Author’s response to reviews

Title: Mortality in patients with diabetic foot ulcer: a retrospective study of 513 cases from a single centre in the Northern Territory of Australia.

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Author’s response to reviews:

11 October 2018

James Mockridge, PhD
Editor, BMC Endocrine Disorders

Dear Dr Mockridge

Please find enclosed a revised version of the manuscript entitled “Mortality in patients with diabetic foot ulcer: a retrospective study of 513 cases from a single centre in the Northern Territory of Australia”, by Kanakamani Jeyaraman, Thomas Berhane, Mark Hamilton, Abhilash P. Chandra and Henrik Falhammar.

We thank you and the two reviewers for the very constructive and positive comments. We have included a detailed response to the specific points raised and indicated where in the manuscript the changes are to be found. The changes have been highlighted in the manuscript with yellow color.

We think the manuscript has overall improved by all these changes and we hope you can now consider the manuscript acceptable for publication in the BMC Endocrine disorders journal.

Sincerely,

Dr Kanakamani Jeyaraman
Our responses to the comments:

Technical Comments:

1. Please provide 'Declarations' heading.

Answer: This has now been added in the revised manuscript (Page 8).

2. A STROBE checklist should be provided.

Answer: A STROBE checklist has now been provided with the revised manuscript.

Reviewer 1-

Comment 1- Page 3 Line 76 "Peripheral vascular disease (PVD) was defined by history, decreased or absent pedal pulses or with imaging." Could the authors be more specific?

Answer: PVD was based on the clinical diagnosis documented by the vascular surgeon who treated that particular patient. This was based on clinical features like rest pain, gangrene and abnormalities in pulse examination. For those who underwent imaging like arterial Doppler, CT or MR angiography, the imaging results were included in the definition of PVD. This has now been clarified on Page 3 in the revised manuscript: “The definition of peripheral vascular disease (PVD) was based on the clinical diagnosis documented by the treating vascular surgeon and if available, by imaging such as arterial Doppler and angiography.”

Comment 2- Page 4 Line 79 "Chronic Kidney Disease (CKD) was considered to be present on the basis of albuminuria, creatinine, and eGFR." What were the actual thresholds of these parameters to make a diagnosis of CKD Was this CKD stage 3 or4 or 5?

Answer: The KDIGO criteria was used for the definition of chronic kidney disease (CKD).

Kidney damage for ≥3 months, as defined by structural or functional abnormalities of the kidney, with or without decreased GFR, that can lead to decreased GFR, manifest by either:

Pathologic abnormalities; or
Markers of kidney damage, including abnormalities in the composition of the blood or urine, or abnormalities in imaging tests

GFR <60 mL/min/1.73 m2 for ≥3 months, with or without kidney damage

In our study, patients with persistent albuminuria with moderately (3-30mg/mmol) or severely (>30mg/mmol) increased ACR of with or without a decline in GFR was classified as having CKD. Those with albuminuria were further staged depending on eGFR (>90 stage 1, 60-89 stage 2, 30-59 stage 3, 15-29 stage 4 and <15 stage 5). We collected data on the different stages of CKD. For statistical purposes, all stages of CKD were grouped as CKD and those with normoalbuminuria and normal GFR were classified as No CKD. The statement has been changed in the manuscript as follows- “Chronic kidney disease (CKD) was defined by the KDIGO criteria [13]. Patients with persistent albuminuria with a urine albumin creatinine ratio (ACR) of 3mg/mmol and above were considered to have CKD. The CKD was further staged according to the glomerular filtration rate (Data not shown).” A reference has been added for the KDIGO criteria.

Comment 3- Page 4 Line 83 "Causes of death were noted from death certificates, if available." In how many patients were death certificates available? How was the cause of death decided when death certificates were not available?

Answer: Out of the 199 deaths, death certificate was available for all who died in the hospital/hospice (n=110). Out of the remaining 89 who died at home, cause of death could not be identified in 22 patients, as there was no death certificate, which we could access. In the remaining 67 patients, the cause of death was noted either from primary health care electronic medical records as documented by the primary health care practitioner (n=37) or if the death occurred soon after discharge from the hospital, the hospital medical records were used to assign the cause of death (n=30). This is commonly the case in patients with end stage renal disease who refused dialysis and requested to be sent home to die. The statement has been changed in the manuscript as follows- “Causes of death were noted from death certificates (n=110). For those without death certificates, electronic medical records were used to assign the cause of death (n=67).”

Comment 4- Page 4 Line 100 "Alcohol consumption was recorded in 63.1% of the study population" Was alcohol consumption quantitated in any way?

Answer: As this was a retrospective study, data was collected form medical records and the quantification of alcohol was not documented systematically. Therefore, we have not elaborated on this further.

Comment 5- Page 4 Line 106 "The most common causes for the DFUs were trauma (45.0%) and infection (29.4%)." I am not sure how infection actually causes an ulcer? Please comment.
Answer: The most common cause was cellulitis starting as pain and inflammation in feet/lower legs, later leading on to a non-healing ulcer. In some cases, this could be due to an infected fissure or infected callus. The statement has been changed in the revised manuscript to clarify this and the following has now been added - “The infection could be a preceding cellulitis, infected fissure or infected callus.”

Comment 6- Page 5 Line 113 “Adjunct hyperbaric therapy was required for a quarter (25.5%). A third (34.3%) was treated with total contact cast and half (51.3%) underwent amputation, over the study duration.” When the authors use the term "amputation" throughout the paper, could they note whether it was major or minor amputation?

Answer: Thanks for this comment. A statement has been added to explain this on Page 5- “A total of 436 amputations happened during this study period with an average of 1.75 ± 1.01 amputations per patient of with the majority (n=337, 77.3%) were minor.”

Reviewer 2:

Comment 1: Overall good analysis and data collection of patients with diabetes and ulceration. The authors have a large population for comparison of many factors. I especially like the comparison between indigenous and non indigenous populations. There has been significant evaluation of risk factors associated with diabetic ulcerations.

Answer: Thank you.

Comment 2: The study would benefit from further evaluation of does severity of ulceration result in different mortality?

Answer: The severity of the ulceration did not affect mortality. The ulcer severity was graded by Wagner’s grade. There were 53 limbs with Wagner grade 3-4 ulcers. In univariate analysis, Wagner’s grade was not associated with mortality (p=0.823). Therefore, it was not included in the multivariate analysis. On Page 5 this has already been mentioned briefly “Gender, remoteness, diabetes duration, ulcer duration, ulcer site, ulcer area, Wagner Grade, amputation, hypertension, smoking, alcohol or other drug abuse, neuropathy, retinopathy, inflammation markers, lipid levels, gamma-glutamyl trans-peptidase and insulin therapy were not associated with mortality (data not shown).”

Comment 3: Perhaps further delve into the connection between CKD and ulcerations? I would also like to know if the authors can suggest some mechanism that relates CKD to ulcerations?

Answer: We hypothesize that the presence of CKD in a patient with diabetes is a proxy for microvascular damage which in turn indicates the presence of neuropathy (both somatic and autonomic) and vascular insufficiency, hence making their feet more prone for ulcers. We have
included a statement in the discussion on Page 6- “CKD may well be a proxy for microvascular damage, which in turn indicates higher risk of neuropathy and vascular insufficiency, both of which are associated with poor wound healing and survival.”

Comment 4: Much work has been done in this field. I would look at mortality in CKD patients without ulcerations as a comparison to see if the presence of ulcerations shortens lifespan. Not all patients with diabetes and ulcerations have CKD, what makes this mortality worse?

Answer: A systematic review done on CKD and mortality risk by Tonelli et al in 2006 showed that the unadjusted relative risk for mortality in patients with CKD compared with those without CKD ranged from 0.94 to 5.0 and was significantly more than 1.0 in 38 of 41 cohorts. In our study we report an unadjusted hazard ratio of 1.63 which seems to be similar to that in the above systematic review of CKD patients without DFU. With the available data, we cannot confirm if DFU increases mortality in patients with CKD. We do not have data and a suitable control group to make further analysis to see if DFU shortens life span in patients with CKD.

Comment 5: I would like to see followup studies with even further followup.

Answer: Thanks for encouraging us to do a follow-up study in the future! The available literature is on studies with a maximum follow-up of 10 years and the current study the maximal follow-up was above 10 years (interquartile range 3.1-9.8 years). Future will tell if a further follow-up of our study will be done in a few years.

Comment 6: The authors should consider putting the table into graph form.

Answer: Initially we had planned to include more figures. However, to make the manuscript more succinct and since the main result was a multivariate analysis, we choose to present it as a table.