Author’s response to reviews

Title: Predictors of lower extremity amputation in patients with diabetic foot ulcer: findings from MEDFUN, a multi-center observational study

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Author’s response to reviews:

RESPONSES TO REVIEWERS’ COMMENTS

REVIEWER #1

The authors have articulated the problem (DFU) and the gap in the literature. The comments below pertain to the manuscript. In places the language used could be refined and there are a few grammatical errors, many, but not all of which I have listed below.

The authors state in line 88:'Details of the study design, patient recruitment, clinical and laboratory measurements, patient management and statistical analysis have been presented in the general paper currently under review by another journal, and are hereby summarized'.

I would be grateful if the authors could clarify how the other paper is different. If it is sufficiently different and this manuscript still has novelty, then my suggestion would be that this sentence needs omitting and a full description of demographics etc should be included. Fundamentally the two main concerns I had were around the diagnosis of vascular disease and the omission of data about the size of the wounds, which clearly could be a determinant for amputation. Clarification of these points along with a little polish in terms of grammar and I think this is a very neat study.
Response: A large data set was gathered in the MEDFUN study which is not publishable in one journal article. The general paper referred to in line 88 contains only descriptive epidemiology of the study. It was submitted to World Journal of Diabetes and was under peer review as at the time of submitting this paper to JFAR. That paper has just been published and the reference has been included in this revised manuscript (reference 18). The current manuscript, although part of the MEDFUN study, is ORIGINAL in its own right having been developed from results of a sub analysis of the MEDFUN data –AMPUTATION- which has not been presented elsewhere. The statement on line 88 has therefore been modified and now reads: “Details of the methodology of the MEDFUN study have been published [18]”.

We agree with the reviewer that wound area may be an important determinant of amputation. Regrettably, it was not one of the parameters recorded in this study. Instead we used wound depth as put forward by the Wagner wound grading system.

Line 1: The first line of the introduction does not read well. 'Owing to' is perhaps not the best way to start a manuscript. Suggest rewrite of this sentence

Response: “Owing to” has been changed to “As a result of”.

Line 49 - it is unclear are there 5million with diabetes of whom 2/3 are undiagnosed, or 5 million and then another 10 million undiagnosed

Response: The sentence has been reworded for clarity. It means that the 5 million diagnosed cases of diabetes in Nigeria represent only about a third of the actual disease burden as about two thirds of the diabetes cases are yet undiagnosed.

Line 50 'is' change to 'are' undiagnosed

Response: This correction has been effected

Line 51 'situation of chronic undetected hyperglycemia is expected to increase the risk of complications several folds. Consequently, chronic complications are common among individuals with diabetes in Nigeria' would benefit from a rewrite

Response: This part has been rewritten as advised. The sentence now reads: “Consequent upon this high prevalence of chronic undetected hyperglycemia, many individuals with diabetes present with already established chronic complications at the time of diagnosis”.
Line 53 it is increasingly frowned upon to use the word 'diabetic', not something that bothers me but might bother some readers, consider using DRFU - diabetes related foot ulcer

Response: The term “diabetic“ in this context refers to the disease- diabetic foot ulcer- which is a well known terminology used in international literature, including by the International Diabetes Federation. It is not referring to the individual with diabetes which is now being considered as derogatory and offensive. We therefore choose to stick to the term “Diabetic Foot Ulcer”.

Line 60 not great to start a sentence with 'but'
Response: Correction has been effected

Line 62 s needed on three quarter
Response: Correction has been effected

Line 74 'ugly scenario' suggest needs rephrasing
Response: “ugly” has been changed to “unpleasant”.

Line 86 is there an ethics approval number?
Response: No. Our Ethics Committees do not issue approval number but only approval certificate

Line 97 Patients were interviewed on knowledge of proper foot care practices and whether they had received any foot care education prior to foot ulceration - a description of this interview would be helpful
Response: The interview entailed asking about bare-foot walking, daily foot inspection, proper foot wear, use of emollients to prevent dryness of the feet, proper pedicure practice and early treatment of foot problems. These details have been included in the manuscript.

Line 108 'Peripheral artery disease was diagnosed based on impalpable dorsalis pedis and/or posterior tibial artery on manual palpation or significant arterial narrowing (>50%) on Doppler
ultrasonography' I would contend that impalpable pulses are not a good indicator of PAD, please give a rational for this choice. How many patients were diagnosed with ultrasound? It does say in the following paragraph that both lower limbs were ultrasounded. Does this mean that all could have PAD determined by vessel narrowing, and is so which vessels were used, presumably a blockage in the femoral artery would not necessarily be picked up if only distal vessels were scanned. Why were ABPI or TBPI not selected?

Response: We combined both clinical examination and imaging to diagnose vascular disease. Clinically, subjects who had diminished or impalpable peripheral pulses were adjudged to have “suspected” peripheral artery disease (PAD). Such individuals with a clinical suspicion of PAD then underwent Doppler ultrasound scan (DUS) for confirmation. We did not have enough resources to image all the participants. Therefore, those with normal peripheral pulses did not undergo vascular imaging. For those who underwent DUS, both lower limbs were scanned and narrowing at any level of the lower limb arteries was considered confirmatory for PAD. We did not do ABPI or TBPI due to the inconveniences associated with this procedure in patients with wounds, most of which were infected.

Line 123 'We defined amputation above the mid-tarsal bone or involving the big toe as major amputation, otherwise it was minor’ suggest rephrase the last few words

Response: The sentence has been rephrased and now reads: “We defined amputation above the mid-tarsal bone or involving the big toe as major amputation, otherwise it was considered as minor amputation”.

Line 126 Again - it sounds like there is a duplicate paper - please explain

Response: There is no “duplicate” paper, as has been explained above.

Line 196 suggest change sequel to consequence

Response: “sequel” has been changed to “consequence”.

Discussion

Some well made points, and good comparisons to existing literature. Limitations of HbA1c could be discussed (it does not capture fluctuations in BGL) as well as the limitations of the Wagner (does not capture wound size).
Response: We appreciate the kind words. We however feel that delving into the limitations of the Wagner grading system and HBA1c testing would be veering off outside the scope of this paper which is not intended to appraise the clinical utility of these entities. We therefore humbly suggest that the "Discussion" be limited to our research findings.

REVIEWER #2

There has clearly been a large amount of work in the conduction of this study and for the preparation of this report. However several amendments need to be taken care of.

Abstract:

- In the Results section, "...Proteinuria (P 0,021)" should be corrected to 'Proteinuria (P 0.021)'.

Response: This has been effected (line 32)

- In the Results section (as also in Line 256-257 in the Discussion Section), since participants recruited were hospitalised, risk factors such as glycaemic control may not be reflective of the whole diabetic population as glucose levels may be less likely to be controlled when not under constant medical attention. This may be affecting its significance with regards to risk factors of LEA.

Response: Yes, possible modifying effect of hospitalization (and hence better glycemic control) on HbA1c exists. It was baseline HbA1c that was measured in this study which was reflective of pre-hospitalization glucose control. Similar scenarios also played out for most of the other “modifiable” risk factors assessed such as wound infection, anemia, white cell count, ESR, etc which are also amenable to change in-hospital. We assessed how their status at baseline related to the admission outcomes.

- In the Conclusion section, ulcer grading was done through Wagner classification system (as also in Line 100-101 in the Methods section). A more recent grading system might have been used; for example the Eurodiale study have used the PEDIS system.

Response: We agree that the more recent PEDIS classification system developed by the International Working Group on Diabetic Foot (IWGDF) is more comprehensive and gradually gaining popularity. However the simpler Wagner grading system is easier to apply by the
bedside. Despite its limitation, it has been found to reliably predict amputation in most studies and therefore still retains wider usage and clinical relevance.

Background:

This section should be revised since it provides no focus on the several risk factors of LEA which is the main focus of the study. A critical review of the literature is of paramount importance to improve the quality of the paper

Response: In this section, we introduced the subject (diabetic foot ulcer) and briefly reviewed literature on lower extremity amputation and its clinical importance. More extensive literature review on the risk factors for amputation was done in the “Discussion” section.

- Various grammatical amendments are required;

Line 55: ulceration instead of "ulcer". This also applies to the rest of the report when "diabetic foot ulcer" or "duration of ulcer" is written.

Response: We humbly wish to stick to the term “ulcer” rather than “ulceration” as suggested. While the former is a disease, the latter is more of the process leading to the disease. Diabetic foot ulcer (rather than ulceration) is a well recognized clinical entity in international literature.

Line 57: Rewording required "Recent update suggests..."

Response: The sentence has been reworded.

Line 59: hospital admissions instead of "...hospital admission."

Response: Letter “s” has been added to “admission”

- Line 60-61: Rewording and citation required. "But perhaps the most...is lower extremity amputation (LEA)."

Response: The sentence has been reworded. “Perhaps” as used in the sentence implies that the thought expressed therein is that of the author and not backed by concrete evidence. It therefore requires no citation.
- Line 69-70: "...comparable to breast and prostate malignancies in males and females respectively." should be switched since breast malignancies are referring to females and prostate malignancies are referring to males.

Response: Proper assignment of disease to gender has been effected.

- Line 74: More appropriate scientific language should be considered, "Efforts to prevent this ugly scenario..."

Response: “ugly” has been changed to “unpleasant”

- Line 76: Rewording required since Nigeria is a country and not a "locality".

Response: “our locality” has been changed to “Nigeria”.

Methods:

This section could have been better structured into different sections including, study design, inclusion/exclusion criteria etc.

Response: It is a summary of the methods that was provided in this manuscript. Details of the MEDFUN study have been published and hereby referenced (reference 18). Hence we did not restructure the methods into sub-themes.

- Line 84: The inclusion/exclusion criteria when recruiting participants is very poorly described, where no exclusion criteria was mentioned (such as active ulceration of less than a month). Are there any confounding variables which might affect results in this study?

Response: The inclusion criterion was adults (≥ 18 years) with type 1 or type 2 diabetes who were hospitalized for diabetic foot ulcer and gave consent to participate. Of course patients who were less than 18 years, had diabetes other than type 1 or 2, or who had ulcers that were not adjudged to be diabetic foot ulcer (e.g. venous ulcers) were excluded. Active ulceration of less than a month was not an exclusion criterion.

- Line 88-90 and Line 126-128 the authors need to clarify whether this paper is presently being considered for publication elsewhere. If yes, this would invalidate this paper for publication.
Response: This paper is NOT being considered anywhere for publication. However, a large data set, too large for publishable in one journal article, was gathered in the MEDFUN study. The general paper referred to in line 88 contains descriptive epidemiology of the study including detailed and structured methodology. It was submitted to World Journal of Diabetes and has just been published and referenced in this revised manuscript (reference 18). The current manuscript, although part of the MEDFUN study, is ORIGINAL in its own right having been developed from results of a sub analysis of the MEDFUN data –AMPUTATION- which has not been presented elsewhere. The statement on line 88 has therefore been modified and now reads: “Details of the methodology of the MEDFUN study have been published [18]”.

- Line 92-96 This is not the correct method of determining whether a patient is living with type I or type II DM. "Distinction between type 1 and type 2 DM was made clinically based on combined parameters of age and method of diabetes control." This, thus, raises serious questions regarding the validity of this paper

Response: Distinction between type I and type II DM is routinely done CLINICALLY in most hospitals in Nigeria including tertiary care centers. Due to absence of facilities and resources, we do not routinely assay for auto antibodies such as anti-GAD 65 or measure plasma C-peptide.

- Line 106: What types of foot deformities were reported? Were any arthritic changes or biomechanical abnormalities of the lower limb taken into consideration?

Response: We were interested in foot deformities attributable to diabetic neuropathy such as clawing of the toes, bunions, hammer toes, pes cavus or planus, Charcot foot, etc.

- Line 106-108: How was the scoring system of the monofilament test and tuning fork test? How was peripheral neuropathy determined?

Response: The monofilament was applied perpendicularly on the plantar surface of the non ulcerated foot at each of five standard points including the 1st, 3rd and 5th digits, 1st metatarsal head and heel. At each point, enough pressure to buckle the monofilament was applied. Loss of sensation on at least 2 sites was considered positive for neuropathy.

- Line 108-111: Was peripheral arterial disease diagnosed based only on pulse palpation OR Doppler ultrasonography? A better description of the tests performed and what was included or excluded with regards to PAD and neuropathy need to be clarified further.
Response: We combined both clinical examination and imaging to diagnose peripheral artery disease (PAD). Clinically, subjects who had diminished or impalpable peripheral pulses were adjudged to have “suspected” peripheral artery disease (PAD). Such individuals with a clinical suspicion of PAD then underwent Doppler ultrasound scan (DUS) for confirmation. We did not have enough resources to image all the participants. Therefore, those with normal peripheral pulses did not undergo vascular imaging. For those who underwent DUS, both lower limbs were scanned and narrowing at any level of the lower limb arteries was considered confirmatory for PAD.

- Line 112-117: Were tests of the various possible risk factors of LEA performed only on recruitment of participants? How were the recruited participants followed up with regards to the variables being tested for in this study?

Response: Yes, tests of the various possible risk factors of LEA were performed only at enrollment which was the first week of hospitalization. The recruited participants received standard multi-disciplinary care during the period of follow-up until he/she exited the hospital.

- Line 123-124: Citation required. "We defined...otherwise it was minor."

Response: Similar to other studies on this subject, our definition of “major” and “minor” amputation was arbitrary and therefore not citable. We are not aware of any internationally agreed definition for categorizing amputation as major or minor.

- Line 132-133: Aim of this study is not clear. Are ulcer healing, mortality and duration of hospitalisation also being analysed as stated in the Background section of the Abstract "The study end-points were...mortality."

Response: This paper only deals with data on amputation. Separate manuscripts on wound healing and mortality data are currently being developed.

Discussion:

- Line 213-215: Explain which adjustments were made for "other confounding variables".

Response: In a multivariate logistic regression, the statistical software automatically weights the strengths of each variable and selects variables that show the highest degree of predictability giving an “adjusted” odds ratio.
- Line 256-257: Might participants being hospitalised affected the significant association between HbA1c and LEA? Also, since HbA1c testing was performed only on recruiting of participants and not before LEA was required? This also applies to the other laboratory results, such as ESR levels, where no significance was found.

Response: Yes, the association between LEA and all the baseline parameters that were subject to change with time such as HbA1c, wound infection, acute phase reactants, etc, is also likely to change with time.

REVIEWER #3

We are very grateful to the reviewer for taking out time and efforts to contribute in improving our paper. Unlike other reviewers however, comments from this reviewer were not tracked to specific line numbers in the manuscript, thereby making it difficult for us to link some of the comments to specific areas of the paper. As a result, some of the responses which we hereby provide inline may be based on our assumption of which part of the manuscript the reviewer may be referring to. We sincerely apologize if some of these responses fail to address the reviewer’s concerns.

Comment:

Thank you for the opportunity to review this paper. Data regarding populations with diabetes related foot disease is always needed, especially from developing countries. This paper requires some revision before being suitable for publication and I hope the feedback below is useful:

- the biggest issue for me is the conclusions drawn from the data. The authors state that identification of the predictors for LEA will ‘prompt’ quick attention to these issues which implies there might be a reduction in LEA rates as a result. I don't believe this is the case as the majority of predictors identified in this study (Wagner Grade 5 ulcer grade, deep infection etc) indicate serious and significant end point disease, in which case the life may be saved but likelihood of limb salvage is extremely poor. I would prefer the findings were simply presented as indicators of greater likelihood for need for LEA as opposed to an opportunity for clinical intervention to save the limb.

Response:
In lines 41-42 in the “ABSTRACT” section we wrote: “Prompt attention to these risk factors may reduce amputation rate among these patients”.

Similarly, in lines 284-288 in the “CONCLUSION” section, we wrote: “We believe that the findings in this study would assist general practitioners identify high risk patients who may benefit from early referral to specialist centers, and also guide foot care specialists in taking appropriate and timely clinical decisions. This may go a long way in reducing LEA rate in people with DFU in our environment”.

It follows from the foregoing that only a mere probability that risk factor identification may reduce LEA rate was expressed in this paper rather than a categorical statement which cannot be made on the basis of this study.

Nevertheless, risk factor identification for a disease outcome, especially where modifiable, often has the potential to improve the outcome. If this is not so, then what purpose does it serve to identify disease risk factors? In the case of DFU-related amputation, some researchers have even gone as far as developing a risk scoring system for LEA ostensibly to triage patients into risk categories for the purpose of identifying high risk patients both for timely intervention and allocation of health resources. Such efforts no doubt are geared towards reducing both LEA and mortality.

Comment:

The presence of proteinuria and leucocytosis could be misleading as these can occur in the presence of acute, severe infection, but resolve once infection is controlled.

Response

We are in agreement. This may explain why they lost statistical significance on multivariate analysis, suggesting that they do not independently predict LEA as explained in lines 263-266 and 269-271.

Comment

It would be useful for the authors to include the follow up period for patients included in the study. One of the end points noted was 'ulcer healing' and certainly in Australia it is very rare for a patient to be discharged from hospital with a healed wound?

Response
This was an observational study in which baseline data were collected at presentation followed by standard care and then data on outcome collected at exit. In our practice, owing to poor affordability of care, patients do not have to heal completely before they are discharged from the hospital. Patients whose wounds show healthy granulation tissue may be discharged in the absence of other contraindications, to continue out-patient treatment.

Comment

In the Background section there is a line that implies diabetes is an infectious disease - it is clearly a language / grammar issue but should be clarified.

Response

We are unable to trace such statement.

Comment

Use of the word 'avoidable' in relation to DFU oversimplifies the complexity of how / why people develop foot ulcers - it is preferable to use terms such as 'potentially preventable'

Response

We are sorry but we are again unable to pinpoint the exact place being referred to.

Comment

The reference to other parts of this study that are currently under review for publication confuses this paper. Given the earlier work is not yet available to the reader to reference, I suggest you write this paper without making reference to other work that is related.

Response

This paper is NOT being considered anywhere for publication. However, a large data set, too large for publishable in one journal article, was gathered in the MEDFUN study. The general paper referred to in line 88 contains descriptive epidemiology of the study including detailed and structured methodology. It was submitted to World Journal of Diabetes and was under peer review as at the time of submitting this paper to JFAR. That paper has just been published and the reference has been included in this revised manuscript (reference 18). The current manuscript, although part of the MEDFUN study, is ORIGINAL in its own right having been developed from results of a sub analysis of the MEDFUN data –AMPUTATION- which has not
been present elsewhere. The statement on line 88 has therefore been modified and now reads: “Details of the methodology of the MEDFUN study have been published [18].”

Comment

Is there a reason the authors used the Wagner grading system as opposed to one more specific to DFU?

Response

To our knowledge, Wagner grading system was developed specifically for diabetic foot. Developed since 1987, it became the most widely used diabetic foot grading system and the most popular in most studies on diabetic foot. We are aware of other grading systems such as the University of Texas and the more recent PEDIS system. Despite its limitations of not taking into account, wound size and vascular integrity of the foot, the Wagner grading system has the advantage of easy applicability by the bedside. Besides, it has also been demonstrated to have good correlation with diabetic foot outcomes.

Comment

Can the authors justify why the diagnosis of PAD is based on pulse palpation OR vascular imaging? These are significantly different in terms of clinical diagnostic accuracy so I would suggest using one or the other is preferable and if ALL participants underwent vascular imaging that this is used as the diagnostic tool. Similarly why is 50% narrowing used as the imaging criteria?

Response

We combined both clinical examination and imaging to diagnose vascular disease. Clinically, subjects who had diminished or impalpable peripheral pulses were adjudged to have “suspected” peripheral artery disease (PAD). Such individuals with a clinical suspicion of PAD then underwent Doppler ultrasound scan (DUS) for confirmation. We did not have enough resources to image all the participants. Therefore, those with normal peripheral pulses did not undergo vascular imaging. For those who underwent DUS, both lower limbs were scanned and narrowing at any level of the lower limb arteries was considered confirmatory for PAD. Some degree of atherosclerosis is a usual finding in most people especially older age or in the presence of cardiovascular risk factors. Narrowing of 50% or more is radiologically considered significant to impair tissue perfusion while 70% or more is considered as critical stenosis.
Comment

The authors need to clarify their definition of 'major amputation' as amputation involving the big toe is not generally classified as a major amputation.

Response

Similar to other studies on this subject, our definition of “major” and “minor” amputation was arbitrary. We are not aware of any internationally agreed definition for categorizing amputation as major and minor. Nevertheless, while there is no controversy in classifying amputation above the mid-tarsal joint as “major” amputation, that of the big toe remains controversial. Its consideration as a major amputation stems from the fact that the big toe bears three times more weight than all the other digits combined during normal ambulation. Ambulatory functioning is therefore greatly adversely affected following amputation of the big toe.

Comment

In Table 1 is 'ulcer duration' in days - specify.

Response

Yes, and that has been stated.