Is the metabolic cost of walking higher in people with diabetes?

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Running title: Cost of walking and joint work in diabetic neuropathy

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ABSTRACT

People with diabetes walk slower and display biomechanical gait alterations compared to controls, but it remains unknown whether the metabolic cost of walking (CoW) is elevated. The aim of this study was to investigate the CoW and the lower limb concentric joint work as a major determinant of the CoW, in patients with diabetes and diabetic peripheral neuropathy (DPN). 31 non-diabetic controls (Ctrl); 22 diabetic patients without peripheral neuropathy (DM) and 14 patients with moderate/severe DPN, underwent gait analysis using a motion analysis system and force plates and treadmill walking using gas analyser to measure oxygen uptake. The CoW was significantly higher particularly in the DPN group compared to controls and also in the DM group (at selected speeds only) compared to controls, across a range of matched walking speeds. Despite the higher CoW in patients with diabetes, concentric lower limb joint work was significantly lower in DM and DPN groups compared to controls. The higher CoW is likely due to energetic inefficiencies associated with diabetes and DPN reflecting physiological and biomechanical characteristics. The lower concentric joint work in patients with diabetes might be a consequence of kinematic gait alterations and may represent a natural strategy aimed at minimizing the CoW.

Keywords: walking efficiency, diabetic neuropathy, joint work, oxygen consumption, lower limb biomechanics.

INTRODUCTION

Diabetes mellitus (DM) is a disease with a global reach, the prevalence of which is increasing at an alarming rate, with type 2 diabetes being particularly common among older adults. The prevalence of diabetes in most developed countries ranges between 2.1% (Iceland) and 10.5% Brazil (70, 82, 13). The world health organisation estimates that by 2025 as many as 200–300 million people worldwide will have developed type 2 diabetes (69).

Diabetic peripheral neuropathy (DPN) is one of the most common complications associated with diabetes occurring in 30–50% of patients and causing dysfunction of peripheral nerves (17, 22). Diabetic neuropathy affects sensory, motor and autonomic components of the nervous system. In terms of complications arising from diabetic neuropathy and impacting upon gait, a loss of sensory perception and impaired muscle function are major factors.

Diabetes patients have consistently been shown to display a slower self-selected walking speed, and take shorter strides compared to age-matched controls (19, 46, 28). Diabetic patients also generate lower knee and ankle joint moments compared to controls during walking (56, 52, 14). It could be suggested that diabetic patients walk more slowly at least in part to keep the joint moment demands of gait lower, which may therefore explain their lower walking speed. However, lower joint moments during gait in diabetic patients have also been shown to be independent of walking speed (14).

The cost of walking (CoW) is another important factor that could contribute towards dictating a slower self-selected walking speed in diabetes patients. As walking speed increases, joint moments and work are expected to increase (24, 79), increasing the CoW. The slower self-selected speed may therefore reflect the most efficient strategy for diabetes patients as previously shown in other populations (53, 6, 49, 84).

The CoW is known to be higher in healthy elderly people compared to young adults, which

likely reflects energetic inefficiencies in older people (53). Despite previous studies describing gait alterations in people with diabetes, the CoW and its relation to walking speed remains unknown in this clinical population. Lower limb concentric joint work is closely related to the CoW, with higher joint work being linked to a higher CoW (24, 79). Knee and ankle concentric joint work has recently been shown to be lower in people with diabetes during walking at a self-selected speed compared to controls (14), which might suggest a lower CoW as a result. However, there are also a number of energetic inefficiencies present in patients with diabetes that might increase the CoW for any given speed. For example, the effects of non-enzymatic glycation has been shown to stiffen tendons in animal models of diabetes (30, 58, 61, 62, 63). A stiffer Achilles tendon may reduce the amount of elastic energy stored in the tendon during walking (based upon the assumption of lower forces and therefore smaller elongations resulting from the lower joint moments developed in diabetic patients compared to controls). Reduced elastic energy storage in the Achilles tendon would increase the amount of energy required from ankle muscles, thereby increasing the CoW. Other factors that could contribute to energetic inefficiencies during walking in diabetic patients include altered leverage around the foot due to diabetic foot deformities and increased antagonist muscle co-activation (80, 19, 33). The aim of this study was therefore to investigate the CoW (and the lower limb joint work as a major determinant of the CoW) in patients with diabetes and diabetic neuropathy compared to controls at a range of matched walking speeds. We hypothesised that due to the above-mentioned inefficiencies in diabetes patients, they would display a higher CoW when walking at the same speed compared to controls and that this would be more marked in diabetes patients with DPN compared to those without.

MATERIALS AND METHODS

Participants

After receiving ethical approval from all relevant bodies, a total of sixty seven participants gave written informed consent to participate in this study. All procedures in this study complied with the declaration of Helsinki. All participants were aged over 40 years and were allocated into one of three groups: healthy controls without diabetes or peripheral neuropathy (Ctrl, n=31, 19 men), patients with diabetes but no neuropathy (DM, n=22, 12 men) and patients with diabetes and moderate-severe peripheral neuropathy (DPN, n=14, 14 men). All participants were assessed to confirm they satisfied the inclusion criteria for each group. Exclusion criteria for participation in the study were vascular disease, unstable ischemic heart, neurological, rheumatic disease, cerebral injury, disorders of the vestibular system, musculoskeletal injury, recent surgery affecting gait, foot or lower limb amputation (amputation of the hallux; amputation of more than two lesser toes on one foot; amputation of part of/whole foot) and open foot ulcer. Information about duration and type of diabetes, smoking habits and use of current medication was obtained via questionnaire. The majority of the DM and the DPN patients reported taking insulin, cholesterol-lowering medication and diabetes medication, while from the whole sample (including controls) only 2 people reported smoking. Participant characteristics are displayed in Table 1.

Assessment of peripheral neuropathy

A clinical evaluation was undertaken to quantify neuropathy in diabetic patients and to confirm the absence of neuropathy in healthy controls. Peripheral neuropathy was assessed by using the modified Neuropathy Disability Score (mNDS) and the vibration perception threshold (VPT). The mNDS is a combined score taken from tests measuring the patient's ability to detect

temperature, pain, vibration and the Achilles tendon reflex (10). The VPT was assessed by placing the probe of the biothesiometer on the apex of the hallux and increasing the level of vibration until detected by the participant. A random blood glucose test was performed in the Ctrl group to confirm the absence of diabetes and the above neuropathy tests conducted to confirm the absence of neuropathy in the Ctrl group resulting from any aetiology.

Gait analysis

Participants were asked to walk along a 10-metre walkway in the gait laboratory. Participants were instructed to walk the length of the walkway at a series of different walking speeds performed in a specific order (0.6, 0.8, 1.0, 1.2, 1.4 and 1.6 m/s). Walking speed was controlled by measuring the velocity of a marker attached to the sacrum after each trial from the motion analysis data and providing immediate feedback for participants as to whether they needed to walk more quickly or more slowly on the next trial to achieve the required speed. Participant's starting position was altered by the experimenters to ensure a ‘clean’ (i.e., no overlap outside the force platform) foot-strike on one or two of the force platforms per walking trial without alteration to their natural gait. Walking trials were repeated until at least three ‘clean’ foot contacts with the force platforms were made per limb, per speed condition. Kinematics were collected at 100 Hz using a full-body modified Plug-In-Gait marker set with 54 markers and a 10-camera Vicon motion capture system (Vicon, Oxford, UK) positioned around the 10-meter walkway. Kinetics were simultaneously collected at 1000 Hz from three force platforms (Kistler, Zurich, Switzerland) embedded into the middle of the walkway. Where possible markers were placed directly onto the skin; to minimise movement artefacts resulting from loose clothing all participants wore tight-fitting shorts and tops. All participants wore specialist diabetic shoes (MedSurg, Darco, Raisting, Germany) with a neutral foot-bed, ensuring the

diabetic patients walked with safe, appropriate footwear whilst minimising the effect of footwear by standardising across all participants.

Oxygen uptake measurements and metabolic calculations

Prior to testing, all participants completed walking familiarisation sessions for a minimum of 6 minutes on the treadmill to become accustomed to the task of treadmill walking and enable a natural walking style to be achieved. Measurements of expired air were acquired whilst participants walked on a motor-driven treadmill (Woodway Ergo ELG 70, Weil am Rhein, Germany) set at six different walking velocities (0.6, 0.8, 1.0, 1.2, 1.4 and 1.6 m/s). The treadmill was inclined by 1% from horizontal for the purpose of increasing the similarity of oxygen uptake demands with level ground walking as previously shown (34, 38). Participants wore a facemask, which passed expired air into an automated analyser (Cortex Metalyser 3B, Biophysik, Leipzig, Germany). The analyser, calibrated prior to each testing session, provided breath-by-breath data sent via telemetry to a computer. Oxygen consumption (VO_2) was measured continuously using this online system. The net VO_2 during walking was determined as:

Net VO_2 = gross VO_2 - resting VO_2[×]

[×]*resting VO_2 was measured during quiet standing on the treadmill prior to walking.*

Net VO_2 was expressed relative to body mass for all participants. The cost of walking was calculated using the mean rate of oxygen consumption for VO_2 data collected between the 3rd and 4th minute of each stage.

Net VO_2 was converted to joules using an energetic equivalent and calculated using the specific respiratory exchange ratio (RER) value from each participant as (29): VO2 • (4.94 •

RER + 16.04). The CoW was calculated by dividing VO_2 by the walking speed and multiplying this value for the energy equivalent. Using the RER and calculating the energetic equivalent in this way takes into account possible differences between groups due to the contribution of the anaerobic energy system. Nine participants (Ctrl=3, DM=1, DPN=5) were unable to walk for a sufficient period of time at 1.6 m/s to derive adequate VO_2 measurements at this specific speed.

Gait biomechanical analysis

Temporal–spatial parameters (walking speed, stance time) were calculated from the gait analysis testing session described above using Visual 3D software (C-motion Inc., MD, USA), using the process of inverse dynamics to calculate joint powers. Power curves during stance were calculated to assess concentric (positive) periods of power during the stance phase to calculate concentric joint work done, defined as the positive power-time integral (14). Concentric joint work done was then subsequently normalised to body mass. Work done (ankle, knee, and hip) was calculated taking into account data from both legs, across at least three trials (data from at least six stance phases).

Statistics

A one-way analysis of variance (ANOVA) was performed for all variables to assess between group differences. If the ANOVA was significant, a Fisher's least significant difference (LSD) post-hoc test was used to test for differences between the diabetes groups (DM and DPN) and the control group. All values presented are means and standard deviation. All statistical tests were performed on SPSS statistical package (SPSS v21, Chicago, Illinois) with significance set at $p<0.05$.

RESULTS

Participant characteristics

There were significant differences between the groups in age, body mass and BMI, which were significantly greater in the DPN group (Table 1, $p<0.01$).

Neuropathy assessments

As expected, the DPN group displayed significantly higher values for the VPT and the mNDS compared to the Ctrl group (Table 1). The VPT and mNDS for the DM group were not significantly different from the Ctrl, underlining that this diabetic patient group had no neuropathy (Table 1).

Temporal–spatial gait parameters

The DPN group displayed significantly longer single limb stance times and shorter step lengths in all given speeds compared to Ctrl group (Table 2).

Total joint work during walking at different speeds

Total concentric work showed a very consistent pattern across all speeds with the Ctrl group displaying the highest values, followed by lower values in the DM group and the lowest values observed in the DPN group (Fig. 1). Compared to the Ctrl group, significantly lower joint work was observed at all speeds for the DPN group and all but 1.4 m/s for the DM group.

Ankle, knee and hip joint work during walking

Ankle concentric joint work was lower for the DPN group compared to the Ctrl group,

reaching significance at gait velocities of 0.8; 1.2; 1.4 and 1.6 m/s (Fig. 1). Knee concentric joint work was significantly lower in the DPN group compared to Ctrl at gait velocities of 0.6; 0.8; 1.0; 1.2 and 1.6 m/s. In the DM group, knee concentric joint work was significantly lower compared to Ctrl at the gait velocity of 0.6 m/s. Hip concentric joint work was lower for the DPN group compared to Ctrl reaching significance at velocities of 0.6; 0.8 and 1.6 m/s.

Cost of walking at different speeds

There were significant differences in the CoW between the groups across the matched speeds tested, with the general pattern of a higher CoW in the DPN group, followed by the DM group and the lowest CoW in the Ctrl group (Table 2; Fig. 2). Significant differences in the CoW were mainly found between the DPN and Ctrl groups (at 0.6; 0.8; 1.0; 1.2 and 1.6 m/s), with some significant differences also present between DM and Ctrl groups at the higher gait velocities (1.4 and 1.6 m/s).

DISCUSSION

This study has shown for the first time that when walking speed is matched, patients with diabetic neuropathy have a higher CoW compared to controls (Fig. 2). Despite a higher CoW, patients with diabetic neuropathy showed significantly reduced concentric lower limb joint work compared to controls at these matched speeds. The finding of lower joint work in patients with diabetic neuropathy is surprising considering that under 'normal' conditions lower concentric work is clearly linked to a lower CoW (67, 57), but we suggest possible reasons for this below.

The finding of a higher CoW in patients with diabetic neuropathy when walking speed was matched likely reflects energetic inefficiencies resulting from a number of physiological and biomechanical factors. Firstly, animal models of diabetes have shown that tendons are stiffer due to the effects of non-enzymatic glycation. In human diabetic patients, this likely applies to the long Achilles tendon, which plays a major role in energy saving during walking under 'normal' circumstances (3). Stiffening of the Achilles tendon with diabetes and especially diabetic neuropathy (presumably due to longer exposure with poor glycaemic control), would reduce the extensibility of the tendon. Based upon the lower joint moments developed in patients with diabetic neuropathy during gait (46, 52, 56, 81), it would be expected that the force on the Achilles tendon would be lower compared to controls. The stiffer Achilles tendon of patients with diabetic neuropathy would be expected to elongate less compared to controls, storing less elastic energy and requiring more energy to be generated by the plantar flexor muscles (assuming similar hysteresis compared to controls), thereby contributing to a higher CoW in diabetes patients.

Higher levels of muscle co-activation during walking have been reported in diabetic patients compared to controls (1, 32). Considering that locomotion should reflect a fine balance

between activation and de-activation of agonist and antagonist muscles during specific phases of the gait cycle, an increase in the level of muscle co-activation will increase metabolic energy cost and could therefore be another factor contributing to increase the CoW at a given speed in patients with DPN. Foot deformities are common in diabetic patients (29, 78) and even subtle changes in foot structure would alter the application of force to the ground during walking (43, 51). Changes in the application of force to the ground during walking (and running) will alter the mechanical leverage around the ankle joint, i.e., the external moment arm. This has been shown both in humans and animals (7, 8, 9, 5, 41, 42, 68, 12) and therefore such changes may increase the CoW in patients with DPN. Another contributing factor to the higher CoW in the DPN group is the increased step frequency (the DPN group had a shorter step length for a given speed, therefore requiring a higher step frequency) and greater body mass compared to the DM and the Ctrl groups. These two factors (increased step frequency and greater body mass) would increase the internal work required for moving the lower limbs and may contribute to a higher CoW in people with diabetes and particularly those with DPN (54).

A higher CoW was clearly evident in patients with diabetes (DM group) and particularly in those with diabetic neuropathy (DPN group) across the matched walking speeds. In this study we examined a range of different walking speeds (from 0.6 until 1.6 m/s) and observed that the differences in the CoW between groups were most evident at the lower gait velocities (0.6-1.2 m/s; Fig. 2). At the higher walking speeds, the pattern changes slightly with the CoW still remaining higher in patients with diabetes and diabetic neuropathy compared to controls, but with the differences being less evident than at the slower walking speeds. This may be explained by patients with diabetic neuropathy moving closer towards their maximal oxygen uptake when walking at velocities of 1.4 m/s and above. It is well known that diabetes patients engage in less physical activity (48, 55, 72, 73) and are therefore likely less fit i.e., have a

lower maximal oxygen uptake compared to non-diabetic controls (40, 65, 66). It is also a possibility that diabetes patients might have reached the lactate threshold earlier than controls (i.e., at lower walking speeds), which could have influenced the VO_2 kinetics and the time to reach a relatively constant VO_2. Specifically, with heavy exercise above the lactate threshold the VO_2 slow component (i.e., the gradual rise in VO_2 with constant workload) may be more pronounced (77) and there is a risk that diabetes patients may have reached their lactate threshold earlier than controls, thereby influencing our estimate for the CoW differently between diabetes and control participants. Although we did not measure the lactate threshold or the maximal oxygen uptake in our participants, previous studies have shown that the lactate threshold occurs in other populations at a VO_2 between 50 and 55 ml/kg/min, or at running speeds of between 3.75 and 4.73 m/s (64, 26, 83, 2). These VO_2 values (50-55 ml/kg/min) and running speeds (3.75-4.73 m/s) are considerably higher compared to those measured in our study (VO_2 values of up to 13 ml/kg/min and walking speeds of up to 1.6 m/s; Table 2), and despite these previous reports being in healthy populations, it may suggest that all participants in the present study were well below their lactate threshold. Future work could be conducted to compare the CoW between these groups at relative exercise intensities, taking into account individual lactate thresholds.

The CoW data in the present study are comparable with a number of previous studies conducted in similar populations reporting values ranging between 1.1 and 5 J $(kg\ m)^{-1}$ (76, 25, 75, 35, 15, 36, 6, 16, 18, 20, 53, 59). In the DPN group the CoW showed a U-shaped relationship with walking speed as previously reported in other populations (53), but this relationship was not as clearly evident in the DM and Ctrl groups (Fig 2). All three groups showed the same consistent pattern of increasing net VO_2 with increasing walking speed. Slight differences in the RER values between groups likely explain the lack of a consistent U-

shaped relationship between the CoW and walking speed across all three groups. The DPN group displayed particularly high standard deviations for the CoW (Fig. 2) and VO_2 data (Table 2). This high within-group variance is a consistent characteristic reported in previous studies with DPN patients for other gait variables, but here we also highlight the within-group variance associated with VO_2 and CoW parameters in DPN patients.

Across the matched walking speeds in the present study, there was a consistent pattern of lower total concentric joint work being developed by the DM group and particularly the DPN group compared to controls (Fig. 1). A slower walking speed is a consistent finding of previous studies in diabetic patients (5, 52, 60, 28). Whilst most other studies have examined only self-selected walking speed (45, 21), the present study is the first to examine a range of different functionally relevant matched walking speeds (between 0.6 and 1.6 m/s) in the diabetic patient population. Since lower limb joint work is known to be closely linked to the CoW, joint work was examined in the present study to provide insight to the mechanism(s) for group differences in the CoW. We found a consistent pattern of lower joint work in the DM group and particularly in the DPN group compared to the Ctrl group for the hip, knee and ankle joints across walking speeds (Fig. 1). Theoretically, the same lower limb joint work was associated with a higher CoW in diabetic patients and particularly in patients with DPN, which can be observed by projecting vertically from any point on the x-axis on Fig. 3.

It was surprising that diabetic patients were actually able to match the same walking speed as controls despite generating significantly reduced lower limb joint work. This interesting aspect might be explained by a number of kinematic alterations to gait made by diabetic patients with implications for joint kinetics. This may represent an ‘altered gait strategy’ in people with diabetes to enable them to meet the task demands in the face of compromised musculoskeletal properties and already elevated CoW due to energetic inefficiencies. Diabetic patients display a

reduced lower limb range of motion during walking compared to controls. This is achieved at least in part via shorter steps taken by diabetic patients during walking (Table 2). It is known that DM and DPN patients are able to lower joint moments and walk with shorter steps and this translates to less flexed joints, which in general means that the moment arms of the ground reaction force are smaller compared to the situation with more flexed joints. Smaller moment arms will lower the joint moments and since joint work is derived from the product of joint moments and joint angular speed (joint power), this kinematic strategy likely contributes towards reducing the joint work done during walking. Concentric contractions are associated with a relatively high metabolic load, whereas in contrast, this is much lower for isometric and eccentric contractions (27, 23). Despite these strategies to lower the joint moments, patients with DPN have a higher CoW presumably due to metabolic inefficiencies discussed above. If patients with DPN did not employ these 'altered gait strategies' presumably the CoW would be even higher.

There are some limitations in the present study that should be acknowledged. Firstly, several participants were not able not complete walking on the treadmill at the highest speed (1.6 m/s). Secondly, body mass was significantly different between groups, however, this should not affect the two main parameters of the CoW and joint work, since both parameters were normalised for body mass. Also, the higher body mass in patients with DPN is a well-known characteristic of this population described in the literature (45, 39, 37). Although only a mean of 10 years difference, patients in the DPN group were significantly older than controls (66 to 56 years, respectively), which might be a confounding factor for some of the variables examined. We did not measure blood lactate to confirm that all participants were working below their lactate threshold. This is a consideration since the VO_2 slow component is much more pronounced during exercise above the lactate threshold compared to below as discussed

above. Although the intensity of the exercise during walking in the present study was unlikely sufficient for participants to exceed their lactate threshold based on comparison with previous studies (64, 26, 83, 2), it remains a note of caution since it would affect our interpretation of the CoW data if there were between-group differences in the onset of the lactate threshold occurring within the range of walking speeds examined.

We have shown that the CoW is higher in patients with diabetes and particularly in those with diabetic neuropathy compared to controls when walking speed is matched. This higher CoW is likely due to energetic inefficiencies in diabetic patients reflecting physiological and biomechanical characteristics and occurs despite the development of lower concentric joint work in patients with diabetes and diabetic neuropathy.

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COMPETING INTERESTS

None of the authors had any financial or personal conflict of interest with regard to this study.

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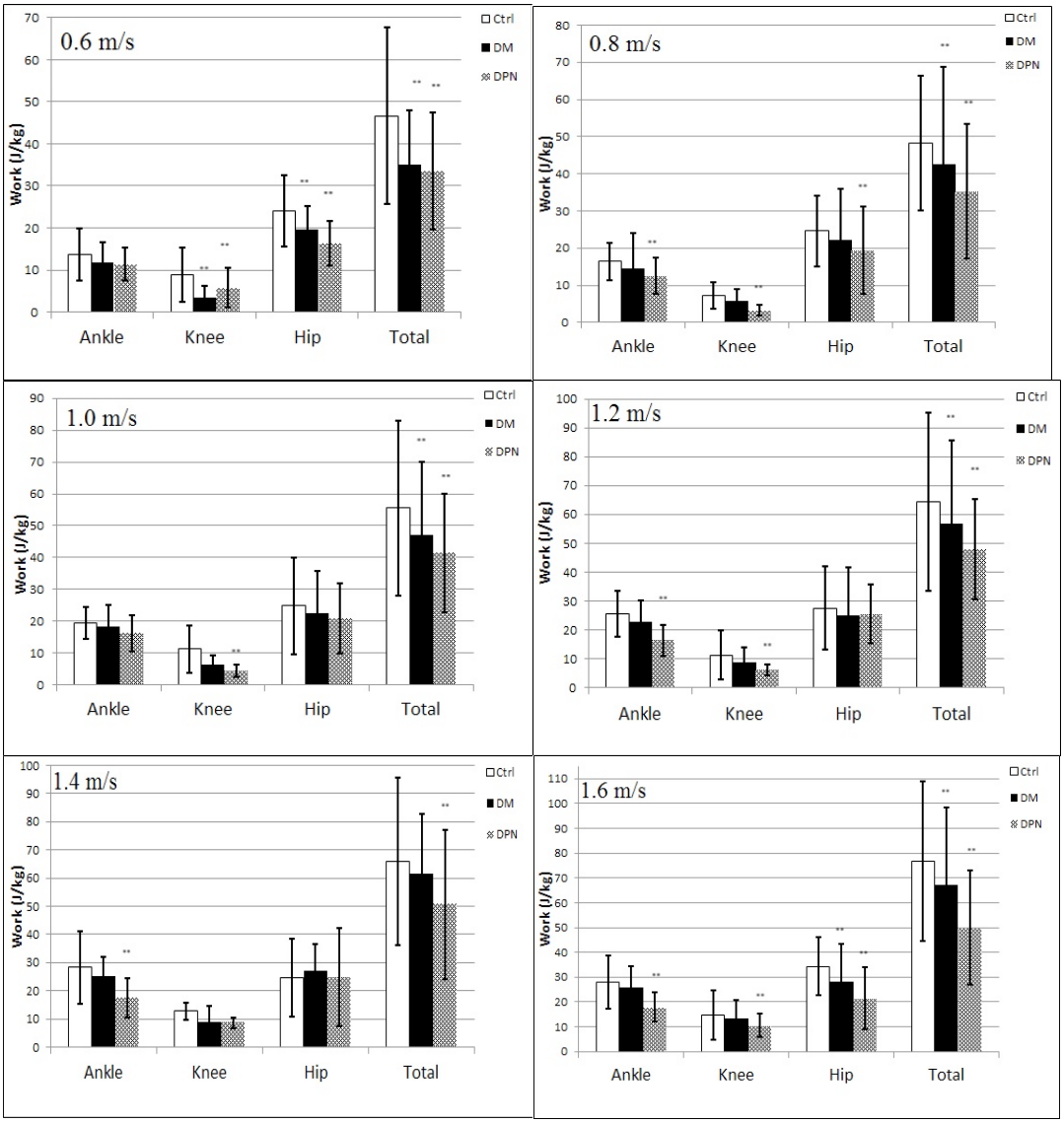

Figure 1. Lower limb ankle, knee, hip and total concentric joint work across walking speeds from 0.6 to 1.6 m/s for healthy controls (Ctrl, n=31), diabetic patients with no neuropathy (DM, n=22) and diabetic patients with moderate/severe neuropathy (DPN, n=14). Values are group means and SD, **denotes significantly (P<0.01) different from the control group.

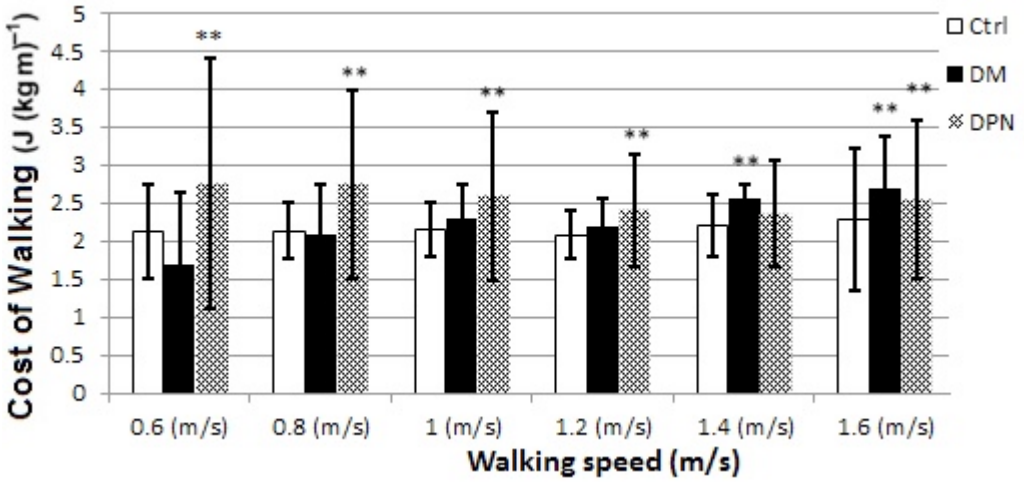

Figure 2. The cost of walking (CoW) plotted across walking speeds from 0.6 to 1.6 m/s for healthy controls (Ctrl, n=31), diabetic patients with no neuropathy (DM, n=22) and diabetic patients with moderate/severe neuropathy (DPN, n=14). Nine participants (Ctrl=3, DM=1, DPN=5) were unable to walk for long enough to calculate the CoW at 1.6 m/s. Values are group means and SD, **denotes significantly (P<0.01) different from the control group.

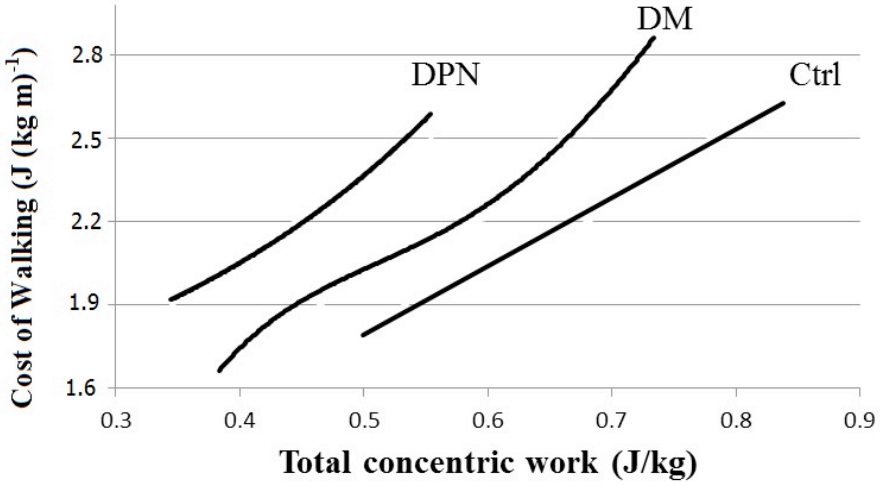

Figure 3. Mean data for the cost of walking (CoW) plotted against total concentric work during walking at walking speeds from 0.6 to 1.6 m/s for healthy controls (Ctrl, n=31), diabetic patients with no neuropathy (DM, n=22) and diabetic patients with moderate/severe neuropathy (DPN, n=14). The curves were fitted with a cubic function to yield R^2 values over 0.98.

Table 1. Participant characteristics and results from neuropathy assessments.

Variable	Group		
	Ctrl	DM	DPN
Age (yr)	56 (10)	51 (9)**	66 (14)**
Body mass (kg)	76 (10)	80.5 (12)	91.5 (18)**
Height (m)	1.72 (0.12)	1.71 (0.09)	1.73 (0.11)
BMI (kg/m^2)	26 (3)	28 (4)	31 (4)**
NDS (Score/10)	1 (1)	2 (1)	7 (2)**
VPT (Volts)	6.1 (3.4)	8.2 (3.4)	27.4 (9.1)**
Diabetes duration (years)	-	14 (12)	14 (11)
Type 1 diabetes	-	7	4
Type 2 diabetes	-	15	10

Healthy controls (Ctrl, n=31), diabetic patients with no neuropathy (DM, n=22) and diabetic patients with moderate/severe neuropathy (DPN, n=14). Significant differences from the Ctrl group are denoted by *($P<0.05$) or ** ($P<0.01$). BMI = body mass index, NDS = neuropathy disability score, VPT = vibration perception threshold. Values are means (standard deviations).

Table 2. Temporal-spatial gait parameters and net oxygen uptake.

Variable	Group		
	Ctrl	DM	DPN
0.6 m/s			
Actual speed (m/s)	0.57 (0.24)	0.59 (0.16)	0.61(0.11)
Step length (m)	0.59 (0.20)	0.57 (0.24)	0.51 (0.09)**
Single limb stance time (sec)	0.902 (0.20)	0.841(0.23)	0.958 (0.05)**
Net VO_2 (ml/min kg)	3.81 (1.11)	3.05 (1.69)	4.93 (2.95)**
RER	0.89 (0.05)	0.93 (0.08)	0.96 (0.09)
0.8 m/s			
Actual speed (m/s)	0.82 (0.27)	0.78 (0.21)	0.77 (0.19)
Step length (m)	0.63 (0.21)	0.57 (0.21)	0.53 (0.05)**
Single limb stance time (sec)	0.801 (0.15)	0.842 (0.21)	0.960 (0.05)**
Net VO_2 (ml/min kg)	5.11 (0.89)	5.00 (1.55)	6.56 (2.94)**
RER	0.86 (0.09)	0.87 (0.11)	0.97 (0.07)
1.0 m/s			
Actual speed (m/s)	1.02 (0.17)	1.04 (0.28)	0.97 (0.13)
Step length (m)	0.69 (0.15)	0.67 (0.05)	0.64 (0.04)*
Single limb stance time (sec)	0.713 (0.13)	0.741 (0.05)	0.884 (0.05)*
Net VO_2 (ml/min kg)	6.44 (1.08)	6.89 (1.32)	7.75 (3.29)**
RER	0.84 (0.04)	0.91 (0.06)	0.93 (0.03)
1.2 m/s			
Actual speed (m/s)	1.18 (0.16)	1.22 (0.15)	1.22 (0.23)
Step length (m)	0.76 (0.11)	0.75 (0.17)	0.69 (0.07)*
Single limb stance time (sec)	0.579 (0.31)	0.617 (0.05)	0.682 (0.06)*
Net VO_2 (ml/min kg)	7.46 (1.15)	7.89 (1.29)	8.62 (2.65)**
RER	0.87 (0.08)	0.91 (0.04)	0.91 (0.07)
1.4 m/s			
Actual speed (m/s)	1.45 (0.19)	1.44 (0.12)	1.46 (0.19)
Step length (m)	0.79 (0.12)	0.77 (0.17)	0.71 (0.11)*
Single limb stance time (sec)	0.555 (0.15)	0.579 (0.21)	0.621 (0.14)*
Net VO_2 (ml/min kg)	9.22 (1.69)	10.73 (0.80)**	9.87 (2.89)
RER	0.90 (0.07)	0.89 (0.05)	0.93 (0.06)
1.6 m/s			
Actual speed (m/s)	1.62 (0.27)	1.57 (0.17)	1.59 (0.12)
Step length (m)	0.81 (0.11)	0.80 (0.04)	0.74 (0.02)*
Single limb stance time (sec)	0.499 (0.15)	0.498 (0.11)	0.525 (0.01)*
Net VO_2 (ml/min kg)	10.97 (4.45)	12.84 (3.35)**	12.19 (4.99)**
RER	0.89 (0.04)	0.90 (0.07)	0.98 (0.06)

Healthy controls (Ctrl, n=31), diabetic patients with no neuropathy (DM, n=22) and diabetic patients with moderate/severe neuropathy (DPN, n=14). Significant differences from the Ctrl group are denoted by *($P<0.05$) or **($P<0.01$). Values are means (standard deviations). Gait parameters were collected on the laboratory walkway.