Author's response to reviews

Title: Prediction of plantar pressure from clinical and radiological measurements in patients with diabetes

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Author's response to reviews: see over
Dear Editors,

We would like to respectfully thank the editorial board and the referees for the helpful and elaborate comments on our manuscript “Prediction of plantar pressure from clinical and radiological measurements in patients with diabetes”.

Due to circumstances I wasn't able to respond earlier to comments of the reviewers. I trust that you will appreciate that these circumstances were beyond my control. Meanwhile, please accept my apologies for the inconvenience caused. Thank you all for your patience in this matter.

We have considered the comments of the reviewers and we have changed the manuscript. Please find the list of the comments and changes below.

The changes made in the manuscript are highlighted in yellow. We hope that the revised manuscript is now appropriate for publication in “BMC Endocrine Disorders”.

We thank you for your interest in our article.

Yours sincerely,

Nick Guldemond, clinical researcher
On behalf of the fellow authors

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Encl.
- Revised manuscript
- List of the changes in the manuscript.
Our reply to the issues the reviewers have raised together with the changes made in the manuscript are listed below.

Comments Reviewer #1

1. Is the question posed by the authors well defined? The central question based around the clinical/radiographic prediction of plantar pressures is well defined. The results section presents a series of comparative analyses of clinical and radiographic between diabetic patients with and without peripheral neuropathy. A hypothesis for this aspect of the study is not established. As the authors acknowledge in the discussion, the findings are consistent with those reported elsewhere so do not make any significant new contribution to the field. The work makes an original contribution to the field. It challenges previous plantar pressure prediction analyses by well establish groups which is commendable.

This concerns the referee's remark that the "... results section presents a series of comparative analyses of clinical and radiographic between diabetic patients with and without peripheral neuropathy. A hypothesis for this aspect of the study is not established".

We agree with the referee that a specific hypothesis is not pronounced in the manuscript. The objective of our study was merely to investigate if local peak pressure of diabetic patients can be predicted from their clinical and/or radiographic data. Still we think the referee has made a valid point here, so we added in the introduction of the revised manuscript the reasons why peripheral neuropathic as well as non-neuropathic diabetic patients were included in the study.

We supplemented this text to the discussion:

‘The objective of this study was to assess the relationship between clinical measurements, radiological data and barefoot plantar pressure in order to find clinical measures that predict local peak pressure in patients with diabetes. To evaluate the effect of peripheral neuropathy as a predictor in this study, we included both patients with – and without peripheral neuropathy. We also evaluated previously proposed regression models by various authors with the same and/or similar variables as those obtained in our current study.’

2. There are two major limitations of the data which require some clarification: A statistically valid reason needs to be provided on why feet rather than subjects (with one foot chosen randomly) were used. There is a comprehensive body of literature which raises the problems and pitfalls of using two body sites from the same patient so the approach requires stronger justification.

We fear some misunderstanding has taken place. In the manuscript's methods section 'Statistical analysis', it is clearly stated how was proceeded in analysing the data concerning the methodological problem of feet nested within patients. However, the blame for the misunderstanding be due to our rather concise description of how it was done. At first a repeated ANOVA on peak pressures was done for all seven regions of the patients to test whether left or right feet differ on peak pressure. This can be seen as a multiple paired t-test on feet scores of diabetic patients. From the results it turned out that there were no statistical significant differences on peak pressure between feet within patients. Next, the feet scores on peak pressure were averaged over both feet and these averaged scores were used as 'dependent' variables in regression analysis. We have –hopefully– clarified the text of this section in the revised manuscript.

3. The pre-requisites for regression analysis are partly explained but further detail is required.

We have rewritten the entire section of the Statistical analysis in the revised manuscript and made extra remarks on how regression analysis was done and under which assumptions.

We changed the text as follows:
‘To meet assumptions of normality of statistical distributions peak plantar pressure scores were natural log transformed. At first, data from 186 feet were used for analysis. Repeated measures ANOVA showed no statistical significant differences between left and right feet as a general effect in the repeated measures model, nor specified for the peak pressures scores (i.e. the interactions of peak pressure with left or right side), nor specified for regional peak pressure (i.e. the interactions of regional peak pressure with left or right side). Therefore it was legitimate in the eventual data analysis to average scores over left and right sides. Next, stepwise regression analysis modelling was performed to determine which of the clinical or radiological measures will explain how much of the variance in averaged local barefoot plantar peak pressure, in each of the six forefoot regions and the whole forefoot separately. At first, all potential predictors of each subsets (clinical or radiological) were entered into the regression model through ‘forward selection’ and the resulting model with predictors having only statistical significant effects were noted. In the second step, all potential predictors are entered simultaneously and ‘backward elimination’ was applied until a model was found with predictors having statistical significant effects only. Finally, a cross-section of both resulting models was made using predictors having statistically significant effects in both models and this cross-section of predictors is ‘force-entered’ into the final regression model[44, 45]. Comprehensive models are assembled from the significant effects of both clinical or radiological predictors following the same three-step procedure. Previously found results from literature were compared with results from our procedure. All regression analysis models were performed using list wise deletion of missing cases. To prevent type I error as much as possible in the multiple use of regression analysis, a Bonferroni correction was applied through the division by the number of plantar regions. Therefore, an alpha level of 0.01 was chosen to judge statistical significance.’

4. There is no specific section in the discussion which clearly identifies the weaknesses in the current study.

We have given attention to the weaker aspects of the study in the new revised manuscript, especially on the validity of the models used and the practical applicability of the models.

5. There is some lack of detail related to predication analyses which have used imaging variables based on magnetic resonance and ultrasound imaging.

We agree with the reviewer. We supplemented the text with information about the clinical and imaging variables of the previously proposed models:

‘The models proposed by Mueller et al. for MT-1 (hallux valgus angle, Morton’s index, body weight) to MT-3 (hammer toe deformity, soft tissue stiffness, calcaneal inclination) and MT-5 (hammer toe deformity, Morton’s index) were statistically significant: MT-1 region r .32, r² .105 SE 0.50 (p=.001); MT-2 region r .32, r² .103, SE 0.43 (p=.001); MT-3 region r .22, r² .046, SE 0.38, (p=.013) and MT-5 region R .29, r² .072, SE 0.61 (p=.004). This was also true for the model for prediction of plantar pressure under the forefoot by Ahroni et al. (body weight, insulin use) and the model for the MT-1 region suggested by Payne et al. (MTP-1 range of motion, Michigan Neuropathy Score): r .46, r² .212, SE 0.19 (p=.001) and r .36, r² .131, SE 0.49 (p=.001), respectively.’

6. In the abstract/results section (page 2) it is not clear what is meant by MT-1 (173 kPa) and MT-5 region (88 kPa). Is the mean difference?

We added the following text:

(Page 2) ‘Forefoot pressures were significant higher in patients with neuropathy, compared to patients without neuropathy for the whole forefoot, the MT-1 region and the MT-5 region (respectively 138 kPa, 173 kPa and 88 kPa higher: mean difference).’
Page 11

‘Forefoot pressures were significant higher in patients with neuropathy, compared to patients without neuropathy for the whole forefoot, the MT-1 region and the MT-5 region (respectively 138 kPa, 173 kPa and 88 kPa higher: mean difference), table 2.’

7. Figure 1 and 2 may be redundant if the authors choose to remove the analyses comparing neuropathic and non-neuropathic subjects.

Please, see our response on comment 10.

8. Similarly, tables 2-4 may also be redundant.

Please, see our response on comment 10.

9. A clearer, statistically valid explanation must be provided on the use of feet rather than subjects. This should be linked to sample size estimations linked to the regression analyses and published formulae or rules of thumb. These may be violated when patients rather than feet are considered where more than 5 or 6 independent predictor variables are entered.

Power analysis for this study was done on patients rather than feet. Assuming a normally distributed ‘dependent’ peak pressure requiring approximately 50 patients we assumed that no more than 5 to 6 predictors were to be found with statistically significant effects within the regression analysis. With presumably no interactive effects between predictors this brings the numbers required for a valid analysis up to 100-110. In the newly performed regression analysis in the revised manuscript we limited our definition of the statistical significance to a p-value of <0.01, because of multiple testing in analysis. Numbers of predictors with statistically significant effects will therefore be limited too. The number of patients used (n=93) will be more than adequate. With reference to our response on comment 3. (above).

10. Either establish a hypothesis for testing clinical/radiographic between neuropaths and non-neuropaths or remove the analyses from the first section of the results (page 10/11).

We adopted the suggestion of the reviewer and added the following text:

‘The primary objective of this study was to assess the relationship between clinical measurements, radiological data and barefoot plantar pressure in order to find clinical measures that predict local peak pressure in patients with diabetes. In addition, we also evaluated previously proposed regression models by various authors with the same and/or similar variables as those obtained in our current study. To evaluate the effect of peripheral neuropathy as a predictor in this study, we included both patients with – and without peripheral neuropathy. The secondary objective of this study was to assess the differences in clinical measurements, radiological data and barefoot peak pressure between patients with – and without peripheral neuropathy.’

11. A fuller explanation must be given for the entry of variables into the prediction analysis based on univariate analysis, collinearity, and other features such as missing values and outliers.

Our response on comment 3. and pertaining text present a detailed description of the analysis procedures. Univariate analysis results (Pearson correlation coefficients) only played a minor part in selecting potential predictors of peak pressure. Collinearity is only a matter of discussion when predictors are intrinsically entwined from one causal origin (i.e. statistical incest), and not just high correlated. This was not the case. The residual analysis represented as Bland & Altman plots (figures 3 and 4) are indicative for outliers and will provide the interested reader sufficient information.
12. There appear to be 21 individually reported regression analyses so by chance alone one of these models may be statistically significant. Therefore, provide a clearer explanation of how multiple comparisons were handled in the statistical analyses.

We have restricted the definition of statistical significance for regression analysis in the new revised article to $p<0.01$ to preclude any possible type I errors in this respect. All regression analyses have been repeated under this new rule. With reference to our response on comment 3. (above).

13. Provide a separate section in the discussion identifying the potential sources of weakness in your study and how these may have biased your findings.

We agree with the reviewer and we supplemented the text as follows:

‘This study was directed from a practical and ecological research perspective, which means that the patients were mostly screened according through common practice procedures: e.g. goniometry, blood pressure measurements, etc. According to scientific criteria, these common practice procedures often have inferior clinimetric qualities and are likely to contribute to inherent variability. Maybe other clinical or radiological measurements are less prone to inherent variability and may be stronger predictors for local peak pressure. We studied diabetic patients without foot complications such as severe deformities and gait abnormalities. Some of the results might well be different in patients with these complications of diabetes. Nevertheless, we think it is important to identify patients with elevated plantar pressures in their early stage of disease in order to take appropriate preventive measures. The screening of these kind of patients is typically done in peripheral care centres where there is no radiological facility or plantar pressures equipment are available.’

We want also point to the paragraph under the section ‘Prediction models with the same or similar parameters applied to the present data set’, where we carefully appraise our findings.
Comments Reviewer #2

14. It could be useful to change ‘plantar pressure’ in ‘peak plantar pressure’ in the title because only the peak pressures are investigated in this study.

We agree with the reviewer and adopted the title accordingly.

15. page 2: second sentence in methods: ‘barefoot’ instead of ‘bare foot’

We corrected the text.

16. page 5: under patients: deformities are excluded: what are the criteria for exclusion based on orthopaedic deformities? Later in the study the authors mention the rate of toe deformity. This does not match with the former mentioned exclusion criteria on page 5.

We agree with the reviewer and we supplemented the text as follows:

‘Exclusion criteria were a history of rheumatoid arthritis, severe foot trauma, severe deformity i.e. which require orthopaedic shoes and/or surgery of the foot.’

17. Page 5: under patients: Is limited joint mobility important in the exclusion criteria?

We are not totally certain whether we have understood the question of the reviewer. We were interested in limited joint mobility as an independent factor in the prediction of peak pressure. As such, we didn’t consider limited joint mobility as an exclusion criterion.

18. Page 5: table 1: the mean value of HbA1c is rather high, which means that the majority of patients are not well regulated. This is just a remark and can not be changed, of course.

We thank the reviewer for his attentiveness. The high mean value of HbA1c could be explained by the relatively large number of patients who were referred by the GP for their first outpatient clinic consult in our specialized hospital. At the moment of inclusion, these patients were most likely not yet adequately regulated.

19. Page 6: are you sure that the technical failure (exclusion of a number of trials) with the EMED system has not influenced the data you are using in this study?

The corrupted plantar pressure data was due to floppy drive and/or disc failure (we have an old EMED SF-4 system without hard disk). Either data from a series of measurements could be read without problems of the disc was unreadable. Data which we used for analysis were errorless and contained all data from the trials.

20. Page 6: Barefoot pressure measurement: why are the peak pressures measured and analysed in this study. Mean pressures and impulses could also be very harmful.

We agree with the reviewer that other parameters for plantar loading may also be important as predictor for tissue damage. Since all these parameters are highly correlated, we chose peak pressure as most common used measure in the field of plantar pressure measurement. Please, see also our response to comment 44.

21. Page 7: you mention twice criteria for scoring. It is unclear for readers which criteria fit to which test.
We removed ‘criteria for scoring’ in the second sentence and changed the text as follows: ‘Additionally, light touch sense was related to the anatomical level below which it was impaired: no abnormalities (0), toe (1), mid-foot (2), ankle (3), mid-calf (4) and knee (5).’

22. Page 7: Orthopaedic assessment: the authors explain the exact position of the bisections for MTP 1 measurement. Why are these details about the ankle joint and the hallux valgus angle not mentioned?

We provided references for the procedure of the ankle joint and the hallux valgus angle measurement, while we could not find the exact reference for MTP-1 measurement procedure. If the reviewer is willing to provide this reference, than we will be very grateful.

23. Page 8: The medial arch was subjectively classified: why has the navicular height, which is reliable, not been used?

From a practical and ecological research perspective, patients were mostly screened through common orthopaedic clinical assessment procedures (common practice). Which means that according to scientific criteria, not all ‘best’ available tests and measurements were performed. However, the navicular height was obtained through radiographic assessment which is strongly correlated with clinically determined navicular height.

24. Page 10: Plantar pressure: change the last sentence perhaps into: Forefoot pressures were significant higher in patients with neuropathy, compared to patients without neuropathy for the whole forefoot, the MT-1 region and the MT-5 region (respectively 138 kPa, 173 kPa and 88 kPa higher).

We agree with the reviewer and we supplemented the text as follows:

‘Forefoot pressures were significant higher in patients with neuropathy, compared to patients without neuropathy for the whole forefoot, the MT-1 region and the MT-5 region (respectively 138 kPa, 173 kPa and 88 kPa higher: mean difference), table 2.’

25. Page 11: clinical measurements: No differences with respect to ABI, toe pressure and passive ankle DF. What about VPT and the Valk score?

We added asterisks to table 3 to indicate that there were statistically significant differences in VPT and Valk scores.

26. Page 11: Callus formation and toe deformity: ‘Most callus formation was found’ better change into ‘Most important callus formation was…’

We adopted the suggestion of the reviewer and changed the text as follows:

‘Most important callus formation was found under the hallux and the head of MT-1, while the least callus formation was found under the lateral side of the forefoot: MT-3 to MT-5.’

27. Page 11 and 12: % of calcaneal alignment and arch height are not exactly 100% in total

We corrected the typing errors.


We thank the reviewer for his attentiveness. We corrected the text.
29. Page 13: add into the first sentence: ...and the 'Valk score' for three regions and the whole forefoot. We adopted the suggestion of the reviewer and changes the text as follows:

‘Callus formation was a relevant clinical predictor for all regions and the ‘Valk score’ for two regions and the whole forefoot.’ …statistical analysis was repeated with stricter criteria, please see our response on comment 2.

30. Page 13: …resulted in the largest explained variance. Mention perhaps the exact amount of variance. We adopted the suggestion of the reviewer and changed the text as follows:

‘For most regions, the comprehensive model i.e. the combination of clinical and radiological predictors, resulted in the largest explained variance: 26% (forefoot), 34% (MT-1 region), 25% (MT-2 region), 16% (MT-3 region), 13% (MT-4 region) and 29% (MT-5 region), table 5.’

31. Page 13 and 14: The previous proposed regression models possibly belong more in the discussion than here. We believe it is better for the convenience of the reader to provide information here about the origin of the concerning models than solely presenting the results of our simulations.

32. Page 16: first sentence: A similar relationship…..previous studies. Where did you measure the soft tissue thickness on radiographic images? The soft tissue thickness was determined through measurements on lateral radiographs; i.e. sesamoid height and MT-5 head height. This procedure was the same as described in Cavanagh PR, Morag E, Boulton AJ, Young MJ, Deffner KT, Pammer SE: The relationship of static foot structure to dynamic foot function. J Biomech 1997, 30(3):p243-250.

33. Page 16: Next paragraph: Some parameters obtained…….hallux alignment. I read before that there was no significant difference in arch height between NP and non NP. This does not match with the latter sentence. We supplemented the text as follows:

‘Some parameters obtained from lateral and anterior–posterior radiographs indicate similar classifications found through clinical examination, such as arch height and hallux alignment, although no statistically significant differences were found.’

34. Page 16: first paragraph under regression models: Is R² considered as high or low and where is the limit? The coefficient of determination R² is a measure of the global fit of the model. Approximately 35 percent of the variation in the response variable can be explained by the regressors. The remaining 65 percent could be explained by concealed variables or inherent variability. Normative classifications as high or low is depending on the research question, the study design, etc. Therefore a strict definition of normative classifications or cut-off level is not appropriate. From the perspective of the primary research question in our study, the R² can be considered as low, which we translated into: ‘The prediction models constructed with regression modeling were not useful in clinical practice, because of considerable discrepancies between the predicted and the actual peak pressure values.’
35. Page 16: bare foot -> barefoot (2x)
We corrected the text.

36. Page 16: Why do the authors only use a regression model for MT-1?
We could choose any other region for the visual presentation, but the results of our MT-1 regression model could now be compared with the MT-1 regression model from Cavanagh.

37. Page 19: last reference: Title between ().
We corrected the text.

38. Page 22: Reference 62: gait and posture is written in capitals
We corrected the text.

39. Table 2: Bare foot -> barefoot
We corrected the text.

40. Table 2: *PNP- versus PNP + p<0.05 & **p<0.005 better change into PNP versus PNP + *p<0.05 & **p<0.005
We adopted the suggestion of the reviewer and changed the text accordingly.

41. Table 4: Motons index -> Mortons index?
We corrected the text.

42. Table 4: an explanation (or figure?) about some measurements could be interesting for the reader.
We agree with the reviewer, but for the benefit of being brief and comprehensive we decided to limit our visual presentation. Moreover, for the interested reader we provided references for papers with excellent descriptions and visual presentations.

43. The table with the regression models: is it table 5 of figure 5???
We corrected the text.
Throughout their study, the authors focused on peak plantar pressures. Previous studies have reported that while elevated foot pressures are an important risk factor in the development of ulcerations, foot pressure is a poor tool by itself to predict foot ulcers (Lavery LA, et al: Diabetes Care 2003, 26:1069). Other factors previously discussed which could potentially influence the development of skin breakdown in neuropathic diabetic individuals include the amount of time the patient spends on a point of high plantar pressure (pressure-time integral) as well as the number of repetitions at the point of high pressure over a period of time (activity induced repetitive stress). Since authors only focused on peak plantar pressures, the reviewer believes that the authors should discuss these other potential factors that influence the development of plantar ulcers that the authors did not evaluate in their as a limitation of the study in their revision.

We would like to make clear that the objective of this study was to find indicators for peak pressure and not the for the prediction of ulcer development, which is far to complicated. Indeed, peak pressure is the most common used measure for clinical risk stratification. Therefore, we chose this parameter instead of the pressure-time integral. Moreover, there still a lack of evidence and incomprehension (experimentally and clinically) about the role of pressure-time integral in the development of ulcers. Please, see also our response to comment 20.

Previous research has reported that plantar pressures are significantly higher under callused regions of the foot (Young MJ, et al: Diabet Med 1992 9:55 and Menz HB, et al: Clin Exp Dermatol 2007 32:375). It does not appear after reading the manuscript that the authors removed any callus build-up from their subjects prior to collecting plantar pressure data. If this is a correct assumption, the authors should describe the reason for not removing their subject’s callosities prior to pressure data collection and what impact this could have had on the peak pressure data collected in this study. For example, the authors note on page 11 that the most callus formation was found under the hallux and head of MT-1.

The callus formation was not removed prior to the data collection, because this was a factor of interest in the prediction of peak pressure.

Accordingly, callus formation is just like any other factor which influence peak pressure: e.g. limited joint mobility or claw toes. Therefore we think there is no need to clarify the effect of callus formation in particular.

The distribution of callus formation was quite similar in both groups and there is no evidence or likely explanation that the effect of callus formation is different in subjects with neuropathy versus those without neuropathy. Furthermore, we found no interaction effects of callus formation and neuropathy. Please, see also our response on the previous comment.

In the copy of the paper the reviewer downloaded, there are two different Tables labelled number 4 and also a Figure 5. In the manuscript, the authors refer to Table 5 on page 12, but there is no Table 5. It would appear that the second Table 4 (entitled: Regression models) is actually Table 5 and should be re-numbered.

We corrected the text.
48. There is no mention of Figure 5 in the manuscript and it would appear that Figure 5 and the second Table 4 are identical and Figure 5 can be removed from the paper. The authors need to address and correct this issue in their revision.

We corrected the text.