Author’s response to reviews

Title: Current epidemiology of diabetic retinopathy in patients with type 1 diabetes: a national multicenter study in Brazil.

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Author’s response to reviews:

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We would like to thank the reviewers for their valuable comments. These comments will certainly improve the quality of our manuscript.

Reviewer reports:

Viswanathan Mohan (Reviewer 1):

It is a good cross-sectional study with a reasonably large sample size that has been done in people with type 1 diabetes (T1D) in Brazil and has looked at prevalence of diabetic retinopathy (DR) and vision threatening DR (VTDR) and the associated risk factors. The study has shown that other than the traditional risk factors (duration of diabetes and HbA1c), uric acid was found as an additional risk factor associated with DR.

1. The retinopathy (DR) has been diagnosed by fundus examination (indirect ophthalmoscopy) by ophthalmologists done at different centers in Brazil in this study. Since many ophthalmologists have been involved in diagnosis of DR in this study, there is a possibility of inter-observer variation in detection of DR or identifying VTDR. Please mention if there any assessment of inter-observer variability or agreement between the various examiners with respect to assessment of DR/STDR.

Answer:

We described in the Methods section (Data collection), page 9, line 211, that the ophthalmologists enrolled in the screening for diabetic retinopathy, attended previously a meeting where they were
trained to standardize the exam and the terminology. All the ophthalmologists were experienced retinal specialists and the classification criteria followed an international standardization of classification of diabetic retinopathy (ref. 16).

Concerning the assessment of inter-observer variability, we agree with the reviewer, but this was not performed in the present study. Considering that this was a multicenter study in Brazil, a huge country with continental dimension, we were unable to match all the exams due to logistics impossibility. We included this information as a limitation of the study, in discussion section, page 19, line 421.

2. Table 1 can possibly be skipped as Table 2 has all the variables comparing clinical and biochemical information of patients with and without DR/VTDR.

Answer:

Table 1 has some information which are not present in table 2, as follows: age of diagnosis, diet adherence, insulin regimens, and the prevalence of the different levels of diabetic retinopathy. Besides that, table 1 refers to the information of the whole group (1,644 patients) and table 2 analyzes the variables separately according to the type of diabetic retinopathy. Although we consider relevant to keep both tables, we leave the final decision to the reviewer.

3. Use of ACE inhibitors has been shown to be significant in patients with DR in Table 2. A few words to elaborate on it can be added to the discussion section

Answer:

We appreciate the suggestion and added in the Discussion section a possible explanation for the present result. We believe that the use of ACE inhibitors has been significant because its use is related to arterial hypertension, a variable that was also significant in descriptive as well in multivariate analysis. We included that in Discussion section, page 16, line 359.
When we check the data in table 3, we realize that we forgot to put the significant results of the use of ACE inhibitor also in the group with retinopathy present vs. absent. We have already corrected the table and apologize for this mistake.

Deborah A. Chyun (Reviewer 2):

1. Inclusion criterion of no DKA may have selectively omitted subjects at high risk of outcome. This needs to be acknowledged.

Answer:

The presence of DKA in the last 3 months prior to the study was an exclusion criterion, and we agreed that we may have omitted high-risk patients. However, these patients generally maintain poor glycemic control and glycemic instability that could interfere in the evaluation of retinopathy.

When reviewing the manuscript, we realized that we included in the study patients with less than 5 years of diabetes. Of the 1644 patients evaluated for diabetic retinopathy, 115 had less than 5 years of disease, 105 had no diabetic retinopathy, 7 had mild non-proliferative diabetic retinopathy and 1 had moderate non-proliferative retinopathy. We apologize and correct in the text, Methods section, page 7, line 153. We also included this information as a limitation of the study, in Discussion section, page 19, line 423.

2. How do you account for lower risk with higher levels LDL?

Answer:

We believe that patients with high levels of LDL probably use statins or fibrates and these drugs could have a protector effect on diabetic retinopathy. The impact of statins and fibrates on reducing diabetic retinopathy is still a debate. However, studies on patients type 2 diabetes have shown, that the use of fibrates and statins prevent the progression of diabetic retinopathy and reduce the requirements of laser therapy, independent of the effect on cholesterol control or levels. We
included this explanation in results section, page 15, line 328, and in discussion, page 17, line 391, with the corresponding references.

3. How is adherence to diet assessed?

Answer:

Self-reported adherence to diet was evaluated using questions related to nutritional factors associated with diet, such as whether the patient followed a prescribed diet and adherence of patients to the reported diet. Adherence was defined as following the reported diet at least 80% of the time (ref. 12).

Kurubaran Ganasegeran (Reviewer 3):

Thank you for giving me the opportunity to review this manuscript. The manuscript is a cross-sectional study with a large nationwide representative sample. I have few minor comments that I feel the authors need to address before the manuscript qualifies for publication.

1. Please describe briefly the sampling technique and sample size determination of the study. Why was the participants only selected from an urban setting?

Answer:

The sample size of the present study was based on the Brazilian Multicenter Type 1 Diabetes Study described elsewhere, according to the number of patients studied in each region of the country (ref. 12). We aimed to maintain the representativeness of the distribution of T1D cases across each geographic
region of Brazil, estimated according to the population distribution reported by the 2000 Brazilian Institute of Geography and Statistics Census (IBGE), ref 17.

The population of Brazil is divided into 85% in urban areas, based on IBGE’s data and our study included centers only in these regions because they are where most patients with type 1 diabetes are treated.

We have added the above information, in Methods section, page 9, line 221.

2. In the methods part, the part on data collection is difficult to gauge. Please explain by having the following sub-sections: instruments used/measurements, procedures, baseline parameters (please define all parameters used to measure with references). The current description has no references provided.

Answer:

We mentioned in Methods (data collection-laboratorial data) section, page 8, line 189, that we adopted the American Diabetes Association's (ADA) goals for adequate metabolic and clinical control. However, we have included the requested parameters in the text, with their respective references (Methods, page 8, line 190). We also included in methods, the sub-sections (clinical data, page 7, line 164, laboratorial data, page 8, line184, diabetic retinopathy data, page 9, line 208, sample data calculation and evaluation of economic status, page 9, line 221).

3. Statistical analyses should be mentioned as descriptive, univariate and multivariate analysis.

Answer:

We corrected the terms in Methods, statistical analysis section, page 10, line 239 and 243. Also in results section, pages 12 (line 277), 13 (line 299) and 14 (line 316).
4. How did the authors determined on what factors were to be included in the multivariate model? At univariate level, the crude OR should have been mentioned as well.

Answer:

We considered all variables with \( p \leq 0.1 \) in the univariate and some variables of interest like gender and economic status to included in the multivariate analysis. In relation to the crude OR, we created a table and added as an additional table file (additional files, tables S2 and S3). We entered this information in the text, methods section (statistical analysis subsection, page 10, line 244) and in results section, page 14, line 311. However, if the reviewer considers it necessary, we can include the tables in the main text.

Yours sincerely,

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