Author's response to reviews

Title: SOD2 gene Val16Ala polymorphism is associated with macroalbuminuria in Mexican Type 2 Diabetes patients: a comparative study and meta-analysis

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Author's response to reviews: see over
Dear Dr. Tim Sands

Executive Editor

BMC Medical Genetics

Dear Dr. Tim Sands

We are responding the comments to our research article “SOD2 gene Val16Ala polymorphism is associated with macroalbuminuria in Mexican Type 2 Diabetes patients: a comparative study and meta-analysis.”

We thank the reviewers for the helpful comments and suggestions. We have modified the manuscript according to the comments of the reviewers. The modifications of the manuscript are highlighted in gray. Detailed information is provided below.

Sincerely yours

Iván de Jesús Ascencio Montiel
Response to Reviewers

Title: SOD2 gene Val16Ala polymorphism is associated with macroalbuminuria in Mexican Type 2 Diabetes patients: a comparative study and meta-analysis

Reviewer: Maria E Tejero.

Comment 1: “There are many confounders that are not considered in the manuscript such as variation in other enzymatic and non-enzymatic antioxidants of different sources, practice of regular physical activity, type of diabetes medication, duration and intensity of smoking. Some of these variables are difficult to analyze, however the possible contribution to the observed results should be discussed”

Answer: We included in our analysis many of the factors that have been associated to macroalbuminuria in previous studies (sex, duration of type 2 diabetes, hypertension, lipid profile, smoking, HbA1c, and hypertension treatment with ACE or ARB) and we made an effort to avoid the inclusion of participants with some other traits that could be potentially associated with macroalbuminuria (urinary tract infection, hematuria, acute febrile illness, vigorous exercise and acute heart failure). However, as pointed out by the reviewer, our study did not contemplate many other potential factors (enzymatic and non-enzymatic antioxidants of different sources, practice of regular physical activity, type of diabetes medication, duration and intensity of smoking). We have modified the manuscript to indicate these limitations of the study.

Comment 2: “The discussion is focused on the genetic analyses, and does not elaborate on other interesting results such as those presented in Table 3, showing data of the logistic regression. What is the contribution of the analyzed genetic variation in SOD2 within the proposed model?”

Answer: We have added text to discuss the results for the other factors included in the logistic regression analysis (e.g. significant results for sex, duration of type 2 diabetes, BMI, blood pressure, lipid profile, smoking, HbA1c, hypertension diagnosis and treatment). As we now indicate in the manuscript, many of our results are consistent with what has been reported in other studies.

As for the relative contribution of the polymorphism within the logistic model, we now provide pseudo R2 values before and after introduction of rs4880 in the logistic models. We find that addition of the SOD polymorphism only marginally increases the pseudo R2 values.
Comment 3: “The authors mentioned that no evidence of urinary tract infection, hematuria, acute febrile illness, vigorous exercise and acute heart failure were observed in all the participants, how was this determined?”

Answer: This was determined by clinical examination and general urine testing, and we have modified the text to state this more clearly.

Comment 4: “It would be of interest to present information on other DM2 abnormalities related to oxidative stress, such as retinopathy or neuropathy in the compared groups”

Answer: We have modified the text to report that no information was available regarding retinopathy or neuropathy.

Comment 5: “It calls attention that current and previous smoking has an OR of 0.407.”

Answer: We found an inverse association between smoking and macroalbuminuria. As we now mention in the manuscript, smoking has been found to be a risk factor for DN in previous studies. However, other studies have failed to confirm these findings.

We also note that, although we had information about current or previous tobacco use, we did not have data about other relevant factors, such as duration or intensity of smoking, and this is one of the limitations of this study.
Reviewer: VenkataSaroja Voruganti.

Comment 1: “Conclusions should be toned down and talk about what was found in the study, such as ‘significant association was found between SOD2 Val16Ala polymorphism and macroalbuminuria and C allele was found to have protective effect against macroalbuminuria’. Although this polymorphism is a missense one, causal effect is not shown in this manuscript, therefore should not be mentioned in conclusions, okay to do so in discussion.”

Answer: We have modified the manuscript according to the reviewer’s comments.

Comment 2: “Abstract: Number of subjects with macroalbuminuria is much less than those with normoalbuminuria.”

Answer: As we indicate in the modified version of the manuscript, this is due to the low prevalence of macroalbuminuria among type 2 diabetes patients. For example De Pablos et al. have reported that the prevalence of macroalbuminuria among T2D patients in a Spanish population was approximately 12% [35], and in Mexico the prevalence has been estimated between 9 and 10% [36, 37].

Comment 3: “Discussion: The statement “our data strongly suggests that the significant results observed in the full dataset are not due to the presence of population stratification” is misleading. AIMs were available for only less than half of the sample (~45%) and cannot be generalized to the whole sample.”

Answer: We have slightly modified the text to make our statement more clear. As we indicate in the modified version of the manuscript, “Overall, our data suggests that the significant results observed in the analysis of the full dataset are not due to the presence of population stratification. If stratification was responsible for the results observed in the full sample, we would expect that an analysis of the subsample incorporating ancestry in the statistical models would lead to differences in the ORs observed in both samples. Instead, the ORs are similar in both analyses (in fact, the ORs for the CC and CT genotypes are slightly lower in the model including ancestry than those observed in the full sample, without correction for variation in ancestral proportions).”

Comment 4: “Needs some grammatical corrections”

Answer: We made some grammatical corrections in the modified version of the manuscript.
Comment 5: “Statistical analysis: First sentence- Pearson tests are conducted for correlations between continuous variables and not for assessing group differences in categorical variables.”

Answer: We have corrected the manuscript.

Comment 6: “Results: Number of normalbuminuria subjects is given as 882 instead of 875”

Answer: We changed the number of normoalbuminuria subjects 882 for 875 in the results section.

Comment 7: “Results: Second paragraph, in the sentence, ‘Using an unconstrained genetic model, the genotypes CT and CC had lower odds ratios of..., it should be ‘macroalbuminuria’ instead of ‘microalbuminuria’.”

Answer: We have replaced the word ‘microalbuminuria’ for ‘macroalbuminuria’ in the second paragraph of results section.

Comment 8: “The word ‘higher’ for p values is confusing. Write them as stronger or weaker”

Answer: We changed the word ‘higher’ to ‘weaker’ for p values.

Comment 9: “P values and odds ratio can be restricted to two digits after decimal point.”

Answer: We restricted the odds ratio values to two digits. However, we have maintained three decimal digits for p values.