Author’s response to reviews

Title: Predictors of vascular complications among type II diabetes mellitus patients at University of Gondar Referral Hospital: a retrospective follow-up study.

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Version: 1 Date: 07 Jun 2018

Author’s response to reviews:

Subject: Submission of a revised manuscript to BMC endocrine disorders

Dear Editor,

I am pleased to submit the revised research article BEND-D-18-00039 for consideration of publication in BMC endocrine disorders. In this revised manuscript, we have addressed all the questions raised by the reviewers point by point.

We believe that this revised manuscript is appropriate for publication by BMC endocrine disorders because it is in line with the aim and the scope of the journal. Our manuscript creates a paradigm for future studies on diabetes and its complications.
This manuscript has not been published and is not under consideration for publication elsewhere. We have no conflicts of interest to disclose.

Please address all correspondence concerning this manuscript to me at haileabfekadu@gmail.com

Thank you for your consideration!

Sincerely,

Haileab Fekadu

Corresponding author

CHII-MIN HWU (Reviewer 1)

Questions

1. The major limit of the study is its study design. Data were collected after the primary outcome having already been detected. Many of the sources of sample distortion bias are hidden. Any systemic difference in ascertainment of outcome will result in a biased sample. For example, the authors did not explain exactly how they ascertained the study patients. We also do not known inclusion and exclusion criteria for data registry. We require information about building the study dataset. Unfortunately, the investigators did not provide it in the present manuscript.

Answer-Thank you very much for this nice comment for the improvement of the manuscript and we accepted it. Study subjects are selected randomly by using simple random sampling technique among Type 2 DM patients who are newly diagnosed between September 2005 and August 2012 G.C.
The inclusion a criterion was newly diagnosed Type 2 DM patients who are newly diagnosed between September 2005 and August 2012. The exclusion criteria was all newly diagnosed type 2 DM patients who have any of the vascular complication at the start of the study and newly diagnosed type 2 DM patients who have a missing on key variable and this criteria’s are included in the edited version of the manuscript.

2. I am confused by the primary outcome of this study. Mixing occurrence of micro- and macro-vascular complications into a composite endpoint seems to acknowledge that all vascular complications occurred in these patients were attribute to DM, which might not always be the case.

Answer-Thank you very much for showing as the gap of this study and we accepted the comment. Yes this is one of the limitations of the study and we included this as a limitation in the last paragraph of the discussion part.

3. As stated by the authors in the Discussion, the current composite endpoint would overestimate diabetic vascular complication rate in patients with diabetes. In this study, the incidence rate of any vascular complication in these newly-diagnosed patients was 4% a year, which is higher than results from other studies. I wish the investigators could present results of individual component of the outcome, not just the composite outcome as a whole.

Answer- Thank you so much again for your comment and we accepted the comment.

The incidence density for each of the individual vascular complications was also calculated and it was found to be 18.4/100 person year observation for retinopathy, 14.4/100 person year observation for nephropathy, 18.9/100 person year observation for neuropathy 17.0/100 person year observation for stork, 16.7/100 person year observation for CHD and 15.1/100 person year observation. This is already mentioned on the result section of the manuscript and in some parts of the discussion.
4. The present study only included data from patients from a single hospital. The subject number is not large enough to conclude anything generalize to general patient population.

Answer- Thank you very much for this basic comment to improve the quality of the manuscript. To check sufficiency of samples, minimum sample size (364) was determined for the incidence and predictors using st power command of software Stata version 14.0. The institution where the study conducted is one of the few hospitals which have large diabetic follow up center which serve many people and there is a uniform standard of care for all DM patients in all follow-up centers in the country. So this sample can be a representative for all type 2 DM patients and it is adequate to conclude or to make generalizations about the general patient population.

5. Please use the term "type 2 diabetes mellitus" instead of "type II diabetes mellitus".

Answer- Thank you very much. We accepted the comment and corrected it on the revised version of the manuscript.

Aldo Ferreira-Hermosillo, MD, MSc (Reviewer 2)

Questions

1. The meaning of an abbreviation should be specified from the first time it is used. In different sections of the manuscript, there are abbreviations not clarified (e.g. in Abstract section, line 46 : AHR).

Answer- Thank you very much. We accepted the comment and corrected it on the revised version of the manuscript.

2. The key words "vascular complication" and "University of Gondar" are not MeSH terms.

Answer- Thank you very much. We accepted the comment. We have removed “university of Gondar” and “vascular complication” from the key words list and we added the word “predictor”

3. The manuscript has misspellings that are repeated systematically (e.g. "dieses", "Stork", "patents", "co morbidity").
Answer- Thank you very much. We accepted the comment and corrected it on the revised version of the manuscript.

4. The authors must clarify what does "Institution based" study means. I think authors refer to a single-center study.

Answer- Thank you very much for the comment and we apologize for not making it clear. The word “Institution based” is used to show that the study is done in a single institution that means the data collection was done only on patients who came to the hospital (University of Gondar referral hospital) and no data is taken from the general community who didn’t come to the hospital.

5. Material section lacks of the diagnostic criteria used to define each vascular complication assessed (this must be specified despite the study only recorded it from clinical chart).

Answer- Thank you very much for this key and basic comment for the improvement of the manuscript and we accepted the comment. We have stated the diagnostic criteria used to diagnose each of the vascular complications in the materials section of the revised manuscript with reference. The diagnostic criteria’s used are:

- Retinopathy- diabetic retinopathy was defined by both direct and indirect ophthalmoscopy assessments done by retinal specialists confirmed by fundus photography.

- Neuropathy- Diabetic neuropathy was defined by the history of numbness, paraesthesia, tingling sensation confirmed by touch sensation by 10gm monofilament, vibration sense by biothesiometer and ankle reflex.

- Nephropathy- Diabetic nephropathy was defined worsening of blood pressure control, swelling of feet ankle, hands or eyes, increased need to urinate, protein in the urine with a confirmation by tests like blood test, urine test, renal function test and imaging test

- Coronary heart diseases(CHD)- CHD was diagnosed by symptoms of chest pain(angina), shortness of breath or patients with symptoms of heart attack like crushing pressure in the chest and pain in the shoulder or arm, sometimes with shortness of breath and sweating with a confirmation by electrocardiogram (ECG) or echocardiogram
• Peripheral Arterial diseases (PAD) PAD was defined by the presence of history of intermittent claudication, coldness in the lower leg or foot especially when compared with the other side, weak or absent peripheral pulse in the legs or feet with a confirmation by Doppler ultrasound.

• Stroke. Stroke is defined as patients with sudden trouble in speaking and understanding, sudden paralysis or numbness of the face, arm or leg, sudden trouble with walking confirmed with computerized tomography (CT) scan or magnetic resonance imaging (MRI).

6. The authors must clarify what does positive or negative "protein urea" refers to.

Answer- Thank you so much for this constructive comment. We accepted the comment and we apologize for not making it clear. In our study protein urea defined as positive if the urine albumin concentration is between 30 milligram (mg)/24 hours and 300 mg/24 hours and negative if it is <30mg/24 hours. This is also included in the revised version of the manuscript.

7. The manuscript present data with IQR, however, they present a single number. Does it belongs to 25 or 75 percentile?

Answer- Thank you. We accepted the comment. The IQR in the previous manuscript represents the difference of the 75th and 25th percentile but we have corrected this in our revised manuscript by putting the values of the 25th and 75th percentile together like (25th percentile-75th percentile).

8. Table 1 and table 2 lack of units of the variables. In addition, a table legend should be added to clarify abbreviations used.

Answer- Thank so much for giving us this nice comment to improve the quality of our manuscript. We merged table one and two together within one table. We included the units of measurements used for the variables like age, cholesterol, HDL-C, LDL-C, triglyceride, BMI, Creatinine, FBS, SBP, DBP and the table legend clarifying the abbreviations used in the table is also added. All the corrections are attached to the revised version of the revised manuscript.

9. In the "Result" section, information of "Predictors of vascular complication among type II DM patients" should be summarized since information is repeated in table 2.
Answer- Thank you very much we accepted the comment. In the revised version of the manuscript we summarized “predictors of vascular complication among type 2 DM patients” of the result section by removing redundancies that are already stated on the table like the Adjusted hazard ratio with its 95% confidence interval.

10. In table 3, authors must specify by which variables the HR was adjusted.

Answer- Thank you for this nice comment and we apologize for not making it clear. The adjusted hazard ratio was found by adjusting each variable by all possible confounding factors that are included in the study.

11. The discussion section compares data obtained with those of other countries like India and Taiwan. However due to the study didn't describe diagnostic criteria used, this data can't be compared.

Answer- Firstly I want to say thank you for this constructive and basic comment to improve the quality of our manuscript. We clearly stated the diagnostic criteria’s used to diagnose each of the vascular complications in the revised manuscript with the references used. Most of the diagnostic criteria’s used by our study are similar with other studies so we can make comparisons of our result with other countries. The diagnostic criteria’s used are;

• Retinopathy- diabetic retinopathy was defined by both direct and indirect ophthalmoscopy assessments done by retinal specialists confirmed by fundus photography.

• Neuropathy- Diabetic neuropathy was defined by the history of numbness, paraesthesia, tingling sensation confirmed by touch sensation by 10gm monofilament, vibration sense by biothesiometer and ankle reflex.

• Nephropathy- Diabetic nephropathy was defined worsening of blood pressure control, swelling of feet ankle, hands or eyes, increased need to urinate, protein in the urine with a confirmation by tests like blood test, urine test, renal function test and imaging test
• Coronary heart diseases (CHD) - CHD was diagnosed by symptoms of chest pain (angina), shortness of breath or patients with symptoms of heart attack like crushing pressure in the chest and pain in the shoulder or arm, sometimes with shortness of breath and sweating with a confirmation by electrocardiogram (ECG) or echocardiogram.

• Peripheral Arterial diseases (PAD) - PAD was defined by the presence of history of intermittent claudication, coldness in the lower leg or foot especially when compared with the other side, weak or absent peripheral pulse in the legs or feet with a confirmation by Doppler ultrasound.

• Stroke. Stroke is defined as patients with sudden trouble in speaking and understanding, sudden paralysis or numbness of the face, arm or leg, sudden trouble with walking confirmed with computerized tomography (CT) scan or magnetic resonance imaging (MRI).

12. The authors observed that sex seems to be related with vascular complications. Did they perform a statistical analysis stratified by sex? (This could be important for sex-modified variables as c-HDL). Additionally the authors explain that "factors like PCOS, preeclampsia, gestational DM or physical activities" could be associated to the differences in vascular complication incidence between male and female. However none of these variables was assessed.

Answer- Thank you for this nice constructive comment. Stratified analysis by sex was not done in our study we simply want to see the direct effect of sex on vascular complications adjusted by all the variables in the study including the HDL-C without stratification. The factors like PCOS preeclampsia gestational DM and physical activities were already assessed by other studies previously and these factors were found to have a significant effect on the incidence of vascular complications that is why we have used these factors as a supportive evidence for our finding in sex.

13. Explanations about the importance of lipids in the development of vascular complications are too basic. Details about the pathophysiological mechanism involved should be included.

Answer- Thank you again for this nice comment to improve the quality of the manuscript and we accepted the comment. The basic pathophysiologic mechanisms involved in lipids for the
development of vascular complications are already stated in the manuscript and the full details about the mechanisms can be found in the references that are cited that is why we didn’t write the details about the pathophysiologic mechanisms.

14. The English language needs to be reviewed.

Answer- Thank you very much. We accepted the comment and corrected it on the revised version of the manuscript.

15. The background section doesn't highlight the importance of the study.

Answer- Thank you for your comment and this is a good input to improve the quality of our paper. In the background we included some points that show the importance of the study. Some of the points are: Ethiopia is facing a double burden problem because type 2 DM is currently increasing due to different factors such as aging, urbanization, increasing prevalence of obesity. Even though the rate type 2 DM and its associated vascular complications are increasing there is limited updated information about the problem so this study can be an input for the information gap we have about the current magnitude of the problem and its associated factors. The other importance of the study was to provide information for health professionals, policy makers and other governmental and non-governmental organizations to maximize efforts on prevention and risk minimization of vascular complication and deaths due to the complication in the country as well as in the study area. There is also some difference between findings of previous studies in the variables like sex therefore this study can be one evidence for answering this type of differences. This study can also be used as a reference or baseline for other researchers who will work on complications of DM. in conclusion this are the points that show the importance of the study.

16. Authors in title page have two institutional addresses; nevertheless all seem to be affiliated to first one. I suggest to correct institutional addresses.

Answer- Thank you very much. We accepted the comment and corrected it on the revised version of the manuscript.

17. I suggest summarizing "methods" and "result" section in Abstract. Both sections contain the number of patients.
Answer- Thank you very much. We accepted the comment. We rewrite the result section by removing the number of patients.

18. There are misspelled words in conclusion section in the abstract: "was remaining" (line 53), "co morbidity" (line 56), "deslipidemia" (line 56).

Answer - Thank you very much. We accepted the comment and corrected it on the revised version of the manuscript.

19. The paragraph 3 of page 4 (Background section) seems to be incomplete.

Answer - Thank you very much. We accepted the comment and corrected it on the revised version of the manuscript.

Amutha Anandakumar, PhD (Reviewer 3)

Questions

1. Currently we use the term "Type 2" diabetes instead "Type II". Answer- Thank you very much. We accepted the comment and corrected it on the revised version of the manuscript.

2. In the Abstract, all the abbreviations should be expanded when used for the first time.

Answer - Thank you very much. We accepted the comment and corrected it on the revised version of the manuscript.

3. Thorough spell check should be done throughout the manuscript.

Answer - Thank you very much. We accepted the comment and corrected it on the revised version of the manuscript.

4. What was mean age at diagnosis and duration of diabetes? What was the duration of diabetes at the time of screening/registered for the study e.g. 3 months, 6 months or 12 months duration. In short, define newly diagnosed diabetes. How many of them have not started treatment at the time of registration?
Answer- Thank you so much for this nice comment. This is really a good input to improve the quality of the paper. Mean age at diagnosis = 51.7 years (SD=11.5 years).

- The duration of diabetes at the time of screening is unknown because we have registered the first day that the patients are diagnosed as having diabetes for the first time. It is also the first time for the patients to know they have diabetes and that is why we define them as newly diagnosed.

- None of the patients started the treatment before the time of diagnosis/registration because they don’t even know that they have the diseases so they started treatment after diagnosis.

5. What were the vascular complications the authors intend to estimate in this study? If it is retinopathy, nephropathy, neuropathy, stroke, CHD and PAD, what was the definition criteria used? Were the patients assessed for complications at the start of the study and at the end of follow up? The authors have given importance to the predictors but not the complications. A separate table can be given showing the incident rate of all the complications and their independent predictors for each complication.

Answer- First I would like to say thank you for this constructive comment and we apologize for not making this points clear. We have incorporated the diagnostic criteria’s (definitions) used for the diagnosis of each of the vascular complications in the material section of the revised manuscript and the definitions are;

• Retinopathy- diabetic retinopathy was defined by both direct and indirect ophthalmoscopy assessments done by retinal specialists confirmed by fundus photography.
• Neuropathy- Diabetic neuropathy was defined by the history of numbness, paraesthesia, tingling sensation confirmed by touch sensation by 10gm monofilament, vibration sense by biothesiometer and ankle reflex.
• Nephropathy- Diabetic nephropathy was defined worsening of blood pressure control, swelling of feet ankle, hands or eyes, increased need to urinate, protein in the urine with a confirmation by tests like blood test, urine test, renal function test and imaging test.
• Coronary heart diseases (CHD)- CHD was diagnosed by symptoms of chest pain (angina), shortness of breath or patients with symptoms of heart attack like crushing pressure in the chest and pain in the shoulder or arm, sometimes with shortness of breath and sweating with a confirmation by electrocardiogram (ECG) or echocardiogram.

• Peripheral Arterial diseases (PAD) PAD was defined by the presence of history of intermittent claudication, coldness in the lower leg or foot especially when compared with the other side, weak or absent peripheral pulse in the legs or feet with a confirmation by Doppler ultrasound.

• Stroke. Stroke is defined as patients with sudden trouble in speaking and understanding, sudden paralysis or numbness of the face, arm or leg, sudden trouble with walking confirmed with computerized tomography (CT) scan or magnetic resonance imaging (MRI).

- At the start all of the newly diagnosed type 2 DM patients were assessed for all of these complications and those who were free from any of the vascular complications were included in to the study. The assessment for complications were continued to be done in every follow up appointment the patient comes to the hospital until the end of the study.

- In this study we mainly planed to see the general burden of vascular complications and predictors for all of the vascular complications that’s why we didn’t prepare a separate table for each vascular complication.

6. Table 1 can be remodified by giving both the frequency and percentages (n [%] and Mean ± SD [standard deviation] for whichever variables possible.

   Answer- Thank you very much for this nice comment. We accepted the comment. We have remodified the table by merging table 1 and 2 and we have created a new table that incorporate and describe both categorical and continuous variables we have so we reduce the number of tables to 2. The new table is attached in the revised manuscript.

7. In Table 3, it has been given as Adjusted HR, but nowhere in the text, they have mentioned for what they have adjusted. Also, what do the stars denote should be given as foot
note below the table? In this, one of the predictor's family history shows those who don't have positive family history have high risk of complications. This data needs to be verified.

Answer- Thank you for this nice comment and we apologize for not making it clear. The adjusted hazard ratio was found by adjusting each variable by all possible confounding factors that are included in the study in table 3. The foot note containing the definitions for the stars and all other abbreviations in the table are included in the revised manuscript.

-In our multivariable analysis by using Gompertz cox regression model family history was not found to have a significant association with the risk of vascular complications because we find a P-value >0.05. So we cannot say that patients with no family history has higher risk of vascular complication. Even when we compare the simple frequency from table 1, higher numbers of vascular complications are registered among patients' who had family history.

8. What was the definition and guidelines used for hypertension and cholesterolemia. Give references.

Answer- Thank you for this nice comment and we apologize for not making it clear. We gave our definitions used for hypertension and cholesterolemia(HDL-C, LDL-C, cholesterol and triglyceride) with their reference in the revised version of the manuscript.