Author’s response to reviews

Title: Adherence to antidiabetic medication and factors associated with non-adherence among patients with type-2 diabetes mellitus in two regional hospitals in Cameroon

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Author’s response to reviews:

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The Editor,

BMC Endocrine Disorders

Re: “Adherence to antidiabetic medication and factors associated with non-adherence among patients with type-2 diabetes mellitus in two regional hospitals in Cameroon”. Manuscript ID: BEND-D-17-00244

Dear Editor,

Thank you for the opportunity to revise our manuscript referenced above for publication as an original article in your journal.

We have revised our manuscript and all review comments raised have been addressed in a point-by-point manner. Changes made on the initial manuscript have been highlighted in yellow. We hope you will find this version of the manuscript suitable for publication.
Yours sincerely,

L. N. Aminde, M.D.

(On behalf of the authors)

Reviewer’s comments

Rasaq Adisa (Reviewer 1):

Abstract page

Line 6/7 (Background) - compliance and adherence used interchangeably, they connote different meaning.

Response to reviewer: Thank you for your comment. The term adherence has now been used consistently.

Line 29/30 (result) - Rephrase first statement as "A total of 195 patients were recruited.

Response to reviewer: Thank you for this suggestion. The first statement has been rephrased as proposed.

Line 32 - abbreviation CI should be inserted in front of "confidence interval

Response to reviewer: Thank you for the suggestion. The abbreviation has been inserted.

Line 48 (conclusion) - remove "very", while the last two lines can be better rephrased, there should be consistent use of "adherence" all through

Response to reviewer: The word “very” has been removed and adherence has been used consistently throughout the manuscript.

Key words: Lines 58/59, should be Cameroon, Medication adherence, Type 2 diabetes

Response to reviewer: Thank you for this suggestion. The keywords have been replaced.
BACKGROUND

Inadequate review of literature in paragraph 1 & 2 (Lines 3-41), Lines 30-40 needs further explanation to fit the existing literature, line 40 - statement just hanging without any meaning

Response to reviewer: Thank you for comment. The literature review has been improved.

Lines 44 - 60 seems watery the way it is reported and can be better rephrased

Response to reviewer: Thank you for your remark. These statements have been rephrased.

Action: Statements rephrased to read: “There have been several studies which have explored medication adherence to antidiabetic medications with varying results. A hospital-based study in the United Arab Emirates reported a prevalence of adherence to antidiabetic medications to be 84 % (11); while similar studies in Ethiopia and Uganda obtained prevalence of 85.1 and 83.3 % respectively (12, 13). Conversely, studies in Switzerland and Botswana provided lower prevalence of 40% and 52% respectively (14, 15)”

2nd page of background - lines 8 -18, incorporate those statements in bracket

Response to reviewer: Thank you for this suggestion which has been implemented as requested.

There is insufficient literature search and reference, occasional grammatical errors. Need to closely address all these

Response to reviewer: Thank you for your comment. The literature review has been expanded the manuscript cross-checked for grammatical errors.

METHODS

Study design and setting: Line 42- replace "during" with "from". Line 48 - move "respectively" to after "Cameroon"

Response to reviewer: Thank you for these suggestions. They have been implemented as proposed.
Sampling and study participants: Line 3-the choice of convenient sampling seems non rigorous enough to support any significance difference that may be observed because of high probability of bias in the recruitment process.

Response to reviewer: Thank you for this comment. Due to the limited number of patients reporting to these out-patient clinics, we implemented a convenient and consecutive sampling method to ensure that all eligible patients were given the chance to be included in the study during the recruitment process. We however agree that this may lead to selection bias as not all patients may have had follow-up visits during this period and may therefore not have a chance of being included in the study. We have included this as a potential limitation.

Action: The last phrase of the limitations section in the discussion now reads: “Also the use of a convenience consecutive sampling may have led to selection bias as not all type 2 diabetes patients in the out-patient departments will have had follow-up visits during the recruitment process.”

Generally, very uncomfortable with the use of "We", rephrase without losing meaning. Sentence construction is poor in some instances.

Response to reviewer: Thank you for the suggestion. We have rephrased these statements accordingly throughout.

What inform the choice of this cut-off in line 41?

Response to reviewer: We have provided further detail regarding our choice of the cut-off used for adherence which reads;

“Adherence was defined as a score of 27 or more while non-adherence was defined by a score less than 27. This cut-off is guided by the scoring system applied in the Morisky Medication Adherence Scale, if participants had taken at least 95% of prescribed doses. This approach has been used in previous published studies (21) and thus helped in comparability of our findings.”

RESULTS

General characteristics- what does it mean?

Response to reviewer: Thank you for this observation. This has been changed to “sociodemographic characteristics”.
Is 195 representative of the Type 2 diabetes in Cameroon? No sample size calculation to justify this.

Response to reviewer: Thank you for this question. The prevalence of type 2 diabetes in Cameroon like in most developing countries ranges from 6 – 8% (Cameroon National Diabetes and Hypertension Programme). However, most of these patients are not linked to care and even amongst those who are linked to care, retention rates are very poor (<60%). Hence, only a small number of patients present to the outpatient clinics of the hospitals where the studies are carried out. This question therefore raises another important hypothesis – retention in diabetes care – which we have included in our manuscript as one of the fields that needs further studies.

Line 13; 175 used FBS for assessment of glycaemic control but in Table 1, 174 reported, why the discrepancy?

Response to reviewer: Thank you for this observation. This was an error in summation which has now been corrected as the actual figure is 174.

What about drugs for other comorbid conditions reported? e.g. hypertension, CKD etc

Response to reviewer: Thank you for this comment. Unfortunately, this was an oversight which was not included in the data collection tool of this study. We hope to capture this element in future studies.

Prevalence and reason; Rephrase line 29/30 -- as were part of the reasons cited for non-adherence

Response to reviewer: Thank you for this comment. This has been changed as requested.

Is there no overlapping or multiple responses? How was this treated?

Response to reviewer: Thank you for this comment. There were multiple responses for “co-morbidity” and “reasons for non-adherence”. To reduce the effect of overlapping, each of the investigated pathology (hypertension, chronic renal disease, heart failure and stroke) under “co-morbidity” were considered as distinct variables in the logistic regression. Regarding the results for the “reasons for non-adherence”, a table (Table 2) was presented to report percentages of each reason. These percentages do not sum up to 100, and this could explain that overlapping was taken into consideration.
Line 35 should be Medication Compliance Question.

Response to reviewer: Thank you for this suggestion which has been implemented as proposed.

Line 42 -55, which direction is the significance difference? Not clear

Response to reviewer: Thank you for this comment. We have rephrased this paragraph to be clearer.

Action: It now reads: “In multivariable analysis, participants who were aged > 60 years (adjusted odds ratio (aO.R.) = 0.48; 95% confidence interval (CI): 0.25 – 0.94, p = 0.02), participants who consumed alcohol (aO.R. = 2.13; 1.10 – 4.14, p = 0.04) and participants on insulin therapy (aO.R. = 2.85; 1.01 – 8.08, p = 0.04) were more likely to be non-adherent to their antidiabetic medication.”

DISCUSSION

Two centres may not qualify as multicenter.

Response to reviewer: This is a fair comment and we have deleted as appropriate.

A bit of confusion in some explanation to explain the significance difference because of issues of violation of Chi square assumption (values < 5 with variables analysed with chi-square).

Response to reviewer: Thank you for this comment. We used the chi-squared test for comparing categorical variables. In situations where the assumptions for chi squared test were not met, such as cell counts less than 5, we used the Fisher’s exact test. This was mentioned in the section on ‘Data analysis’ which reads;

“Frequencies and percentages were computed for categorical variables and group comparisons done using the chi-squared test (or Fisher’s exact test where appropriate).”

For more clarity in table 1, we have inserted an asterix beside the p-values for variables in which group comparisons were done using the Fisher’s exact test.

Limitations needs to be further expanded to include some of the gaps raised.
Response to reviewer: Thank you for this comment. We have expanded the limitations to include issues raised such as selection bias and the need for more studies with larger sample sizes assessing retention in care.

This reads;

“In addition, the use of a convenience consecutive sampling may have led to selection bias as not all type 2 diabetes patients in the out-patient departments will have had follow-up visits during the recruitment process. As a result, interpretation of our findings in terms of generalizability should be done with caution. Furthermore, the small sample size in this study explained by the low turnout of patients in the outpatient diabetes clinics of the study centres highlights the need for larger studies to assess retention in care of diabetes patients in Cameroon.”

Did the authors really sure that the study is the first in Cameroon to address this problem?

Response to reviewer: Thank you for this comment. From a brief scoping review of the literature, we were unable to find any other study which reported adherence rates or the reasons for non-adherence to antidiabetic medications in Cameroon.

CONCLUSIONS: Line 35, violation of Chi square rule make some conclusion invalid in Table 1

Response to reviewer: Thank you. We have clarified this issue in prior response above. In addition, the use of a multivariable regression analysis provides robust confidence to the independent predictors obtained.

Need for a table to capture response of patients to MAQ in likert scale incorporating the score categorization with cut-point

Response to reviewer: Thank you for this comment. We had provided this table with participant responses as supplementary material. As recommended, we have now inserted it in the main manuscript as table 3.

Table 1: Prevalence as part of Table 1 is not clearly reflected rather there should be another table as mentioned to address that
Response to reviewer: Thank you for your comment. The overall prevalence of non-adherence was described under the section “Results” and sub-section “Prevalence and reasons for non-adherence to antidiabetic medication”. Table 1 complements this report by describing in details the prevalence according to the variables.

Number of valid respondents is not equal to 195 in all cases, the valid "n" should be appropriately reflected.

Response to reviewer: Thank you for this observation. Some of the numbers of respondents per variable couldn’t sum-up to 195 due to missing values. These have been included in the Table 1. However, the total number of respondents for the variable “co-morbidity” could not add up to 195 exactly because there were multiple and overlapping answers.

Under the variable "Hospital setting" 194 reported, does it means that one respondent does not belong to any hospital?

Response to reviewer: Thank you for pointing this out. It was a typo error. The one patient belongs to the hospital LRH and it has been rectified on the table.

Table 2, How does the author arrived at the % reported? What is the n total 106, 195, or 133? I suspect 106 was used which is not correct because categorization into adherence vrs nonadherence was done after participants' responses have been collected. Clarify.

Response to reviewer: Thank for your observation. Initially the 106 non-adherent patients were used as the denominator. We however agree with you that it is not supposed to be used. The total number of patients (195) was used as the denominator and corrections made in the table and text.

Is there multiple response?

Response to reviewer: Thank you for this comment. Yes, there were multiple response and this has been clarified in previous responses above.

Table 3: not properly defined. What is "Ref"? What does all the values indicate CI, OR etc? Table should speaks for itself

Response to reviewer: Thank you for this observation. Abbreviations have now been defined to make the table self-explanatory.

Reviewer 2 (Reviewer 2): PEER REVIEWER COMMENTS: To view the full report from the academic peer reviewer, please see the attached file.
REVIEWER COMMENTS FROM REPORT: The authors have conducted a study on non-adherence to medication among type 2 diabetics from two hospitals. The topic has been well selected as diabetes is a growing problem. However, this methodology leaves much to be desired.

The sample is convenience, limiting external validity.

Response to reviewer: Thank you for this comment. As explained above, the prevalence of type 2 diabetes in Cameroon like in most developing countries ranges from 6 – 8% (Cameroon National Diabetes and Hypertension Programme). However, most of these patients are not linked to care and even amongst those who are linked to care, retention rates are very poor (<60%). Hence, only a small number of patients present to the outpatient clinics of the hospitals where the studies are carried out. We therefore attempted to carry out a convenience consecutive sampling to include all patients who presented to the clinics during the data collection periods. This question therefore raises another important hypothesis – retention in diabetes care – which we have included in our manuscript as one of the fields that needs further studies. We have acknowledged this in the study limitations, which reads;

“In addition, the use of a convenience consecutive sampling may have led to selection bias as not all type 2 diabetes patients in the out-patient departments will have had follow-up visits during the recruitment process. As a result, interpretation of our findings in terms of generalizability should be done with caution. Furthermore, the small sample size in this study explained by the low turnout of patients in the outpatient diabetes clinics of the study centres highlights the need for larger studies to assess retention in care of diabetes patients in Cameroon.”

The authors state the mean age as 60.5 years without stating the SD. Similarly, they have mentioned a mean BMI of 29.9 without mentioning SD.

Response to reviewer: Thank you for this observation. The standard deviations have now been included.

REQUESTED REVISIONS:

Because of a lack of external validity due to convenience sampling, the paper falls short of an original research paper. The authors may consider publishing it as a brief communication as a "letter to editor" in a different format.

Response: Thank you for raising this concern. We agree with the reviewer that our use of a non-random and convenience sampling may result in selection bias, and the hospital-based nature of the study additionally limits its external validity. In our responses to prior review comments
above, we have provided some justification for our recourse to convenience consecutive sampling, in which we recruited all eligible patients presenting to the diabetes clinics of the two study hospitals. This rather gave an opportunity to capture the maximum possible patients in the diabetes clinics. While large random sample community-based study is likely to provide a more externally valid estimate, limitations in logistics and funding couldn’t permit us conduct such a study. We have discussed these limitations in the manuscript. However, despite these shortcomings, this study provides (to our knowledge) the first estimate of non-adherence to anti-diabetic medication in Cameroon, determinants of non-adherence and patient reasons for non-adherence which had hitherto not been explored in Cameroon. In addition, this study provides a contribution to the evidence on diabetes care in hospital settings as well as gaps needing attention and further study. Our results would be handy for health policy makers as they design and work towards implementing strategies to improve diabetes care in Cameroon. We thus believe our manuscript merits to be published as an original research paper.

Miguel Goncalves (Reviewer 3): No comments. The statistical analysis is well documented.

Response to reviewer: Thank you for your kind comments.