PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Risk of diabetic foot ulcer and its associated factors among Bangladeshi subjects: a multi-centric cross-sectional study
AUTHORS	Banik, Palash; Barua, Lingkan; Moniruzzaman, Mohammad; Mondal, Rajib; Zaman, Farhana; Ali, Liaquat

VERSION 1 – REVIEW

REVIEWER	Bilal binYounis Shalamar Medical & Dental College, Endocrine/Medicine
REVIEW RETURNED	07-Sep-2019

GENERAL COMMENTS	1. The method of identifying the retinopathy needs further evaluation 2. What percentage of patient were assessed through mono filament and what % through thermometry and were the results matched in both the patients 3 Same with the palpatory method as compared to hand held Doppler. Please mention any variability of the results which could make difference in % of people at risk.

REVIEWER	Michael Edmonds King's College Hospital UK
REVIEW RETURNED	10-Oct-2019

GENERAL COMMENTS	Points for Comment Page 6 Line 128 “Exclusion criteria included presence of DFU during interview, acute illness of the subjects, unwilling to participate or those with mental instability. To meet the eligibility, the subjects were screened as having no DFU based on their self-reported statement, clinical history, foot examination and medical records review. “ Presumably patients with a history of DFU were not excluded Page 6 Line 138 “The questionnaire collected sociodemographic, behavioral risk factors (tobacco use, physical inactivity), diabetes (duration, medication) and its complications (retinopathy, nephropathy), and foot problem related information (neuropathy, PAD, trauma, Foot hygiene) of the participants. The blood glucose levels (fasting/random) and presence of diabetic nephropathy or retinopathy related information of the participants were extracted from their diabetes record book.”

	How were all these criteria defined as being present or not? Page 7 Line 153 “We screened each patient to identify lower extremity complications and presence of any risk factors like ulcerations, amputation, peripheral neuropathy (PN), PAD, foot deformities, limited joint mobility, and abnormal foot pressures using the methods followed by Lavery et al. “ How were these factors defined? Page 7 Line1 57 “Weinstein monofilament and vibration perception threshold tester to assess peripheral neuropathy (PN),” How was neuropathy actually defined? Page 7 Line 159 “Goniometer to identify foot deformity” How was this done? Page 9 Line 210 “In our study, we found only three respondents having PAD.” This is surprising and worthy of further comment and possible explanation. Were the Ankle brachial indices artefactually high? Page 10 Line 236 “EDUCATIONAL STATUS Numbers of patients , “ 210,440,363,195 do not add up to 1200

VERSION 1 – AUTHOR RESPONSE

Response to the reviewer 1

A] Comment 1: The method of identifying the retinopathy needs further evaluation.

Response: In our manuscript we mentioned that retinopathy related information of the participants were extracted from their diabetes record book (page number 06, line number 156-158). All the diabetes care centres of Diabetic Association of Bangladesh (DAB) used to keep record of all diabetes related information of a patient in a single book individually. All the patients are usually screened to identify presence of any diabetes related complications like retinopathy by a highly qualified ophthalmologist and the status is recorded in that book. In our study, we collected diabetes retinopathy related information from that record book of each participant and it was authentic. This is because all the diabetes centres under DAB follow a uniform method of diabetes care. Like first submission, in the limitation section of revised manuscript (page number 20-21, line numbers 433-444) we also apologized regarding this issue.

B] Comment 2: What percentage of patient were assessed through monofilament and what % through thermometry and were the results matched in both the patients?

Response: Unfortunately, we did not use thermometry as that time (year 2012) it was not available in the diabetes centres of Bangladesh and study fund was insufficient to apply it.

C] Comment 3: Same with the palpatory method as compared to hand held Doppler. Please mention any variability of the results which could make difference in % of people at risk.

Response: In our study peripheral arterial disease (PAD) was defined as “non-palpable dorsalis pedis or posterior tibial arterial pulse and ankle brachial index (ABI) in either foot < 0.80” (page numbers 7-8, line numbers 185-187). It indicated that we applied single definition based on simultaneously applied

two methods: (1) feeling of pulse on dorsalis pedis and posterior tibial artery and (2) ABI using hand held Doppler. As we did not define PAD separately for each of the method and estimate risk accordingly, hence risk difference between those is not important. Moreover, it was not aligned with the objective of this study to compare the risk difference based on the aforementioned methods. Hence, we did not discuss about this issue. In our study, we considered PAD when any participant full-filled two criteria simultaneously. Absence of any one of the criteria excluded PAD in this study. Possibly this restriction reduced the number of patients with PAD.

Response to the reviewer 2

A) Comment 1:

Page 6 Line 128

"Exclusion criteria included presence of DFU during interview, acute illness of the subjects, unwilling to participate or those with mental instability. To meet the eligibility, the subjects were screened as having no DFU based on their self-reported statement, clinical history, foot examination and medical records review. "Presumably patients with a history of DFU were not excluded

Response:

Yes, we included those having previous history of DFU. This was because the modified version of IWGDF risk classification counted 'ulcer history'. Moreover, history of previous DFU is considered as a strong risk factors of re-ulceration as 40% will have a recurrence within 1 year (https://www.hindawi.com/journals/jdr/2019/9038171/ref/). In our discussion we also mentioned that "the risk in patients with previous history of foot ulceration is expected to increase to 17–60% over the next three years" (page number 16, line number 324).

B) Comment 2:

"The questionnaire collected sociodemographic, behavioral risk factors (tobacco use, physical inactivity), diabetes (duration, medication) and its complications (retinopathy, nephropathy), and foot problem related information (neuropathy, PAD, trauma, Foot hygiene) of the participants. The blood glucose levels (fasting/random) and presence of diabetic nephropathy or retinopathy related information of the participants were extracted from their diabetes record book." How were all these criteria defined as being present or not?

Response:

There were some information that were recalled based and others based on clinical examinations. The recalled based option collected information by means of 'yes/no'. In some instances, we collected information (age/duration of diabetes/income) and during analysis categorized as 'yes/no'. For example, if any participant informed that he/she was a current smoker/smokeless tobacco user, then we marked it as 'yes'. For complications and blood glucose related information, we evaluated the diabetes record book. In that case, we collected the blood glucose levels and categorized as 'controlled' and 'uncontrolled. Again, if we found that a participant had retinopathy or nephropathy, we marked it as 'yes' (that means presence of that complication).

Foot problem related information (neuropathy, PAD, trauma, Foot hygiene) were based on clinical examination and marked as either 'present/absent' or 'yes/no'. For example, pedal pulse was marked as 'present/absent' following clinical examination. On the other hand, foot hygiene related questions were asked as "Do you take care of your foot regularly?" and answer was marked as 'yes/no'.

In the table 1, 'yes' was considered for sociodemographic variables and 'present' was considered for neuropathy as well as retinopathy. In table 3, diabetes complication were presented as 'present' and

‘absent’. However, to maintain uniform method of response in the data set, we coded all the information as ‘yes/no’ and added with the provided data set as supplementary file 5. In the data set, ‘present’ was coded as ‘yes’ and ‘absent’ was coded as ‘no’.

C) Comment 3:

“We screened each patient to identify lower extremity complications and presence of any risk factors like ulcerations, amputation, peripheral neuropathy (PN), PAD, foot deformities, limited joint mobility, and abnormal foot pressures using the methods followed by Lavery et al. “How were these factors defined?”

Response:

To define all of these, we have added a new subheading titled as ‘Ascertainment of key variables’ (page numbers 7-8, line numbers 180-202). However, for this manuscript, we excluded the definition of ‘infection’ and ‘abnormal foot pressure’ as we did not imply these two variables to categorize the risk of DFU. If the respected reviewer will suggest, then we must include those.

D) Comment 4:

Page 7 Line1 57

“Weinstein monofilament and vibration perception threshold tester to assess peripheral neuropathy (PN),” How was neuropathy actually defined?

Response:

Definition has added under the subheading titled as ‘Ascertainment of key variables’ (page number 7, line numbers 181-184).

E) Comment 5:

Page 7 Line 159

“Goniometer to identify foot deformity” How was this done?

Response:

In our second submission, we have added a module of diabetic foot screening as a supplementary file (see online supplementary file 1). The detail method of Goniometry applied in this study was described in that module. The module was developed by the concerned authors of this manuscript.

F) Comment 6:

“In our study, we found only three respondents having PAD.” This is surprising and worthy of further comment and possible explanation. Were the Ankle brachial indices artefactually high?

Response:

We think this was due to cut-off value applied to define PAD. Most of the studies of Bangladesh and Indian subcontinent used ABI ≤ 0.9 as a cut-off value to define PAD. In our study, we considered PAD when any participant full-filled two criteria simultaneously: (a) non-palpable dorsalis pedis or posterior tibial arterial pulse and (b) ABI in either foot < 0.80. Absence of any one excluded PAD in this study. We sincerely apologize for this unintentional finding, but please know that we tried our best to maintain the quality of this study (described in detail in our ‘Quality assurance’ section of this manuscript). We have added a brief explanation in our discussion section (page number 17, line numbers 338-342).

G) Comment 7:

Page 10 Line 236 “EDUCATIONAL STATUS Numbers of patients, “210,440,363,195 do not add up to 1200”

Response:

We have corrected this calculation.

VERSION 2 – REVIEW

REVIEWER	Bilal bin Younis Shalamar Medical & Dental College, Endocrine/Medicine
REVIEW RETURNED	22-Nov-2019

GENERAL COMMENTS	The people doing the clinical examinations for neuropathy.PAD and deformity are of same cadre in each centre . was the clinical examination done by nurse ,doctor or podiatrist.

REVIEWER	Michael Edmonds Diabetic Foot Clinic, King's College Hospital London UK
REVIEW RETURNED	07-Dec-2019

GENERAL COMMENTS	Comments Page 5 Line 129 “The best possible way to prevent DFU is the identification of individuals at risk, proper health education and timely follow-up [14].” I feel that this phrase is unduly optimistic Primary prevention of ulcers is difficult as indicated by Jeffcoate et al, in Current Challenges and Opportunities in the Prevention and Management of Diabetic Foot Ulcers Diabetes Care 2018 Apr; 41(4): 645-652., which states “Despite the probability and the belief that foot care education will reduce the occurrence of new ulcers, the evidence to justify the use of any educational intervention for primary prevention is weak: only a small number of randomized controlled trials (RCTs) have been published, and none that reported benefit were of high quality “ Page 7 line 172 “We used a 10 g Semmes–Weinstein monofilament and vibration perception threshold tester to assess PN, Ankle Brachial Index (ABI) to detect PAD” Palpation of pulses was also used in the assessment of PAD Page 11 line 269 “the mean duration of diabetes was 6.9 ±5.9 years and a majority of them had uncontrolled glycaemic status (89.3%). Among the diabetes-related complications, retinopathy (14.3%) was much higher than nephropathy (5.6%).” Retinopathy and nephropathy have still not been defined. This should be noted as a limitation. Page 17, line 338

	"Our study classified very low proportion of T2D subjects as having PAD compared to aforementioned studies " A possible reason for the ABI being above 0.80 in the majority of patients is the presence of medial arterial calcification artefactually raising the ankle pressure. This should be emphasised. Page 19, line 384 "One of the major objectives of this study was to identify the predictors of DFU risk among Bangladeshi T2D population." And Page 21 line 446 "It is the first study in Bangladesh that predicts DFU risk in a moderately large sample of T2D population." I am not sure that the use of the word "predict" is correct. This study was not a prospective study. As I understand the paper, it describes associations with the occurrence of previous ulcers. Patients with active ulcers were not included. This comment also applies to the use of the word "predict" when utilised in a similar context throughout the paper including the title. Minor point Page 6 line 133 Typo :food should be foot However, studies related to diabetic food risk

VERSION 2 – AUTHOR RESPONSE

Response to the reviewer 1

A] Comment 1: The people doing the clinical examinations for neuropathy. PAD and deformity are of same cadre in each centre. Was the clinical examination done by nurse, doctor or podiatrist.

Response:

Dear Reviewer, thank you for your kind and constructive review that help us to improve the paper.

In our "quality assurance" part we have already mentioned that physicians (doctors) were involved in foot examination (page 8, line 208-209).

Response to the reviewer 2

Dear Sir,

Greetings!

Thank you for your kind, constructive and evidence-based review that helped us to improve the paper. We tried our best to align with your review comments to carry the paper up to the maximum standard level.

A) Comment 1:

Page 5 Line 129

"The best possible way to prevent DFU is the identification of individuals at risk, proper

health education and timely follow-up [14].”

I feel that this phrase is unduly optimistic

Primary prevention of ulcers is difficult as indicated by Jeffcoate et al, in Current Challenges and Opportunities in the Prevention and Management of Diabetic Foot Ulcers Diabetes Care 2018 Apr; 41(4): 645-652., which states

“Despite the probability and the belief that foot care education will reduce the occurrence of new ulcers, the evidence to justify the use of any educational intervention for primary prevention is weak: only a small number of randomized controlled trials (RCTs) have been published, and none that reported benefit were of high quality”

Response:

Yes, we agreed with your comment and deleted the line from the manuscript.

B) Comment 2:

“Page 7 line 172

“We used a 10 g Semmes–Weinstein monofilament and vibration perception threshold tester to assess PN, Ankle Brachial Index (ABI) to detect PAD”

Palpation of pulses was also used in the assessment of PAD

Response:

We added ‘palpation of the pulses’ in the sentence.

C) Comment 3:

Page 11 line 269

“the mean duration of diabetes was 6.9 ±5.9 years and a majority of them had uncontrolled glycaemic status (89.3%). Among the diabetes-related complications, retinopathy (14.3%) was much higher than nephropathy (5.6%).”

Retinopathy and nephropathy have still not been defined. This should be noted as a limitation.

Response:

We have included this as a limitation. Page 21, line 444-445

D) Comment 4:

Page 17, line 338

“Our study classified very low proportion of T2D subjects as having PAD compared to aforementioned studies “

A possible reason for the ABI being above 0.80 in the majority of patients is the presence of medial arterial calcification artefactually raising the ankle pressure. This should be emphasized

Response:

As per your suggestion, we have emphasized it at first in our explanation. In addition, we also mentioned the difference of cut-off value used in compared studies to identify PAD. Page 17. line 340-342.

E) Comment 5:

Page 19, line 384

“One of the major objectives of this study was to identify the predictors of DFU risk

among Bangladeshi T2D population.”

And Page 21 line 446

“It is the first study in Bangladesh that predicts DFU risk in a moderately large sample of T2D

population.”

I am not sure that the use of the word “predict” is correct.

This study was not a prospective study. As I understand the paper, it describes associations with the occurrence of previous ulcers. Patients with active ulcers were not included.

This comment also applies to the use of the word “predict” when utilised in a similar context throughout the paper including the title.

Response:

Dear Sir, Thank you very much for such an important observation. We agree with your comment and bring the necessary change throughout the manuscript. We use “associated factors/contributing factors” instead of “predictors” and change our Title as “Risk of diabetic foot ulcer and its associated factors among Bangladeshi subjects: a multi-centric cross-sectional study

F) Comment 6:

Minor point

Page 6 line 133

Typo: food should be foot

However, studies related to diabetic food risk

Response: We have corrected it.

VERSION 3 – REVIEW

REVIEWER	Michael Edmonds King's College Hospital London UK
REVIEW RETURNED	03-Jan-2020

GENERAL COMMENTS	The authors have addressed my points. The Engish grammar will need review Minor point

	Line 417 Contribution factor is better as contributing factor