Author’s response to reviews

Title: Plantar pressures are higher in cases with diabetic foot ulcers compared to controls despite a longer stance phase duration

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Author’s response to reviews:

Dr Tim Shipley
BMC Endocrine Disorders

Dear Dr Shipley,

Re: BEND-D-16-00079. Plantar pressures are higher in cases with diabetic foot ulcers compared to controls despite a longer stance phase duration

Thank you for consideration of our paper for publication in BMC Endocrine Disorders. We thank the section editor and the peer-reviewers who provided constructive feedback on our paper. We have reviewed their comments and have attempted to address these comments in the best way possible. As a result of considering the reviewers comments, we believe we have been able to improve the quality of our manuscript.

You will find tables in the attachment which outline how each individual reviewers comments were addressed. In addition to this, all changes have been highlighted within the manuscript using different colours where appropriate (as per the highlighted text below, using an individual colour for each reviewer).
We wish to disclose that there are no duplicate publications arising from this manuscript. We would like to re-submit this revised manuscript and associated files for your review and for consideration of the study for publication in BMC Endocrine Disorders.

Thank you.

Kind Regards,

Malindu Fernando  
(Corresponding Author)

Reply to the reviewers comments

Reviewer #1

Line 108: Please comment Why 5 years was chosen as a criterion for matching age?

We matched the controls based on an age range of five years as we thought this to be the most appropriate age range to match for and this was based on our protocol. We believe that a +/- 5 years is most frequently used for matching in case control studies. A smaller interval would have made it very difficult to find an age match and hence the risk of losing cases if no adequate controls were found. On the other hand, a wider than 10 year matching range seems to render matching irrelevant as 10 years age difference is likely to have an impact on disease occurrences and biomechanics. Furthermore, we are aware that the magnitude of age related reduction of gait speed (m/s) reported in the literature varies between 0.1% and 0.7% per year (Ohberg et al 1993). Given that gait speed often varies by 5% between trials, it seems appropriate to match participants to a similar age range.

Unfortunately in this instance, there was a significant difference in age between the diabetes control group and the healthy control group. This was however accounted for in the binary logistic regression analyses by adjusting for age. Hence we added this sentence to line 112;

We selected an age range of five years to make recruitment feasible and as we deemed this would be sufficient to reduce any impact that differences in the ages of cases and controls may have on the outcomes.

Line 138: Please indicate whether a walkway was used or not. Also please comment on the order in which the feet landed (i.e. stepping preference, whether it was randomised. The authors are encouraged to consult findings in Naemi et al (2012)Naemi, R., Healy, A., Chockalingam, N. Larose Chevalier, T. (2012). The effect of the use of a walkway and the choice of the foot on plantar pressure assessment when using pressure platforms, The Foot, 22(2): 100-104
We thank the reviewer for pointing this out and for referring us to the study by Naemi et al. We did not use a walk-way during plantar pressure assessment. An extensive account of the methods used to acquire plantar pressure data can be found in our study protocol; http://bmcendocrdisord.biomedcentral.com/articles/10.1186/s12902-015-0057-7.

We did not randomise the stepping preference, but encouraged participants to commence walking with their dominant limb for each walking assessment starting at the same distance away from the pressure platform. We did this to standardise the protocol and to avoid any alterations in gait (and hence variability in plantar pressure distribution) due to limb dominance or loading impact. We were specific to indicate that each walking assessment should commence using the same foot from a standardised distance away from the platform. I.e. to achieve a 3-step protocol for each individual.

It has been documented that the preparation time leading to plantar pressures trials are crucial for establishing a normative or consistent gait pattern, where invitation to walk normally can lead to a slow and cautious gait pattern and multiple trials lead to increased stride length and gait speed which may not be representative of the participants natural gait (Rosenbaum & Becker, 1997). We allowed adequate time for participants to familiarise themselves with the protocol and environment so that steady state gait could be observed. We used a long pressure platform (2 m) to adequately capture both feet during the same walking assessment which is consistent with the recommendations in the paper by Naemi et al.

Therefore, we added the following sentence to line 148;

We did not use a walkway during gait and did not adjust stepping preference. Instead stepping preference was controlled by asking participants to start walking with the dominant foot throughout and by commencing from the same distance away from the platform. Participants were given time to familiarise themselves with the protocol

Table 2: Please indicate what "EGFR" refer to.

We added this to the Table legend in Table 1, line 245; eGFR= estimated glomerular filtration rate (a marker of renal function). We also corrected it in the manuscript.

Table 3: Please double-check the Mean Peak plantar Pressure (mpp) values or unit. The values in N/cm² seem to be very low for Metatarsal area,

We agree with the reviewer that the overall mpp values in our study are significantly lower than other reported values using different platform devices. Our results are however consistent with plantar pressure values obtained in a similar population using the same platform. We are well aware of this dissimilarity and believe that this may be due to differences in sensor configuration between platforms.

We know that differences between platforms, protocols and sensor configurations pose significant limitations when comparing data between studies and this is a clear limitation in the field. We are however confident of our data and have had our data checked by the manufacturing company for any errors and no issues were found in the obtained data. We are also aware that the conductive foam in resistive pressure devices may be prone to damage. The platform was
checked and the sensor array was replaced and calibrated prior to commencing data collection. To highlight the limitation of the difference in pressure values however, we added the following sentence to the limitation section of the discussion, line 432:

There are differences in plantar pressure values obtained using different platforms with different resolutions and various methods of assessment, which is a clear limitation in the field [46]. Our plantar pressure results seem to be lower than other values reported in the literature, but are consistent with others using the same platform to assess participants with diabetes [31].

Reviewer #2

What is the sensitivity of RS scan

We thank the reviewer for their comments. In relation to the sensitivity of the Rs Scan platform system, it is difficult to establish the sensitivity based on available information. Some information regarding the platform can be found on the manufacturers website; http://www.rsscan.com/footscan/high-end/#tab_products. The platform we used was 2m in length, 0.4 m in width and contained 16,384 sensors capturing at 100 Hz. The platform has been used for previous biomechanical research in participants that have diabetes (see above comments).

We are aware of one independent study (Giacomozzi, 2010) which aimed to assess the technical specifications of various plantar pressure platforms, including our device; http://www.sciencedirect.com/science/article/pii/S0966636210000846. However, the sensitivity of the device was not assessed as a part of this study and the Rs Scan data had not been reported in this technical note, since a separate investigation has been agreed with the company. However, the sensor configuration and dimensions of our platform were comparable and compatible with other commonly used platforms.

A more detailed account of the methods used to acquire plantar pressure data and on the platform used can be found in our study protocol; http://bmcendocrdisord.biomedcentral.com/articles/10.1186/s12902-015-0057-7.

Author chosen stance phase duration. Why? As we did not control or assess gait speed, we assessed stance phase duration as a surrogate measure of gait speed in participants using the known temporal relationship between gait speed and stance phase duration. This is highlighted in line 163; The stance-phase duration (length of time in milliseconds that the feet were in contact with the platform) during plantar pressure assessment was recorded and averaged for the five selected trials for each participant as a surrogate measure of gait speed [26].

Also please see line 306 of the discussion; Faster gait speeds (i.e. shorter stance phase durations) have been shown to increase plantar pressure at the heel, medial and central forefoot and the toes 2-5 while decreasing plantar pressure beneath the mid-foot and lateral forefoot [33, 34]. This has been termed a medialisation of the loading pattern [34]. Conversely, a slower gait speed, as
denoted by the longer stance phase duration, would be expected to produce higher plantar pressures beneath the mid-foot and lateral forefoot but lower plantar pressures at all other sites. Other pressure parameters are already published in other journal paper. Why not consider plantar pressure distribution?

We have previous published two systematic reviews/ meta-analyses on similar topics; http://www.ncbi.nlm.nih.gov/pubmed/24035444 and http://journals.plos.org/plosone/article?id=10.1371%2Fjournal.pone.0099050. The first review aimed to distinguish the gait features and plantar pressures in participants with diabetic peripheral neuropathy in comparison to diabetes and healthy controls. The second review attempted to assess plantar pressure differences between participants with a history of foot ulcers compared to participants with diabetic peripheral neuropathy without a history of ulcers. However, in the latter study, we were unable to see a statistical significance in plantar pressures between people with active ulcers when compared to controls with neuropathy without a history of ulcers.

Hence the novelty of the study presented here is that a homogenous, active neuropathic foot ulcer group was assessed in comparison to a diabetes group and to healthy controls. We assessed stance phase duration as a surrogate measure of gait speed and discussed differences in plantar pressures relative to this. We used a pre-established protocol and adjusted our analyses for important confounders and performed corrections for multiple testing. Our study used a much larger sample size than those previously reported and we focused our attention on the distribution of plantar pressure as well as the differences in pressure between cases and controls (as we assessed site specific plantar pressure).

The main rationale of this study was to assess whether plantar pressures are higher in people with active ulcers compared to controls. Please see line 69; In a recent meta-analysis of observational studies, we reported that plantar pressures were not significantly different in people with active DFUs compared to controls with DPN without active DFUs [11]. The result from this analysis may have been due to a lack of statistical power to detect a true difference, or due to the fact that plantar pressures are not significantly different in cases with active DFUs compared to controls [11]. Hence we believe the findings of this study are important to identifying the differences in plantar pressure between participants with active foot ulcers and controls. This study also reports on the baseline assessments for a longitudinal study which followed the participants with diabetes with and without foot ulcers longitudinally to assess changes in plantar pressures over-time and to assess whether plantar pressures remain elevated throughout ulcer progression/healing.

Sample size are not matched e.g. controls subject are less... The process of case-control matching is described in detail in our protocol. We did not match or standardise group sizes but attempted to match cases and controls based on the age and sex of participants. Diseases with a relatively low prevalence create difficulty in obtaining sufficient case numbers and this is a known epidemiological limitation. In foot ulcer patients, factors such as frequent hospitalisation, recurrent infections, limb amputation and the often associated overall poor general health and wellbeing impacts the ability to commit to scientific studies. We anticipated that recruiting cases as going to be difficult and hence we inflated our control groups to account for this difficulty and
to obtain adequate statistical power in excess of 80%. Hence due to difficulty in recruitment, a 1 case: 3 diabetes controls: 3 healthy controls matching process replaced the original 1 case: 4 diabetes controls: 2 healthy controls. This is different to the conventional 1 case: 1 control approach but is an acceptable design choice given the focus of the study and the population of interest.

Why author not consider the footwear hardness?

While we agree with the reviewer that footwear has a role in the progression of ulcer healing and the distribution of plantar pressures, this was beyond the scope of our study and was not an aim of the study. We performed assessments of barefoot gait to assess the foot-to-floor interaction without the added impact of footwear in our participants. We realise that footwear may lead to differences in plantar pressure data and in particular the hardness of the shoe, the density of the sole material and other key factors such as the depth of the shoe, whether orthotics were used inside the shoe all have influences on plantar pressures and this creates a challenge for interpreting pressure data. Therefore, we chose to focus on barefoot plantar pressure which is reflective of the individual gait without the confounding effect of footwear. However future research may focus on the impact of footwear, building on from our data in an active foot ulcer population during barefoot gait. This is reflected in line 424;

We examined barefoot gait rather than shod gait and purposefully did not control gait speed as we wanted to examine the natural gait characteristics of our participants

Section editors comments

From the tables it is apparent that many of the diabetes control group did not have neuropathy based on MNSI. Are the differences observed simply reflect differences in neuropathy status rather than DFU status. As the authors know, many patients with diabetic neuropathy do not develop DFU. Also I found no adjustment for neuropathy status in the analysis.

We thank the editor for their comments on our paper and for pointing out this important limitation of our study. The focus of our study was to assess the plantar pressures in participants with neuropathic foot ulcers compared to diabetes and healthy controls. As pointed out, the severity of neuropathy in our ulcer group was much worse than that present in the control group. We have earlier reported (http://www.sciencedirect.com/science/article/pii/S0268003313001897) that diabetic peripheral neuropathy can manifest in people with a diabetes duration greater than 10 years, as it does in individuals with poor glycaemic control (Kovac et al., 2011; Oguejiofor et al., 2010; Valensi et al., 1997). In addition, small foot muscle atrophy resulting from the effects of hyperglycaemia and small nerve damage have also been confirmed in diabetes patients utilising Magnetic resonance imaging before neuropathy becomes clinically detectable (Greenman et al., 2005). While we agree with the comment that not every individual with peripheral neuropathy will develop a neuropathic foot ulcer, the relative risk of doing so is significantly increased in the presence of peripheral neuropathy as both sensory and autonomic neuropathy independently influence the risk of developing foot ulcers.
Hence as neuropathy is known to promote ulcer development, it was not possible in our study to match cases and controls based on the severity of neuropathy and therefore the diabetes control group represent a mixed group of people with no neuropathy and some degree of neuropathy. Therefore the plantar pressure distributions observed in cases may be due to the presence of neuropathy rather than due a presence of a foot ulcer, however the association of elevated plantar pressures in people with neuropathy has been extensively investigated previously whereas the focus has not been on people with neuropathy with active ulcers.

We were unfortunately unable to adjust for neuropathy status in our logistic regression models due to a lack of statistical power. Given this potential for close associations (part of the pathological pathway) the best statistical approach would be stratification of analysis into neuropathy presence or severity (none, mild, severe). For such a stratified analysis the sample size was unfortunately too small. However another limitation is the fact that we are not able to demonstrate whether higher plantar pressures preceded ulcer development or are a response to the ulcer. Our design may have benefitted from having a separate group of participants with diabetes with neuropathy without a history of ulcers. We believe that such comparisons can be the focus of future studies and were beyond the scope of our study. The cohort of diabetes patients with and without foot ulcers will be followed-up longitudinally to assess how plantar pressures vary over time.

We have alluded to this limitation in line 422 of the discussion; We were unable to adjust all our analyses for multiple factors such as foot deformities, arch type and neuropathy severity due to relatively small group sizes.

In the tables: could the authors report IQR as the values between the 25th and 75th centiles as this is easier to understand.

We have amended all the data tables in the manuscript to represent the 25th and 75th centiles.

A brief description on how these patients were selected will be useful

We added the following information to line 98 to highlight the selection of participants: The DFU and DMC groups were recruited from inpatient wards, outpatient clinics and community health clinics within the Townsville Hospital and Health Service District, Queensland, Australia [21]. The HC group were recruited through community advertising and from staff at the university where the study took place.

Additional inclusions

Inclusion of new data that has been published since this manuscript has been reviewed.

We included reference to another study that was recently published by our group assessing the gait of participants with active ulcers (http://www.clinbiomech.com/article/S0268-0033(16)30095-X/fulltext). As this study was performed in the same cohort of participants, we made reference to this study within the discussion. Please refer to lines 406 to 420 below;
These results highlight that vertical ground reaction forces are also likely to be significantly elevated in cases with DFUs. This is consistent with recent findings in the same cohort [45]. To our knowledge, although it is often speculated, increased ground reaction forces have not been previously reported in people with active DFUs until recently [45]. These findings suggest that people with active DFUs experience significantly higher mechanical stresses during gait. On the other hand, while plantar pressures represent only the vertical component of the applied tissue stress, shear-forces are also a crucial consideration in the formation of DFUs [42]. As the same local area under the foot can experience stresses in opposite directions, investigation of shear forces in cases with DFUs will provide further information regarding tissue stresses [44]. The increased contact areas observed in our cases at several sites is in agreement with the idea that ground reaction forces other than the vertical force (i.e. shear forces) may also be important in DFU formation [42]. This is consistent with the finding that shear forces in the anteriorposterior direction during gait in the same cohort of people with DFUs was significantly higher than in controls [45]. Future studies should focus on assessing shear-pressures, especially at sites of active ulcers.