Author’s response to reviews

Title: Foot Insensitivity Predicts Is Associated With Renal Function Decline In Patients With Type 2 Diabetes: A Cohort Study

Authors:

Q A Altaf (q.altaf@nhs.net)

Hamed Sadiqi (doctorsadiqi.h@gmail.com)

Milan Piya (milanpiya@yahoo.com)

Abd Tahrani (abd.tahrani@nhs.net; abd.tahrani@googlemail.com)

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Author’s response to reviews:

Dear Dr. Shipley,

We thank you for giving us the opportunity to revise our manuscript. We would also like to thank the reviewers for their constructive and helpful suggestions and comments. We have amended the manuscript as instructed by the reviewers and all the amendments are track-changed. Please find our point-by-point response to the reviewers comments below.

We do believe that our manuscript improved significantly following the reviewers suggestions and we hope that it is now acceptable for BMC Endocrine Disorders.

Kind regards

Abd Tahrani

On behalf of all authors
Reviewer #1: Interesting study from Altaf and colleagues. The clinical problem is quite important, and the authors should be given credit for testing a novel risk factor. Overall the data appears valid, but some clarifications in the methods and presentations of results is necessary in this reviewer's opinions. Specific issues highlighted below:

We thank the reviewer for the kind comments.

1. Please spell out 'DPN' in Introduction

Thank you for highlighting this, we apologise for the oversight. We have now spelled DPN as Diabetic Peripheral Neuropathy.

2. Methods: recruited 'White European and South Asian adults with type 2 diabetes': surely you did not recruit these two dichotomous groups selectively? I suspect you recruited patients with type 2 diabetes; in your unit/trust, most patients are either South Asian or White European. Suggest rewording

Thank you, the reviewer is correct in that we recruited patients from our outpatient diabetes clinic. However, in the study protocol we specifically included only White Europeans and South Asians because the vast majority of our patients are from these two ethnicities. We have very small numbers of patients of Afro-Caribbean or Chinese origin in our clinic. These were not recruited into this study as we would have not been able to assess the ethnicity effect in multiple groups due to the relatively small sample size of our study population.

3. Methods: The funding seems to be in the form of salary support, is that right - or was there specific funding for this study?

Thank you, the baseline study was performed as part of a research training fellowship that was awarded by the National Institute for Health Research (NIHR) in the UK for AAT. That funding included salary as well as other costs needed to run the project. AAT is currently still funded by NIHR receiving a different fellowship (Clinician Scientist Award) as mentioned in the acknowledgement and the follow up data was collected after the end of the first fellowship and in part during the second fellowship. To address the reviewer comment we have now added a line in the methods stating that the study was funded by the National Institute for Health Research (NIHR) in the UK.
Was this cohort study done with the specific aim of studying this specific question - or was this a cohort assembled of patients with type 2 diabetes and this study uses the cohort to answer a different question? Looking at references 7 and 8 (7. Tahrani AA, Dubb K, Raymond NT, Begum S, Altaf QA, Sadiqi H et al.: Cardiac autonomic neuropathy predicts renal function decline in patients with type 2 diabetes: a cohort study. Diabetologia 2014, 57: 1249-1256. 8. Tahrani AA, Ali A, Raymond NT, Begum S, Dubb K, Altaf Q et al.: Obstructive Sleep Apnea and Diabetic Nephropathy: A Cohort Study. Diabetes Care 2013, 36: 3718-3725.) it seems there is overlap between this study and those in terms of the patients, is that accurate? It would help the readers if this was made clear - this does not make the data any less valid, but is valuable in terms of the robustness of the results. Overall, it would also be helpful to test multiple predictors of CKD and present those results simultaneously instead of these multiple publications.

We thank the reviewer for this point. The cohort study was not done to answer this particular question per se. The baseline data were collected and funded as a research training fellowship to AAT by NIHR. The follow up data were collected following the end of the research training fellowship and in part during another fellowship awarded to AAT by NIHR. The decision to follow the patients prospectively was taken after cross-sectional associations were observed at baseline. The overall initial project was aimed at assessing factors associated with microvascular complications in patients with Type 2 diabetes with particular focus on sleep apnoea and ethnicity. The study population was extensively characterised at baseline and this allowed for further longitudinal studies. This particular analysis was performed after we had identified associations between obstructive sleep apnoea (OSA) and diabetic neuropathy and eGFR and also the associations between cardiac autonomic neuropathy (CAN) and eGFR. And as diabetic peripheral neuropathy (DPN) can be associated with OSA and CAN we have developed the hypothesis and performed the analyses described in this paper.

We understand the reviewer’s point that all the results could have been published in one paper but this was impractical as it would have resulted in a very large publication given the depth of the analysis performed in each paper. In addition, the papers were testing different hypotheses each related to a new predictor or association.

In all publications arising from this project we included the reference number of the Ethics Committee approval. This is the same reference number across the publications but in order to address the reviewer’s comment we have added the following to the Methods section to make this clearer “Previous publications related to this study population can be found in [7,10,11].”

4. Results: Given the authors previous reports of prediction with CAN and OSA, why did they choose to ignore those two as co-variates in this study?

Thank you for the valuable comment. We did not include these variables in the regression model for several reasons. Not everyone included in this study had a CAN or OSA status verified as
some patients had poor quality recordings during sleep which did not allow us to verify the presence or absence of OSA. Hence including OSA and CAN in the model would reduce the sample size (to 178 from 225) and loss of power as we adjusted for a relatively large number of variables and could also increase multicollinearity. In addition, CAN and/or OSA could in part be the biological link between diabetic peripheral neuropathy and the eGFR decline observed in this study.

We have amended the Discussion to reflect the fact that this was a relatively small, single centre study so that the associations described should be viewed as hypothesis generating. Further, larger multi-centre studies are now required to confirm whether the associations described are correct and in turn to suggest further studies that need to be done to look into mechanisms of the described associations. We have also added the following statement to the end of the second paragraph of the discussion “Hence, the observed relationships between DPN and eGFR in our study could be mediated, at least in part, by the relationships between DPN and OSA and CAN.”

5. Results: A table 4 with details of multivariable/adjusted analysis is necessary. Why is baseline albuminuria missing in the co-variates for GFR progression outcome? Clearer explanation of choice and presentation is necessary

We thank the reviewer for the comment. We have now inserted a table 4 as requested by the reviewer.

Similar to the previous point raised by the reviewer, albuminuria was not inserted into the model due to the presence of missing data which would reduce our sample size for the multiple adjustments used in the regression model. In addition, our hypothesis was not based on assessing the interaction between albuminuria and peripheral neuropathy to assess which is a better predictor of eGFR decline. This should be the focus of future work. We were interested in assessing whether foot insensitivity can predict eGFR decline and/or albuminuria development/progression rather than whether foot insensitivity is better or worse predictor than albuminuria. Furthermore, as we discussed in the manuscript, a significant proportion of patients develop end stage renal disease without prior albuminuria.

We have amended the conclusion to highlight the need to compare with albuminuria in future studies “In summary, patients with Type 2 diabetes and foot insensitivity are at increased risk of greater eGFR decline. Identifying these patients might offer an opportunity to intensify metabolic control and prevent the development of CKD. Future studies of larger sample size and longer follow up duration from multiple centres are needed to assess the diagnostic performance of our findings in predicting CKD development and to compare the performance of the monofilament test with albuminuria.”
6. The word 'predict' is used throughout the paper. Perhaps 'associates' is preferable? The major limitation of this paper, apart from being a small single-centre study without an (perhaps) a priori hypothesis, is that of residual confounding. There are many differences between the two groups (with and without foot sensations) so there quite likely are other factors at play.

Thank you. We have now expanded the study limitations to highlight that it was a single centre study and that the possibility of other confounders cannot be excluded “This was a relatively small, single centre study so that the associations described should be viewed as hypothesis generating. Further, larger multi-centre studies are now required to confirm whether the associations described are correct and in turn to suggest further studies that need to be done to look into mechanisms of the described associations. In addition, despite adjustment for multiple variables in the linear regression, we cannot rule out the presence of other confounders that need to be explored in future studies.” We have now also changed “predict” to “associated with” throughout the manuscript. We have also amended the conclusion to highlight the need for multi-centre studies “In summary, patients with Type 2 diabetes and foot insensitivity are at increased risk of greater eGFR decline. Identifying these patients might offer an opportunity to intensify metabolic control and prevent the development of CKD. Future studies of larger sample size and longer follow up from multiple centres are needed to assess the diagnostic performance of our findings in predicting CKD development and to compare the performance of the monofilament test with albuminuria.”

7. Discussion should be tempered down. Next steps should be validation of this hypothesis generating data in other and larger cohorts. It is perhaps too early to use this for targeted therapy and trials.

Thank you, we agree that further validation and comparison with albuminuria are needed. We have tempered the discussion down by using “associated with” rather than “predict and by expanding the limitation section as described above. We have also expanded the conclusion as detailed in the previous point.

Reviewer #2: In this prospective observational cohort study the authors report increased risk of eGFR decline in T2DM patients with foot insensitivity. Overall, the study is well presented with interesting results for the readership.

We thank the reviewer for the kind and constructive comments and suggestion.

There are few discretionary comments for consideration.

1. It would be of interest to examine if baseline microalbuminuria or ACR predicts eGFR decline and how this compares to foot insensitivity.
We thank the reviewer for this important point. Please refer to our response to point 5 from reviewer 1 for detailed response. In summary, albuminuria was not a predictor of study-end eGFR in this study. We agree that assessing and comparing the performance of the monofilament test vs. albuminuria in predicting eGFR decline would be of great interest; however, due to missing data and the fact that our study was not design to perform such comparison, we are not in a position to decide which test is better in terms of diagnostic performance. This indeed will require a further, larger multi-centre study.

2. If foot insensitivity was more common in white Europeans compared to south Asians, does it confer the same risk in eGFR decline in both populations?

We thank the reviewer for raising this interesting point. Our results are consistent with other groups from the UK that showed a lower prevalence of diabetic neuropathy in South Asians vs. White Europeans with Type 2 diabetes. In Table 3, we presented the subgroup analysis by ethnicity in regards to the relationship between foot insensitivity and the progression to albuminuria and eGFR change. The results in Table 3 showed that foot insensitivity was associated with greater eGFR decline and greater progression to albuminuria in both South Asians and White Europeans, but the between groups differences were greater and statistically significant only in South Asians. The underlying causes of this are not apparent from this study. We think that South Asians who develop peripheral neuropathy and foot insensitivity might have more severe vascular disease than South Asians with normal foot sensitivity and hence more likely to develop further complications (such as CKD). While in White Europeans, there may be factors at play other than foot insensitivity resulting in the eGFR decline such as obesity or OSA as both of these conditions are more common and more severe in White Europeans vs South Asians with Type 2 diabetes.

In fact, repeating the regression analysis in the two ethnicities separately showed that in South Asians (n=102), the monofilament test remained associated with study-end eGFR (B= -6.665, p=0.007), while in White Europeans (n=123) the relationship became non-significant (B= -0.471, p=0.866). This supports our view that in White Europeans there were other factors at play resulting in eGFR decline other than foot insensitivity.

In order to address this point we have added the following paragraph to the discussion “The prevalence of foot insensitivity in our study was higher in White Europeans compared to South Asians which is consistent with previous studies from other groups in the UK [23-25]. However, our results (Table 3) show that while foot insensitivity was associated with greater eGFR decline and greater progression to albuminuria in both South Asians and White Europeans, the between group differences were greater and statistically significant only in the South Asian group. The exact reason for this observation is not clear from this study, but one possible cause is that South Asians who develop foot insensitivity have more severe vascular disease than those with normal
foot sensitivity in spite of foot insensitivity being less common in South Asians vs. White Europeans. Whereas, in White Europeans, there might be other factors at play contributing to the decline in eGFR such as obesity and OSA [10,11].”

3. It would help if more detail can be provided on the regression model used. e.g. were covariates included in separate blocks, which regression method was used e.g. enter, stepwise etc

Thank you. We included all the variables in the model at once using the enter method. We did not use step-wise approach due to the criticisms of this method in the statistical literature and also due to the limitations of our relatively small sample size. We have now amended the methods section to highlight that the enter method was used. We have also added a sentence to Table 4 that shows the regression results to highlight that the enter method was used.