Biomechanical characteristics of peripheral diabetic neuropathy: A systematic review and meta-analysis of findings from the gait cycle, muscle activity and dynamic barefoot plantar pressure.

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Abstract

Background: Diabetic peripheral neuropathy is an important cause of foot ulceration and limb loss. This systematic review and meta-analysis investigated the effect of diabetic peripheral neuropathy on gait, dynamic electromyography and dynamic plantar pressures.

Methods: Electronic databases were searched systematically for articles reporting the effect of diabetic peripheral neuropathy on gait, dynamic electromyography and plantar pressures. Searches were restricted to articles published between January 2000 and April 2012. Outcome measures assessed included spatiotemporal parameters, lower limb kinematics, kinetics, muscle activation and plantar pressure. Meta-analyses were carried out on all outcome measures reported by ≥ 3 studies.

Findings: Sixteen studies were included consisting of 382 neuropathy participants, 216 diabetes controls without neuropathy and 207 healthy controls. Meta-analysis was performed on 11 gait variables. A high level of heterogeneity was noted between studies. Meta-analysis results suggested a longer stance time and moderately higher plantar pressures in diabetic peripheral neuropathy patients at the rearfoot, midfoot and forefoot compared to controls. Systematic review of studies suggested potential differences in the biomechanical characteristics (kinematics, kinetics, EMG) of diabetic neuropathy patients. However these findings were inconsistent and limited by small sample sizes.

Interpretation: Current evidence suggests that patients with diabetic peripheral neuropathy have elevated plantar pressures and occupy a longer duration of time in the stance-phase during gait. Firm conclusions are hampered by the heterogeneity and small sample sizes of available studies.

Key Words – Diabetic Peripheral Neuropathy, Biomechanics, Gait, Diabetes Complications, Type 2 Diabetes, Type 1 Diabetes, Plantar Pressure, Electromyography, Movement analysis, Diabetic Foot, Diabetes Mellitus, Meta-analysis, Systematic Review

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1. Introduction

One of the many consequences of diabetes is the onset of diabetic peripheral neuropathy (DPN) (Shenoy, 2012). The prevalence of DPN ranges from 13 to 68% in diabetes populations (van Dieren et al., 2010). Peripheral neuropathy affects the sensory, motor, and autonomic components of the nervous system, manifesting as a loss of protective sensation, intrinsic foot muscle dysfunction and anhydrosis of the foot (Shenoy, 2012). These manifestations often lead to bony deformities and high plantar pressure areas which result in skin breakdown and ulceration (Boulton et al., 2005). It is believed that the majority of diabetic foot ulcers develop as a result of the repetitive action of mechanical stress (pressure) during gait, in the presence of peripheral neuropathy or loss of protective sensation (Armstrong et al., 2004). Lower-limb amputations in people with diabetes are typically preceded by foot ulceration, suggesting that better understanding of the mechanisms of ulcer development are of vital importance (Singh et al., 2005). This includes better understanding of the biomechanical components (Formosa et al., 2013).

It has been postulated that DPN-related changes in the lower limbs may lead to functional gait variations; predominantly related to reduced range of movement of joints, reduced active muscle power and changes in gait mechanics (Andersen, 2012). The biomechanical changes resulting from DPN may translate to increased plantar pressures in the foot, which contributes to the pathogenesis and development of foot ulcers, especially in the forefoot (Van Deursen, 2004). In particular, the first metatarsophalangeal joint has been implicated as a site of biomechanical dysfunction leading to elevated plantar pressures during gait, promoting ulceration at this site (Turner et al., 2007). Therefore, we hypothesised that reductions in spatiotemporal parameters, increases in kinetics (specifically the vertical ground reaction force and joint moments), and reductions in kinematics of the lower limb (evident as restrictions in the sagittal plane) and altered dynamic electromyography (EMG) findings in those with DPN may manifest from or contribute towards altered plantar pressure loading in this population (Cavanagh et al., 2000). Therefore, this systematic review and meta-analysis aimed to assess the effect of DPN on gait (spatiotemporal parameters, joint angular kinematic

and kinetics), dynamic EMG (muscle activation and deactivation patterns) and dynamic barefoot plantar pressures (plantar foot pressures during gait). We sought case-control studies comparing patients with DPN to those with diabetes mellitus without neuropathy (Diabetes Mellitus Controls) (DMC) or healthy controls (HC).

2. Methods

2.1 Literature search strategy

Electronic databases (Ovid, CINAHL, PubMed, Scopus and Google Scholar) were searched systematically by the first author for articles published between January 2000 to April 2012, reporting studies on DPN in the three biomechanical areas of gait, dynamic EMG and plantar pressure. The initial search was conducted in April 2012. An additional search was conducted in January 2013 to ensure any further articles were also assessed for inclusion prior to publication. No new articles were found. Search results were restricted to articles published between January 2000 and January 2013. Publications prior to the twenty first century were not included to restrict the focus of the review to the most recent findings from studies which assessed gait using current technology, which is more reliable and comprehensive. This is especially true in relation to three dimensional joint angular kinematic analysis which was introduced at around this time (Sutherland, 2001, Sutherland, 2002, Sutherland, 2005). The following keywords and MeSH headings were used:

#1 Gait AND diabetes

#2 electromyograph* AND diabetes

#3 EMG AND diabetes

#4 biomechanic* AND diabetes

#5 kinematic AND diabetes

#6 plantar pressure AND diabetes

#7 (diabetes MeSH) AND 1# AND 2# AND 3# AND 4# AND # 5

#8 (diabetic foot MeSH) AND 1# AND 2# AND 3# AND 4# AND # 5

#9 (diabetic neuropathy MeSH) AND 1# AND 2# AND 3# AND 4# AND # 5

2.2 Selection of studies

The titles and abstracts retrieved from the initial database search were screened by the first author utilising the question 'Did the study investigate one of the three biomechanical areas of interest?' The full text was obtained for articles that remained relevant after the initial screening. One of the authors then reviewed the full text for the final decision on inclusion utilising the entry criteria. All articles meeting these initial criteria had their full-texts retrieved and were then further evaluated by two authors (MF and RC) using the inclusion and exclusion criteria below. All studies meeting the exclusion criteria were removed from the review.

The inclusion criteria were:

1. Studies published between 2000 and 2012;
2. Studies in English language;
3. Studies reporting findings in clearly identified DPN groups in comparison to a DMC and/or a HC group using eligible inclusion and/or screening criteria;
4. Studies investigating barefoot walking. Barefoot investigations were chosen over shod as this was thought to provide insight into biomechanical parameters without the influence of shoes;
5. Studies in adult populations ($\geq$ 18 years old);
6. Study reported findings for at least 1 outcome measure of interest in the review.

Exclusion criteria were:

1. Any study investigating participants gait, EMG or plantar pressure while wearing shoes, inserts or orthotic devices;
2. Any study which included current or past diabetes foot ulcer participants as a part of their DPN or DMC groups;

3. Studies that investigated movement on a treadmill;
4. Studies where reported outcome measures were not comparable with at least one outcome measure of interest and could not be converted;
5. Studies where authors were unable to provide datasets or outcome variables that were compatible for comparison (mean and standard deviation, SD), in place of missing data.

2.3 Outcome measures

Studies were included in the review if they reported at least one of the following outcome measures:

1. Spatiotemporal- walking speed (m/s) with or without stride length (m);
2. Kinetics- reported findings on net moments of force (flexion and extension) for at least one lower limb joint (ankle, knee or hip) and/or reported ground reaction force at initial contact and/or toe-off as separate values;
3. Kinematics- reported range of motion (ROM) findings for at least one lower limb joint (ankle, knee or hip) in both flexion and extension directions;
4. EMG- activation and deactivation durations of any lower limb muscle during walking in % stance or % gait cycle;
5. Plantar pressure- reported on at least one site at the rearfoot or midfoot or forefoot or in any other plantar location in either peak plantar pressure (MPP) or pressure time integral (PTI) or both.

2.4 Assessment of methodological quality of studies

Two assessors (MF and PL) independently evaluated the quality of the studies utilising a modified version of the quality assessment tool by Downs and Black (Downs and Black, 1998). The criteria within the tool which were not applicable to the studies included in this review were omitted from the analysis (see Table 1). The total quality scores were reported as an average score between the two assessors. As a simplified version of the quality assessment instrument tool by Downs and Black

(Downs and Black, 1998) was utilised, the original scoring system for the tool was scaled according to a total score of 18. Therefore, a score of ≤ 7 was considered low quality, 8-11 as fair quality and >11 as good quality.

2.5 Data extraction and reporting

Data extraction was performed by the first author with assistance from a statistician (PB) for data analysis. Data were entered into tables for ease of comparison and grouping of variables. Only studies that reported the outcome measures of interest were used in the statistical analysis that followed. Descriptive characteristics of participants (age, gender, body mass index, BMI), entry criteria for diagnosis of DPN, site of participant recruitment, exclusion criteria used by study and diabetes duration of groups were recorded. Where data were missing or unreported, authors from the studies were contacted in an attempt to obtain or clarify results. Where authors did not reply, the studies were excluded from the review. The MOOSE guidelines for reporting meta-analysis of observational studies were utilised in the synthesis of this review (Stroup et al., 2000).

2.6 Statistical analysis

Where possible, data were transformed into standardised units of measure for comparison and for statistical analysis. Means (weighted by sample size of the study) were calculated for the reported demographic variables. Meta-analysis was carried out on individual outcome measures when more than three studies reported on the particular individual outcome measure. Difference in mean values divided by pooled SD was used to compute effect size, utilising Cohen's d (Cohen, 1988). Heterogeneity of studies was calculated using the Q-statistic and I^2 statistic. Results were reported as standardised mean differences with 95% confidence intervals and p values. In addition to this, the classic fail safe N was also computed, as this gives an estimation of studies needed to be published with a null effect to renounce the effects from the meta-analysis (Persaud, 1996). For purposes of

analysis, a Cohen's d score of zero was interpreted as no difference in effect; a result of 0 to 0.2 was interpreted as a small effect; 0.2-0.5 as a medium effect; and ≥ 0.8 as a large effect (McGough and Faraone, 2009). All statistical analyses were carried out by a statistician (PB).

3. Results

3.1 Search yield

Figure 1 outlines the process and results of each step of the literature search. Overall, 1813 unique records were originally identified. However, 1800 articles were excluded for a variety of reasons, such as inappropriate study design, use of inappropriate comparison groups, unsuitable methods used in data capture, lack of neuropathy classification, missing data, irrelevant data or because data were unable to be acquired from authors. Thus 13 articles remained eligible for inclusion. Three extra articles were located by hand searching reference lists of included articles. Therefore, 16 articles were included in the review. Several studies reported on more than one focus area. Gait findings (spatiotemporal parameters, kinematics and kinetics) were reported in ten studies. Dynamic EMG results were reported in three studies and barefoot dynamic plantar pressure in seven studies. Table 2 displays a summary of the characteristics of participants in included studies.

3.2 Study quality

Although there were minor differences in ratings between quality assessors for studies, the overall agreement between quality assessors was good. There were no studies which had a score ≤ 7 and therefore seven studies were of fair quality (8-11) and nine studies were of good quality (>11) according to the quality assessment instrument (Downs and Black, 1998). The main difference between the studies that achieved a good quality compared to a fair quality was the reporting of actual probability values (i.e. P =0.004) rather than approximate values (i.e. P <0.05) along with a more comprehensive list of confounding variables. Additionally, the 'good quality' studies described the demographic and recruitment sites of the participants in detail and reported the populations of recruitment for groups as being the same or different. This information is important for assessing the

external and internal validity of studies. The majority of 'good quality' studies also used a means of adjustment for confounding with or without using multiple regression analysis.

None of the studies reported sample size calculations. All except two studies had clear aims (Sawacha et al., 2012a, Sawacha et al., 2012b). All studies differed in reporting of confounding variables, especially pertaining to biomechanical outcomes. Important confounders of relevance included diabetes duration, severity of DPN, presence of foot deformity, BMI, gender and presence of claudication pain or presence of peripheral arterial disease (PAD) affecting gait. One study (Melai et al., 2011) did not report any major confounders. One study did not provide random estimates of variability in their manuscript, however this was found in the supplementary material (Sawacha et al., 2012a). It was difficult to ascertain whether or not the recruited samples were representative of the source population in most studies, however some studies stated the recruitment strategy clearly. Only one study commented on the number of participants who accepted and rejected invitation for the study as part of the external validity assessment (Savelberg et al., 2009). Lastly, only one study reported on time frames for recruitment, as it was a part of a larger study (Caselli et al., 2002). For other studies this could not be determined.

3.*3 Participant characteristics*

There were 382 DPN participants (cases) in total from the 16 included studies. The mean group size was 25.5 and ranged from 8 to 76 participants. The age range of participants in the DPN group was 54 to 69 years with a weighted mean age of 61 years. The majority (55%) of subjects were males with a BMI of 24 to 30 kg/m^2 (weighted mean 28 kg/m^2). The weighted mean diabetes duration in the DPN group was 15.2 (range 12 to27) years.

Studies utilised a variety of participant recruitment sources including community outpatient settings (8/16), hospital settings (3/16), volunteers (2/16), previous studies (1/16) or unspecified (2/16). Thirteen studies utilised HC groups for comparison which were recruited on a voluntary basis from

the community or through hospital staff. Nine studies (9/16) used DMC groups usually recruited from the same setting as DPN patients. A summary of the recruitment methods can be found in Table 3.

Table 3 presents screening criteria for the diagnosis of DPN and population source of samples used in each study as well as additional exclusion criteria used. A range of methods were used in the diagnosis of DPN in different studies. Eleven studies utilised a validated screening tool to assess sensory neuropathy. The most commonly used was the Michigan Neuropathy Screening Instrument (MNSI). A few studies used only clinical assessment (4/16) and one study utilised nerve conduction testing to assess both motor and sensory neuropathy (Yavuzer et al., 2006). All studies disqualified patients with previous or current diabetes foot ulcers from inclusion in the DPN group and excluded those with additional orthopaedic and neurological conditions, rheumatological conditions and disabilities which produce walking constraints. Two studies excluded participants with PAD, assessed on clinical examination or with ankle brachial pressure index (ABPI) values <0.85 (Uccioli et al., 2001, Guldemond et al., 2008). Two studies did not specify exclusion criteria (Sawacha et al., 2009a, Caselli et al., 2002).

The DMC group comprised of 216 participants with a mean sample size of 24. The age of patients was 50 to 64 years with a weighted mean age of 57 years. The BMI of this group ranged from 25 to 30 kg/m^2 with a weighted mean of 28 kg/m^2. The majority of participants were male (50%) and the total diabetes duration was lower than for the DPN group; ranging from 8 to 23 years and with a weighted mean of 14 years. The HC group comprised of 207 participants with a mean sample size of 15.9. The age of participants ranged from 46 to 68 years with a weighted mean age of 58 years. The majority of HC participants were male (53%) with a BMI range between 24 and 29 kg/m^2 and with a weighted mean BMI of 25 kg/m^2. The findings from the studies are reported in their respective sections below and in Tables 4-8. Meta-analysis was carried out for 11 separate gait variables (Table 9). Forest-plots of all significant meta-analyses can be found as additional figures (Figures 2-9).

3.5 Spatiotemporal parameters

There was a marked difference in the walking speeds reported amongst the three groups in different studies (Table 4). Three studies reported that DPN participants walked slower than HC subjects (Gomeset al., 2011, Sawacha et al., 2009b, Savelberg et al., 2010) and two studies reported slower walking speeds in the DPN group compared to the DMC patients (Savelberg et al., 2010, Sawacha et al., 2012b). However, two studies reported DPN participants walked faster than both HC and DMC groups (Savelberg et al., 2009a, Yavuzer et al., 2006).

Meta-analysis results combining data from studies for walking speed (DPN group vs. DMC group and DPN group vs. HC group) and stride length (DPN group vs. DMC group) between the three groups demonstrated no significant difference in walking speed and stride length. There was also a high level of heterogenity present. Two studies reported stride length findings for the DPN group compared to the HC group and both studies reported lower values in DPN patients (Sawacha et al., 2009, Savelberg et al., 2010).

One study reported stance phase duration as a percentage of the gait cycle (Sawacha et al., 2012b). These findings were consistent with the above findings suggesting DPN patients had longer percentage duration in the stance phase of gait (Table 4). Meta-analysis combining data from three studies (DPN n=54, DMC n=51) suggested that patients with DPN had a longer stance time at a moderate effect level (standardised mean difference 0.54, 95% CI 0.15-0.93; P=0.006). The heterogeneity between studies was minimal I^2= 0.

3.6 Kinematics

Only one study reported on kinematics at the hip, knee and ankle in both extension and flexion directions (Table 5) (Gomes et al., 2011). While DPN participants exhibited greater hip flexion

(degrees) when compared to HC subjects, the DPN participants also demonstrated reduced hip extension, knee flexion and knee extension when compared to the HC group. Both maximum ankle plantar flexion and ankle dorsiflexion were reduced in DPN participants when compared to the HC group. Meta-analysis was not possible for these results.

3.7 Kinetics

Five studies reported kinetic variables (Yavuzer et al., 2006a, Savelberg et al., 2009b, Sawacha et al., 2012a, Uccioli et al., 2001, Saura et al., 2010) (Tables 5 and 6). Two studies reported on the force generation components at the ankle, knee and hip (Savelberg et al., 2009c, Yavuzer et al., 2006) (Table 6). According to one study, both the braking and propelling forces were reduced in the DPN group compared to both DMC and HC groups (Savelberg et al., 2009b). Both the first maximum support moment and mid stance minimal support moment were elevated in DPN participants compared to the DMC and HC groups; however the second maximum support moment was slightly higher in the DMC group when compared to DPN patients (Savelberg et al., 2009b).

The results for maximum ankle plantar flexion moment were inconsistent. One study reported a higher value in DPN patients compared to controls (Savelberg et al., 2009b); while another study reported a lower value in DPN patients when compared to HC subjects (Yavuzer et al., 2006). Results for knee extension moments were also inconsistent. One study reported reduced extension moments in DPN patients (Savelberg et al., 2009b) and another higher extension moments in DPN patients when compared to both the DMC and HC groups (Yavuzer et al., 2006). However, both studies reported greater knee flexion moment in the DPN group compared to both the DMC and HC groups (Savelberg et al., 2009c, Yavuzer et al., 2006) (Table 6).

According to a single study, the hip extension moment was greater in the DPN group when compared to both control groups (Savelberg et al., 2009b). According to both studies, the hip flexion moment was also reduced in DPN patients compared to both controls (Savelberg et al., 2009b, Yavuzer et al., 2006).

Meta-analysis was only possible for the vertical GRF (first peak) at initial contact. Although reported vertical GRF were higher in DPN patients compared to both HC and DMC groups, the results from the meta-analysis were statistically insignificant with a high level of heterogenity. Meta-analysis was not possible for vertical GRF at toe-off (second peak) (Table 5). However, one study reported a higher vertical GRF value in DPN patients at toe-off (Saura et al., 2010) and another a lower value (Yavuzer et al., 2006).

3.8 Dynamic EMG

Muscle activation was reported for several different lower limb muscle groups (Table 7). Two studies reported findings as % stance phase ((Akashi et al., 2008, GOMES et al., 2011) and one study as % gait cycle (Sawacha et al., 2012b). Three studies reported the duration of activity of the tibialis anterior muscle (Sawacha et al., 2012b, Akashi et al., 2008, Gomes et al., 2011). Meta-analysis suggested a non-significant longer duration of muscle activity in the tibialis anterior muscle in DPN patients when compared to the HC group.

Meta-analysis was not possible for the other muscle groups due to lack of studies. However, according to two studies, the lateral gastrocnemius muscle had reduced duration of activity in DPN patients (% stance phase) when compared to the HC group (Akashi et al., 2008, Sawacha et al., 2012b). On the contrary, assessment of the vastus lateralis muscle suggested a longer duration of activation in DPN patients when compared to the HC group (Akashi et al., 2008, Gomes et al., 2011).

There were conflicting results from two studies which assessed activity of the peroneus longus muscle (Table 7). One study reported reduced duration of muscle activation in DPN patients (% stance phase) compared to the HC group; and another study reported longer duration (% gait cycle) in DPN patients compared to both HC and DMC groups.

The findings from the assessment of the gluteus medius muscle, rectus femoris muscle and medial gastrocnemius muscles were from single studies and are highlighted in Table 7. Both gluteus medius and rectus femoris muscles were reported to have reduced duration of activity (Sawacha et al., 2012b), whilst the medial gastrocnemius was reported to have longer duration of activity (Gomes et al., 2011) in DPN patients.

3.9 Plantar Pressure (Peak Pressure and Pressure time Integral)

Six studies reported plantar pressure data of interest ((Melai et al., 2011, Guldemond et al., 2008, Bacarin et al., 2009, Sacco et al., 2009, Caselli et al., 2002, Sawacha et al., 2012a) (Table 8). The majority of studies reported plantar pressure as MPP while three studies reported PTI (Melai et al., 2011, Bacarin et al., 2009, Sacco et al., 2009).

Meta-analysis combining data from three studies (DPN n=108, HC n= 55) suggested patients with DPN had elevated plantar pressure (both MPP and PTI) at the rearfoot at moderate effect levels (MPP standardised mean difference 0.45, 95% CI 0.09-0.82 $P \leq 0.001$, $I^2=7.0$; and PTI standardised mean difference 0.40, 95% CI 0.05-0.75 p=0.02 $I^2=0$). Both results contained minimal heterogeneity. Meta-analysis results for MPP at the rearfoot were insignificant for DPN patients when compared to DMC patients (Table 9).

Meta-analysis results for the midfoot (DPN n=108, HC n= 55, combining three studies) revealed greater MPP and PTI in DPN patients (MPP standardised mean difference 0.72, 95% CI 0.37-1.08 $P \leq 0.001$ $I^2=0$; and PTI standardised mean difference 0.50, 95% CI 0.15-0.85 p=0.005 $I^2=7.0$). There was minimal heterogeneity between studies.

Meta-analysis for plantar pressure at the forefoot (DPN n=177, DMC n= 102, HC n= 55, combining three studies) demonstrated greater MPP in the forefoot of DPN patients at moderate effect levels compared to the HC group (standardised mean difference 0.55, 95% CI 0.20-0.90 p=0.002 $I^2=0$) and DMC group (standardised mean difference 0.51, 95% CI 0.24-0.78 $P \leq 0.001$ $I^2=10.1$) respectively. Furthermore, meta-analysis for PTI at the forefoot (DPN n=177, HC n= 55, combining three studies) suggested that forefoot PTI was also elevated in DPN patients at moderate effect levels (standardised mean difference 0.66, 95% CI 0.31-1.02; $P \leq 0.001$; $I^2=0$). There was minimal heterogeneity between studies. Meta-analysis results for the hallux (MPP and PTI) comparing plantar pressure between the three groups revealed non-significant differences (Table 9).

Findings from two studies suggested MPP at the plantar aspect of the first metatarsophalangeal joint was higher in the DPN group compared to the DMC group (Guldemond et al., 2008, Melai et al., 2011), while results from one study suggested MPP at the plantar aspect of the first metatarsophalangeal joint was higher in DPN patients compared to the HC group (Melai et al., 2011). According to a single study, the PTI values were higher in DPN patients compared to both DMC and HC groups (Melai et al., 2011). However, according to the same study, there was a lower PTI and MPP for the DPN group in the lesser toes compared to both control groups (Melai et al., 2011) (Table 7).

4. Discussion

To the best of the authors' knowledge this is the first systematic review and meta-analysis of studies investigating the gait cycle, muscle activation and plantar pressure exclusively in DPN patients compared to DMC and HC groups. The aim of this review and meta-analysis was to assess the gait dissimilarities between DPN, DMC and HC subjects in relation to spatiotemporal, kinetic, kinematic, EMG and plantar pressure variables. Our findings, within the limitations of the review, indicate gait differences in DPN patients when compared with DMC and HC subjects, likely resulting from sensory and motor neuropathy (Kovac et al., 2011, Andersen, 2012). The primary advantage of relating both HC and DMC groups to DPN patients was the ability to appreciate subtle differences within each group for comparison and contrast. However, it must be emphasised that there was a high level of heterogeneity for most variables between studies as highlighted by the Q and I^2 statistics. This high level of heterogeneity was also evident in other systematic reviewers investigating plantar pressures in similar patient groups (Monteiro-Soares et al., 2012, Crawford et al., 2007).

DPN is a significant complication of diabetes and accounts for significant morbidity and mortality (Boulton, 1998, Cook and Simonson, 2012). The primary risk factor for DPN is hyperglycaemia as it leads to increased oxidative stress, production of advanced glycation end products, increased polyol pathway flux and protein kinase C activation. All these factors are believed to contribute to micro-vascular disease and nerve dysfunction (Park et al., 2004). The end result of DPN can be catastrophic for patients, as this leads to foot ulceration and increased risk of limb amputation, significant healthcare costs, reduced quality of life and reduced mobility (Price, 2004, Boulton, 2005, Singh et al., 2005). Therefore, understanding the impact of DPN on the biomechanical aspects of human locomotion is clinically important (Formosa et al., 2013).

We hypothesised that spatiotemporal parameters would be significantly reduced in DPN patients compared to both controls. The majority of reported findings indicated that DPN patients walked slower and had reduced stride length when compared to both DMC and HC groups, however, meta-analysis results were statistically insignificant. The only significant finding was that DPN patients expended a longer period of time in the stance phase compared to DMC subjects. We hypothesised that the force generation at the hip, knee and ankle would be significantly increased for both flexion and extension moments in participants with DPN. There were insufficient studies to carry out meta-analysis and the two studies which reported findings demonstrated conflicting results. Regardless of the fact that one study utilised a significantly younger HC group, the differences between studies could not be solely explained by a difference in the age groups (Yavuzer et al., 2006). Irrespective of this, increased knee flexion moment in the DPN group was reported by both studies, emphasising that greater force generation may occur during knee flexion in DPN patients. This finding suggests the possibility that knee flexion might be an important compensation strategy in patients with DPN, as the motor component of DPN manifests in a stocking and glove distribution and affects the distal joints first (Tesfaye and Selvarajah, 2012).

The first maximum support moment (combination of extensor moments at hip, knee and ankle) (Winter, 1980) was higher in the DPN group when compared to the DMC and HC groups (Savelberg et al., 2009). Although reported in a single study, this suggests combined forces at the hip; knee and ankle during the stance phase are greater in DPN patients compared to both control subjects (Savelberg et al., 2009). Further studies are needed to confirm this finding.

Even though meta-analysis of the vertical GRF demonstrated that DPN patients had a higher initial contact force than DMC and HC subjects, the level of heterogeneity in studies was high and the meta-analysis results statistically insignificant. It was anticipated that DPN patients would exhibit higher GRF due to neurological deficit and reduced proprioception but the current findings fail to support

this hypothesis. Similarly, we hypothesised that participants with DPN would exhibit reductions in joint ROM at the hip, knee and ankle during gait, as a result of motor neuropathy (Andersen, 2012). There were few studies investigating lower limb kinematics of DPN patients during locomotion to investigate this hypothesis. One study (Sawacha et al., 2012a) reported kinematic variables of the foot which were outside the scope of this review and were not included. Therefore, current findings for joint angle kinematics were drawn from one publication investigating barefoot lower limb kinematics (Gomes et al., 2011). With the exception of hip flexion, the findings demonstrated reduced ROM in DPN patients compared to HC subjects. This finding was consistent with our hypothesis. A higher proportion of hip flexion is also another possible compensatory mechanism to increase stability in the gait strategy of DPN patients. Increased hip flexion could also be a compensatory mechanism to adjust for impaired ankle dorsiflexion in patients with DPN. We did not directly examine this possibility in the current review. Further studies are needed to clarify the cause of greater joint force in knee flexion and greater degree of hip flexion in patients that have DPN.

Dynamic EMG data suggested that the tibialis anterior muscle remained active for a longer duration of time in DPN patients compared to HC subjects. Meta-analysis suggested that this finding was not statistically significant and demonstrated a high level of heterogeneity. Therefore, it was difficult to ascertain whether this was consistent with our hypothesis of altered muscle activity duration in DPN participants due to mis-firing and reduction in neural pathways associated with muscle recruitment and deactivation. It was also challenging to explain the shorter duration of activity of the lateral gastrocnemius muscle and longer duration of activity of the vastus lateralis muscle and the various reported findings of other muscle groups from individual studies. It seems that there are clear differences in muscle activation between DPN, DM and HC subjects; however the findings from previous studies were not consistent. It could be possible that these observations were due to changes in action potential amplitude and inconsistency in the number of motor units recruited during EMG measurement of lower limb muscle activation in DPN patients, however there is currently insufficient data to support this theory. As hypothesised, the meta-analysis results suggested that DPN participants

have higher dynamic plantar pressures at rearfoot, midfoot and forefoot sites when compared to controls. However, there were insufficient studies to carry out a meta-analysis of data collected at the hallux and lesser toe joints and the results from studies were highly contradictory.

Previous reviews have highlighted gait differences in patients that have diabetes mellitus, but have not concentrated on DPN as the main focus (Wrobel and Najafi, 2010, Allet et al., 2008). The limitations of this review were the small number of included studies, the small number of participants in included studies, the high level of heterogeneity between studies, the investigation of barefoot measurements only, the exclusion of kinematic data of the foot and the language limitation to studies written in English.

We can conclude from the current level of evidence that the only biomechanical factors that seems significantly different in DPN patients compared to DMC and HC groups are elevated plantar pressure and longer stance time, illustrated by moderate effect sizes from standardised mean differences. Therefore, it is probable that elevated plantar pressure coupled with a longer period of time spent in stance in DPN patients contributes to the susceptibility for skin damage through prolonged mechanical load on tissue, leading to skin break-down and ulceration (van Dieren et al., 2010). Although it is possible that reduced spatiotemporal parameters, elevated vertical GRF, longer muscle duration and reduced joint kinematics contribute to foot ulceration; the current knowledge base is insufficient for firm conclusions. There were significant discrepancies between studies reporting findings. Our observations were similar to that of Allet et al and Wrobel and colleagues (Allet et al., 2008, Wrobel and Najafi, 2010).

While all studies in this review utilised procedures for diagnosing DPN in participants, only two studies excluded patients with PAD. PAD has been reported to have significant effects on walking

patterns (Crowther et al., 2007, Crowther et al., 2008). The BMI of all three groups were similar and it is unlikely that this accounted for any difference in gait variables. The mean diabetes duration between DPN and DMC subjects was not significantly different in the studies included. It has been hypothesised that DPN can manifest in people with a diabetes duration greater than 10 years, as it does in those with poor glycaemic control (Oguejiofor et al., 2010, Kovac et al., 2011, 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 MRI, before DPN becomes clinically detectable (Greenman et al., 2005). Therefore, these factors may also influence gait findings in DMC groups when compared to DPN patients. This could be a possible explanation for the similar results in DPN and DMC subjects and lack of statistical significance. However, the scope of this review was also dependent on the sample sizes of original studies, and thus, reported statistical insignificant differences may have been due to lack of power.

There is paucity in biomechanical literature investigating the effects of DPN on barefoot gait parameters, particularly in relationship to the effects of severe neuropathy resulting in foot lesions and its effect on human locomotion. The clinical ramifications from this systematic review are limited due to the high level of heterogeneity and statistically insignificant results from the meta-analyses. However, it was evident that patients with DPN demonstrated greater overall dynamic plantar pressure and forefoot plantar pressure (both MPP and PTI) compared to patients without DPN. Patients with DPN also expended a longer duration of time in the stance phase. Both findings potentially contribute towards ulceration in patients with DPN. Other biomechanical findings were less clear and we therefore encourage future biomechanical studies in DPN to assess factors such as lower limb angular kinematics, kinetics and EMG and to adjust for variables such as PAD, claudication pain and history of foot ulcers in selection of participants with DPN as these factors are highly likely to influence walking patterns.

Conclusion

Current evidence from the literature indicates DPN patients exhibit significantly elevated plantar pressures and occupy a longer duration of time in stance phase during gait compared to controls. We encourage future biomechanical studies in DPN to assess factors such as lower limb angular kinematics, kinetics and EMG.

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Conflicts of interest

The authors wish to declare no relevant conflicts of interest.

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