Author’s response to reviews

Title: Self-Reported Hypoglycemia in Adult Diabetic Patients in East Gojjam, Northwest Ethiopia: Institution Based Cross-Sectional Study

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Author’s response to reviews:

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Subject   Submitting Revised Manuscript after Reviewers comment

SUMMARY OF RESPONSES TO THE PEER REVIEWERS’ COMMENTS

We named here under, submitting revised manuscript titled “Self-Reported Hypoglycemia in Adult Diabetic Patients in East Gojjam, Northwest Ethiopia: Institution Based Cross-Sectional Study”. This manuscript is revised as follows according to Academic editor’s and reviewers’ comment.

For ACADEMIC EDITOR

Point by point response
EDITOR Comments Authors’ Response

1. How the patients were included in the study         Thank you!

Samples were selected by systematic random sampling technique. During study period there were about 1100 diabetic patients who were registered and have regular follow up at follow up clinic. Most of the patients are appointed at interval of four to eight weeks. However, for some patients the frequency of their visits can vary depending on their blood glucose level. The total number of diabetic patients who had follow-up from September 15, 2017 to November 15 2017 was taken to estimate the current patient flow. The sampling fraction (Kth) was calculated by dividing N/n (850/403=2.1), where N=estimated number of patients that will be seen during the study period and n= calculated sample size using single population proportion formula. Then systematic random sampling technique was employed to approach the study participants. The first patient was selected by lottery method from the
first two patients. Then study participant was selected every two patients until the required sample size is achieved. From the selected diabetic patients, 394 of them gave consent and participated in the study.

2. A clarification as to how was hypoglycemia objectively documented

Dear academic editor thanks for your suggestion. During their visit patients were asked about the sign and symptom of hypoglycemia and how they treat. If patients had typical symptoms of hypoglycemia which are improved after administering carbohydrates, glucagon, or other corrective actions, the patients were considered as they did have hypoglycemic event. The fasting blood glucose level was determined for all patients during their visit. Many of the patients with hypoglycemic symptoms go to nearby health facility to check their blood glucose level. Only few patients were able to determine their blood glucose level at home.

3. Additionally, the authors are encouraged to carefully proof read their manuscript to correct numerous English language issues also pointed out by the reviewers. Thank you

We agreed with your suggestion and we have tried to revise it.

For Reviewer #1
Point by point response

Reviewers’ Comments Authors’ Response

1) In the abstract section, authors state that "394 sampled diabetic patients were selected through systematic random sampling technique" meanwhile in the study design section; they state: "all diabetic patients who have follow up at the diabetes clinic were included". The authors must clear if the included patients were randomly selected or by convenience sampling.

Dear reviewer,

Samples were selected by systematic random sampling technique. During study period there were about 1100 diabetic patients who were registered and have regular follow up at follow up clinic. Most of the patients are appointed at interval of four to eight weeks. However, for some patients the frequency of their visits can vary depending on their blood glucose level. The total number of diabetic patients who had follow-up from September 15, 2017 to November 15 2017 (which was 850) was taken to estimate the current patient flow. The sampling fraction (Kth) was calculated by dividing N/n (850/403=2.1), where N=estimated number of patients that will be seen during the study period and n=calculated sample size using single population proportion formula. Then systematic random sampling technique was employed to approach the study participants. The first patient was selected by lottery method from the first two patients. Then study participant was selected every two patients until the required sample size is achieved. From the selected diabetic patients, 394 of them gave consent and participated in the study.

2) In the material and methods section, the authors explain that they defined hypoglycemia like "an event during which there are typical symptoms and improve after administrating carbohydrates or glucagon or if patients measured their plasma glucose concentration and was below 70 mg/dl". Why do the authors decide to include the first definition? Some patients may report hypoglycemia even when their glucose levels are normal (relative hypoglycemia). Why not only consider the information of patients in whom hypoglycemia was demonstrated with plasma concentration? Thank you reviewer.

Some patients may report hypoglycemia even when their glucose levels are normal. The lack of a standard hypoglycemia value make clinical study of hypoglycemia very difficult. However, the American diabetes association (ADA) suggests defining hypoglycemia if patients have typical symptoms which are relieved with glucose intake. Patients were asked if they have ever experienced low blood sugar record (<70mg/dl) or symptoms of low blood sugar previously?e.g. sweating, shaking, headache, palpitation, hunger, passing out and alleviation of symptoms with glucose
administration?
The fasting blood glucose level was determined for all patients during their visit. Many of the patients
with hypoglycemic symptoms go to nearby health facility to check their blood glucose level. Only few
patients were able to determine their blood glucose level at home.
By considering this fact, we consider all self-reported episodes by patients as hypoglycemic events. Thank you.
3) In table 2, in the results section: In order to understand the hypoglycemia phenomena (and the OR
related to use of insulin), the authors should include what type of oral treatments and insulin were used
and what proportion of patients with type 2 diabetes was in treatment with OHA, OHA and insulin and
insulin alone. Thank your reviewer really!
• Now we incorporated the proportion of each type of oral treatments and each types of insulin
that used for treatment. Additionally, these treatments were categorized in to three category OHA, OHA
and insulin and insulin alone in order to make it sound for analysis. Since the presence of small
observation make difficult to use logistic regression analysis Moreover, the proportion of patients with
type 2 diabetes with OHA, OHA and insulin and insulin alone was determined and included on this
version of the paper
Thank you very much!!!

4. In the table 3, the authors describe the frequency of diabetes related complications and comorbidities
in the total population, and in patients with type 1 and type 2. However, they didn't describe if there are
statistical differences among groups. Thank you reviewer!
We describe the statistical differences among patients with type 1 or type 2 diabetes with p value after
proportion calculation.
5) In the same way, figure 1 and table 4 must describe if there were statistical differences among
patients with type 1 or type 2 diabetes. Additionally, I suggest analyzing if there were differences in the
number of hypoglycemic episodes in each population. • Thank you very much!
• We describe the statistical differences among patients with type 1 or type 2 diabetes with p
value after proportion calculation. However, for hypoglycemia we consider it on logistic regression
model analysis to examine whether these variables significantly associated with hypoglycemia or not.
If it is necessary we can add on next revision.
6) I suggest to synthetize the results presented in all the tables. The authors could report the
percentage (and the total number) of those patients that present a particular characteristic (e.g only
those assigned as "Yes"). The readers can assume which one is the negative percentage. Thank you!
We have tried to do so wherever applicable. On some of the tables we wanted to show both types of
characteristics and we kept it the same way.
7) In the table 5, the authors describe OR and adjusted OR. But, which were the factors that were used
to adjust them?
Thank you very much!
Dear reviewer after binary logistic regression 14 studies were entered to the final analysis. As it stated
on line no 232-236 from 14 factors only 4 of them were significant. That means 10 of them were used
to adjust them. And it was already stated on the first and the second paragraph under the subtopic of
“Factors associated with hypoglycemia”.

8) The discussion section didn't highlight the importance of the study.
Thank you reviewer!
We try to highlight the importance of the study on the first paragraph of the discussion
9) The manuscript requires full grammar revision. Thank you very much!
We have tried to improve it.

The main limitation of the study is patient's lack of confirmation of glycemic levels during symptoms and that the authors didn't described the full characteristics of the treatments used by them. Additionally, the conclusions obtained by the authors have been previously proven in other studies.

Thanks reviewer!
This study tried to assess the episode of self-reported hypoglycemia ever since diagnosis. That means if the patient reports the event according to the criteria of ADA, they were considered as they did have hypoglycemia. If the patients have hypoglycemic history but not measure their blood glucose level at the time, it is difficult to know blood glucose level at that time. Many of the patients had difficulty to determine the blood glucose level at that time of the event. We understand that this is one of the limitations of the study. But since the objective was to determine the self-reported incidence in real world setting and we wanted to minimize underestimation of the problem we just take the patients report and the documentations from the patients chart.
Generally hypoglycemia in diabetes is manly studied in clinical trial settings, which might not show the real burden. We believe that the study has great value especially in Ethiopia because of several reasons 1) the patient population and the follow up is different from the developed countries 2) there are no adequate studies which show the burden of hypoglycemia in patients in developing countries 3) developing countries like Ethiopia are having an enormous increase in patients with diabetes and 4) Regional (Sub-Saharan Africa) and relevant data on hypoglycemia should be considered by health care providers and policy makers

Thank you!

For Reviewer #II
Point by point response

Reviewers’ Comments
Authors’ Response

1. This study shows that diabetic patients with type 1 diabetes were more likely than patients with type 2 to present with hypoglycemia. That is not clear in the abstract and therefore should be corrected.

Thank you!

We accept your constrictive comment and we have corrected it.

Thanks again!

2. Line 141: the word literature is written twice  Thank you Reviewer! We have corrected it.

3. Line 174- 53.6% of the subjects had diabetes mellitus type 1, which is an unusual finding and would warrant further clarification i.e. the methods used to identify the type of diabetes mellitus in Ethiopia.

   • Thank you Reviewer!
We appreciate your concern. The methods used to identify the type of diabetes mellitus in Ethiopia are similar to what used in the rest of the world, which are mainly the clinical presentation (age, family history, poly-symptoms, and body habitus) and response to treatment. The proportion of type 1 diabetes is higher than seen in other areas because 1) the study was conducted in a semi-urban area where most of the patients were poor farmers having diabetes mellitus since childhood 2) might be related with childhood viral infections 3) Additionally, in an area where obesity is not common prevalence of type 1 diabetes might be greater than type 2.

These all factors might result in high number of type 1DM when compared with type 2.

4. Line 180- Please clarify how hypertension was documented For a management purpose comorbidity was documented on patient card. Therefore during data collection the data collectors observe their medical history.

5. Line 180/183 - please clarify how retinopathy and the rest of the complications stated were documented
   • Thank you very much!

Diabetic patients who have follow-up in the hospital are screened for chronic complications and on patient card the complications are documented. The data collectors got it from card review.

6. Line 263: The phrase "absolute or relative insulin excess due to insulin therapy" is not correct and should be omitted
   Thank you Reviewer really. We have corrected it.

The bibliographical references are inadequately written and some of the pages of the articles are missing (Line 349, 360, 368)

   Thank you Reviewer. We have corrected it.

The article contains several grammatical mistakes and the authors would be advised to have a native English speaker's contribution.

   Thank you Reviewer. We have corrected it.

Point by Point Response

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