments.

VERSION 2 – REVIEW

REVIEWER	Yoshifumi Saisho Keio University, School of Medicine, Tokyo, Japan
REVIEW RETURNED	29-Aug-2017

GENERAL COMMENTS	The authors mostly, but not sufficiently, responded to the comments. 1. If there are no data available regarding the prevalence of T1DM in Brazil, the authors should comment this in the manuscript for international readers. 2. If the authors included BMI in Table 2, Methods section and Table 1 should also be revised accordingly. 3. It is a surprise that there are no patients with T1DM treated with insulin pump in Brazil. Since the use of insulin pump would affect glycemic control, the authors should state this point clearly in the manuscript. 4. If this study uses a part of the cohort previously published, this point should be clearly described in the manuscript.

REVIEWER	Piotr Ladyzynski Nalecz Institute of Biocybernetics and Biomedical Engineering of the Polish Academy of Sciences, Warsaw, Poland
REVIEW RETURNED	17-Sep-2017

GENERAL COMMENTS	The authors adequately discussed the comments and persuasively answered the questions contained in the review of the original manuscript. This reviewer has no additional comments.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Yoshifumi Saisho
Institution and Country: Keio University, School of Medicine, Tokyo, Japan
Competing Interests: None declared

The authors mostly, but not sufficiently, responded to the comments.

Comment:
1. If there are no data available regarding the prevalence of T1DM in Brazil, the authors should comment this in the manuscript for international readers.

Response: As requested, we added a sentence informing that DM1 disease burden had not been estimated for adults in Brazil (last paragraph of the Introduction Section).

Comment:
2. If the authors included BMI in Table 2, Methods section and Table 1 should also be revised accordingly.

Response: Done.

Comment:
3. It is a surprise that there are no patients with T1DM treated with insulin pump in Brazil. Since the use of insulin pump would affect glycemic control, the authors should state this point clearly in the manuscript.

Response: We stated in the Discussion Section of the manuscript that use of insulin pumps in Brazil is not covered by the public national health system and it is incipient even for patients treated at private health services because insulin pumps are not produced in the country and the imported product is sold at an unaffordable price (>US$ 4,000.00). We added references accordingly.

Comment:
4. If this study uses a part of the cohort previously published, this point should be clearly described in the manuscript.

Response: We described in the first sentence of the Methods Section that detailed information on this cross-sectional, multicenter study was published before.

VERSION 3 – REVIEW

REVIEWER	Yoshifumi Saisho Keio University School of Medicine Tokyo, Japan
REVIEW RETURNED	18-Oct-2017

GENERAL COMMENTS	The authors responded to the comments appropriately.