Contributory Factors to Unsteadiness during Walking Up and Down Stairs in Patients with Diabetic Peripheral Neuropathy

Unsteadiness in patients with neuropathy

(Short running title)

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Abstract

OBJECTIVE— Although patients with diabetic peripheral neuropathy (DPN) are more likely to fall than age-matched controls, the underlying causative factors are not yet fully understood. This study examines the effects of diabetes and neuropathy on strength generation and muscle activation patterns during walking up and down stairs, with implications for fall risk.

RESEARCH DESIGN AND METHODS— Sixty three participants (21 patients with DPN; 21 diabetic controls [D]; and 21 healthy controls [C]) were examined whilst walking up and down a custom-built staircase. The speed of strength generation at the ankle and knee and muscle activation patterns of the ankle and knee extensor muscles were analyzed.

RESULTS— Patients with neuropathy displayed significantly slower ankle and knee strength generation than healthy controls, during stair ascent and descent ($p<0.05$). During ascent, the ankle and knee extensor muscles were activated significantly later by patients with neuropathy, and took longer to reach peak activation ($p<0.05$). During descent, neuropathic patients activated the ankle extensors significantly earlier, and the ankle and knee extensors took significantly longer to reach peak activation ($p<0.05$).

CONCLUSIONS— Patients with DPN are slower at generating strength at the ankle and knee than control participants during walking up and down stairs. These changes,

which are likely caused by altered activations of the extensor muscles increase the likelihood of instability and may be important contributory factors for the increased risk of falling. Resistance exercise training may be a potential clinical intervention for improving these aspects, and thereby potentially reducing fall risk.

Diabetic peripheral neuropathy (DPN) is a chronic complication of diabetes, affecting up to 50% of older patients (1,2). It is characterised by sensory loss in the lower limbs, altered sense of joint position, and impaired muscular function, which can result in alterations to gait (1-5). Patients with neuropathy are five times more likely to fall than age-matched controls, with over half of patients reporting at least one fall per year (6,7). Falls whilst walking down stairs account for 60% of all fall-related deaths, making this activity ten times more hazardous than level ground walking (8). Thus the common daily task of negotiating stairs poses a high fall risk for people with diabetes, and particularly those with peripheral neuropathy.

During walking up and down stairs (ascending and descending), the major muscles surrounding the ankle and knee joints generate strength at the joint, controlling the movement of the body. The speed at which joint strength is produced is an important factor related to unsteadiness, with a slower generation of joint strength indicative of a higher risk of falling (9-11). When walking on stairs, and particularly when walking down stairs, it is very difficult to recover balance following a moment of unsteadiness. Therefore it is of importance to reduce any marked unsteadiness, to prevent a fall occurring on stairs. Patients with diabetic neuropathy display slower joint strength generation when balance is challenged while standing on one leg (12,13). This may have implications for during the single leg stance phases of walking up and down stairs, and could therefore explain the increased chance of falling in this population. Whilst neuromuscular factors related to the individual are expected to be primarily responsible

for unsteadiness, environmental factors such as low light conditions, the carrying of objects and the lack of handrail use are also expected to increase the risk of falling.

Joint strength, and the speed at which it is generated, are the result of muscular forces surrounding the joint. During stair walking, the ankle and knee extensors are the primary muscles controlling the motion of the body (14-16). The timing of when these muscles are 'switched on' (activated), is therefore key to the safe performance of these movements. Previous studies examining muscle activation patterns in patients with diabetic peripheral neuropathy have been inconclusive due to differing measurement techniques, with earlier activations, and later peak activations of the ankle extensors observed during level ground walking (17,18). During stair climbing, the peak activations of the ankle and knee extensors have been observed to be earlier, yet the time when muscles 'switch on' (muscle activation onset) has not yet been measured (19). A better understanding of how diabetic neuropathy affects lower limb muscle activations and the resulting gait alterations can be gained via understanding when specific muscles 'switch on', when they reach 'full' activation, and how long they are 'switched on' for.

The aim of this study was to examine the effects of diabetes and peripheral neuropathy on the speed of joint strength generation and muscle activation patterns during walking up and down stairs (ascent and descent). Here we address the hypothesis that the lower limb muscles of diabetic patients will respond more slowly and be slower to develop the required strength when initially contacting the floor or step during stair walking. We hypothesise that this impaired muscular response will be an important

factor contributing to unsteadiness and that this will be particularly evident on stairs where the physical demands are extremely high compared to level ground walking.

Research Design and Methods

Participants

Sixty-three participants (21 patients with DPN, 21 patients with diabetes but no peripheral neuropathy [D] and 21 healthy control participants [C]) matched for age: (mean±SD: 57.6±9.4, 57.5±12.7 & 57.6±12.5 years, respectively; BMI: 30.1±5.1, 28.1±3.0 & 26.1±3.9 kg.m-2) gave their written informed consent to participate in this study, which was given ethical approval from the relevant bodies. Patients were excluded if they had open ulcers, required the use of a walking aid, had a history of other disorders affecting gait or a visual acuity of <6/18 (of any aetiology).

Neuropathy Assessment

The presence and severity of neuropathy was measured using separate tests: the Modified Neuropathy Disability Score (mNDS)(1,2), and the Vibration Perception Threshold (VPT)(1-2) using a neurothesiometer (Bailey Instruments Ltd. Manchester, UK). Patients were deemed to have moderate to severe neuropathy, and grouped as DPN if in either one or both of their feet they displayed either a mNDS score of ≥6, or a VPT of ≥25 (or both). Patients were deemed to have no neuropathy and were grouped as D, if in both feet they displayed scores for the mNDS of ≤5 and for the VPT of ≤24 (1,2)

Design

Participants attended two testing sessions; where they were examined using a ten-camera motion capture system to capture whole body movements (Vicon, Oxford, UK), connected to embedded force platforms measuring ground reaction forces (Kistler, Winterthur, Switzerland). Motion and force data were recorded simultaneously at 120Hz and 1,000Hz, respectively. In one session they were examined whilst ascending and descending a staircase, and the other during level ground walking as a 'reference condition'. In both sessions they were prepared using the same methods. In the stair negotiation session, muscle activity was assessed from representative lower limb muscles, using wireless electromyographic surface electrodes (Delsys, Boston, USA) recording at 1,000Hz. The analogue signals from the electrodes were synchronised with the Vicon motion capture system and force platforms.

Procedure

Preparation

Fifty seven retro-reflective markers were attached to the participant's body according to standard preparation methods, creating a 15 segment whole body model. All participants wore specialist diabetic shoes (MedSurg, Darco, Raisting, Germany), with a neutral foot-bed to standardise footwear between groups, and to ensure that the diabetic patients walked with appropriate footwear. A brief period of acclimatization to the footwear around the laboratory was provided before testing began.

The electromyographic electrodes to measure muscle activations were placed on the skin over the muscles representative of the major knee and ankle extensors: the vastus lateralis (VL; knee extensors) and medial gastrocnemius (GN; ankle extensors) of both legs.

Stair Negotiation

Participants ascended and descended an eight step staircase, with a step width of 1050mm, depth of 275mm and a step riser height of 175mm. The staircase was instrumented with four force plates (500mm x 275mm; Kistler, Winterthur, Switzerland) embedded into the middle four steps. Participants were asked to walk without the use of the handrails, but were told to use them only lightly throughout the trial if they felt unable to complete the task safely without doing so (number of participants using the handrails: C: 0; D: 4; and DPN: 11). Data were not analysed from trials where handrails were used intermittently (another trial was analysed instead). Participants ascended and descended the staircase until at least five ascents and five descents were recorded. Participants were provided adequate rest between trials to reduce any potential fatigue effects. Trials were not used if the foot contacted the step on either side of the force plates (and the trial was repeated if this occurred). However, due to the positioning of the force plates (occupying the entire middle portion of the steps) it was very uncommon for this to happen, and for testing to require more than 10 trials (five ascents and 5 descents) to satisfy the above criteria.

Level walking

As a reference condition for comparison with stair negotiation, participants were asked to walk along an 8m long walkway with three embedded force plates (Kistler, Winterthur, Switzerland). Participants were required to repeat the movement until five trials were captured, in which the participants struck one of the force plates with the whole of the foot inside the borders of the force plate.

Data Analysis

Speed of Strength Generation

Speed of strength generation at the ankle and knee was measured as the rate at which joint torque was developed (RJTD). A joint torque is the turning force of the joint, and both causes and controls of movement. Therefore the speed at which this force is developed is indicative of the speed at which strength is generated at the joint.

Individual trials were labelled in Vicon Nexus software (Vicon, Oxford, UK). The three most complete trials (in terms of marker presence during the trial) for each person, in each paradigm, were then exported into Visual3D (C-Motion Inc, MD, USA) for analysis. Joint torques were normalized to body mass to enable valid group comparisons.

The RJTD of the support leg was calculated using the gradient of the joint torque-time curve for the ankle and knee. In each stair trial, the joint torque values from each of the four embedded steps were used and the mean taken. However, in some trials not all values were available, so as many were used as possible.

Muscle activation

The same trials used for RJTD analysis were used for the muscle activation analysis. The muscle activation (electromyographic) signals were examined from the leg of the foot contacting the upper middle step of the eight step staircase. Two stages of analysis were performed, the first stage identified when the activation of the muscle began and ended (defined as onset and cessation, respectively), and the second stage identified the peak of the muscle activity profile. In the first stage, the raw muscle activation signals were processed using a bespoke Matlab (Matlab v2008b, Mathworks, Natick, Massachusetts, USA) program, as detailed previously by Buckley *et al.* (20), which identified when muscles are 'switched on and off' (onset and cessation, respectively). The second stage identified muscle activation peaks of each muscle in Visual 3D. The signal was processed using a full wave rectification, a linear envelope with three window frames, and a Butterworth low pass filter with a cut-off frequency of 4Hz. The peak of the signal for each of the VL and GN muscles was then recorded with respect to foot-step contact. To enable accurate comparisons between groups, the commonly dominant peak was measured. The time at which the peak occurred in reference to foot-step contact was measured and defined as the time of peak (TOP), as well as the time difference between the onset of muscle activity and the peak of activity, defined as the time to peak (TTP). Muscle activation timings were presented as bars of activations (Fig 1).

Statistics

All statistical tests were performed on SPSS statistical package (SPSS v18, Chicago, Illinois) with significance set at $p<0.05$. Mean group differences in both speed of strength generation (RJTD), and muscle activation onset, TOP, TTP, and muscle activation duration, were all statistically tested using a one-way analysis of variance (ANOVA) with a Bonferoni post-hoc test, and all significances are reported with respect to the control group. Between gait tasks (stair ascent, stair descent and level walking), differences (mean across all groups) were also tested using a repeated measures ANOVA with Bonferoni post-hoc test, with all significances for this comparison reported with respect to level ground walking. Only participants who completed all three gait tasks were used for this between-paradigm comparison (C: 10 D: 12 DPN: 12).

Results

mNDS and VPT scores

Patients with neuropathy displayed significantly higher mNDS (C: 1.4 ± 1.3; D: 1.9 ± 1.7; DPN: 7.6 ± 3.0; $p<0.05$) and VPT (C: 9.4 ± 5.8; D: 9.2 ± 4.7; DPN: 31.5 ± 9.8 V; $p<0.05$) scores than the C and D groups. There were no differences ($p>0.05$) in the mNDS or VPT between C and D groups, underlining that this diabetes group had no neuropathy.

Gait velocity

The patients with diabetes (D and DPN groups) performed stair ascent (C: 0.48±0.07; D: 0.43±0.07; DPN: 0.38±0.08 $m.s^{-1}$; $p<0.05$), stair descent (C: 0.53±0.09; D: 0.44±0.09; DPN:0.41±0.11 $m.s^{-1}$; $p<0.05$) and level walking (C: 1.39±0.19; D: 1.27±0.18; DPN: 1.18±0.27 $m.s^{-1}$; $p<0.05$) at significantly slower velocities than the control group.

Speed of strength generation (Fig 2.)

During stair ascent, the D and DPN groups displayed significantly slower ankle and knee strength generation than the C group (Fig. 2). During stair descent, the D and DPN groups displayed significantly slower knee strength generation than the C group; the DPN group also displayed significantly slower ankle strength generation than the C group.

Speed of strength generation was significantly higher at both the ankle (Level: 3.8±1.3; Ascent: 5.1±3.07; Descent: 8.7±2.9 Nm.kg.s-1; $p<0.05$) and knee (Level: 8.2±2.6;

Ascent: 10.8±4.0; Descent: 10.66±4.5 Nm.kg.s-1; $p<0.05$) during stair ascent and stair descent, compared to level walking, for all groups.

Muscle Activations during Stair Ascent (Fig 3.)

During stair ascent, the DPN group activated both the knee (VL muscle) and ankle (GN muscle) extensor muscles significantly later than the C group (Fig. 3). The activation peak occurred later for DPN patients in the knee extensors (TOP: C: 0.13±0.05; D: 0.13±0.05; DPN: 0.19±0.10s; $p<0.05$) and ankle extensors (C: 0.61±0.13; D: 0.66±0.13; DPN: 0.86±0.27s; $p<0.05$), resulting in a longer time to reach peak activation (TTP) for the knee extensors, by the DPN group, but no differences were observed for the ankle extensors. The patients with neuropathy activated the knee extensors for significantly longer than the C group, whilst no differences were observed between the groups for the activation duration of the ankle extensors.

Muscle Activations during Stair Descent (Fig. 4)

During stair descent, the DPN group activated the ankle extensors earlier than the C group, whilst the knee extensors were activated at a similar time in all groups (Fig 4). Once activated, the knee and ankle extensors took significantly longer to reach their peak activation (TTP) in both the D and DPN groups compared to the C group. The peak activation of the knee extensors by the DPN group occurred significantly later after foot-step contact (TOP: C: 0.49±0.13; D: 0.62±0.12; DPN: 0.67±0.26s; $p<0.05$), whilst the ankle extensors reached full activation at similar times between groups (TOP: C:

0.06±0.05; D: 0.07±0.05; DPN: 0.05±0.06s; $p<0.05$). The D and DPN groups also activated on the knee and ankle extensors for significantly longer in total.

Conclusions

People with diabetes, and to a greater extent, patients with neuropathy, displayed significantly slower strength generation at both the ankle and knee joints, and altered muscle activation timings during stair ascent and stair descent. The slower strength generation observed in people with diabetes, and particularly in patients with neuropathy, is likely to be a major factor explaining why this population are at a higher risk of falling than aged-matched controls (6-7). The slower strength generation in diabetes patients, both with and without neuropathy, likely results from alterations in muscle activation patterns as discussed below in detail.

Patients with neuropathy generate ankle and knee strength at a significantly slower rate than a control population during the everyday tasks of stair ascent and stair descent (Fig. 2). Those with diabetes but without neuropathy also displayed slower ankle and knee strength generation during these tasks, but not to the same extent as the patients with moderate-severe neuropathy. The reduced speed of strength generation at both the ankle and knee joints is expected to result from a combination of reduced sensory and motor function as a result of polyneuropathy. Due to the reduction, or complete absence, of sensory and proprioceptive information transmitted to the central nervous system from the lower limbs, adequate motor responses cannot be properly co-ordinated to control movement. Essentially, as patients with sensory neuropathy cannot 'feel' when they contact the ground/step they may be inaccurate in the initiation of appropriate muscular responses. Furthermore, neuropathy patients commonly exhibit a

variety of motor deficits in the muscle, including reduced motor nerve conduction velocity, denervation of motor units (predominantly in type II muscle fibres), reduced muscle volume and impaired contractile properties as a result of non-enzymatic glycation (21-24). The combination of these factors is expected to impact on muscle response and subsequently slow the speed at which strength can be generated at the affected joints. Non-neuropathic diabetic patients also display some of the aforementioned factors before sensory characteristics are altered by marked neuropathy (25), which may therefore explain the reduced speed at which diabetes patients without neuropathy (D group) generate joint strength, albeit to a lesser extent than observed in patients with neuropathy (Fig. 2). A slower speed of strength generation has been shown to be a limiting factor to balance recovery during challenges to balance while standing on one leg, a movement similar to the weight acceptance phase of stair negotiation tasks (12-13, 26). Therefore the decreased speed of strength generation observed in patients with neuropathy is expected to reduce their capability to adapt to a perturbation in balance, and may therefore limit the speed at which the stair walking tasks can be performed safely by patients with diabetes.

The timing of when major muscles are first activated and when they reach their peak activation (the parameters of TTP and the TOP, see Fig. 1 for definition of these variables), are expected to directly influence the resultant speed at which joint strength can be generated. During stair ascent, the delayed activation (switching on) of the knee extensors (represented by the VL muscle) and plantar flexors (represented by the GN muscle) by the patients with neuropathy, may be related to insufficient sensory

feedback, hindering the patient's ability to detect when foot-step contact occurs (Fig. 3). Once activated, these muscles take significantly longer to reach their peak activation. In the knee extensors, this may indicate why strength generation was slower at the knee during this movement in patients with neuropathy (Fig. 2). The same may also be applicable to the plantarflexors, however, during stair ascent, the later peak measured from this muscle, is more attributable to the propulsive ankle extension rather than the absorptive control of ankle flexion observed during weight acceptance.

During stair descent, changes are primarily observed in the plantarflexors with a significantly earlier activation, a longer time to reach peak activation (TTP) and longer duration of activation (Fig. 4). The earlier activation of the plantarflexors in patients with DPN is expected to be an anticipatory mechanism, preparing the ankle joint to stabilise before contact with the step actually occurs. Upon foot-step contact, the plantarflexors are slower to reach peak activation in patients with DPN than the controls. This is expected to be an influential factor leading to the reduced speed at which ankle strength is generated by people with neuropathy. The patients with neuropathy also displayed a longer time to reach peak activation (TTP) in the knee extensors, but similarly to during stair ascent, the peak observed in the secondarily activated muscle is related to the propulsive knee extension rather than the strength generated during the weight acceptance phase to control knee flexion. These altered muscle activations are expected to exert a major influence upon the speed at which strength can be generated, particularly the activation onset (switching the muscle on) and the time to reach peak muscle activation. The consequential decreases in speed of strength generation, would

likely lead to an increase in potentially hazardous perturbations to balance during stair negotiation tasks, which may then ultimately result in falls.

The muscle activation timings observed in patients with diabetes but without neuropathy, during both stair ascent and descent, follow a similar trend to the results observed in patients with neuropathy, albeit to a lesser extent. It is likely that these changes are the result of physiological alterations to skeletal muscle, before measureable sensory neuropathy is observed. Non-enymatic glycation as a result of diabetes may affect the contractile machinery of skeletal muscle independently of neuropathy as shown previously on isolated animal muscle (27). This may at least party explain why changes have been observed proximally at the knee extensors as well as distally at the ankle extensors, in diabetes patients without neuropathy.

Our muscle activation findings contrast with previous findings that the TOP occurs significantly later at both the ankle and knee during both stair ascent and descent (19). These differences may be because our data are presented in absolute time, whereas the previous study presented their results as a percentage of stance phase. Although people with diabetes walk more slowly and therefore have a longer stance phase, the activation of muscles and the appropriate speed of strength generation need to occur within a given absolute time-period upon weight acceptance to ensure avoidance of a perturbation to balance. Therefore, we believe presentation of these parameters in absolute time is the most relevant for interpretation of fall risk in this population. These activations and their timings can therefore only be validly measured in absolute time,

especially the onset of the activation and the TTP, which have been highlighted as key variables influencing the speed of strength generation (RJTD). The slower gait velocity in both patient groups with diabetes could potentially impact upon the speed of strength generation. However, an analysis of covariance revealed that the significant differences we identified between the groups remained after accounting for gait velocity as the covariate, highlighting that diabetes and diabetic neuropathy are the determining factors for this parameter.

During both stair negotiation tasks, there is a distinct pattern of a primary muscle group controlling balance during weight acceptance, followed by a secondary muscle group controlling balance during propulsion. During stair descent, the plantar flexors of the support leg control the acceleration of the body's centre of mass during weight acceptance, whilst the knee extensors, activated later, are used primarily to control the propulsive movement during terminal stance. Conversely, during stair ascent, the knee extensors of the support leg are activated during weight acceptance to steady the body upon foot-step contact, whilst the plantar flexors are activated much later to control balance during the propulsion phase. In both stair ascent and stair descent, the ankle and knee were required to generate joint strength at a faster speed than during level ground walking (Fig. 2), further highlighting the increased physical demands required to perform stair negotiation safely. This corroborates with previous observations of higher absolute joint strength (measured as joint torque) being required during stair negotiation tasks than during level ground walking in non-diabetic populations (16, 20, 28). This may further explain why stair ascent and, particularly stair descent, are such hazardous

everyday activities, and therefore pose the highest risk for falls in patients with diabetes and peripheral neuropathy.

Previous studies have shown that targeted resistance training can improve muscle power, strength and speed of strength generation in high fall risk populations such as the elderly (29-31). Such training has been shown to reduce the difficulty of performing everyday tasks, decrease the risk of falling, and consequently cut subsequent hospital admissions (30, 32). Therefore, it is suggested that such training may favourably alter muscle activations and increase the speed of ankle and knee strength development in people with DPN, and be one potential clinical solution for reducing the risk of falling during the everyday task of stair walking.

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Prof. Neil Reeves is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

J.H. Researched and analysed data, and wrote the manuscript. S.B. researched data. F.B. reviewed/edited the manuscript. A.B. reviewed/edited the manuscript. G.C. contributed to the analysis methods. C.M. contributed to the results and discussion and reviewed/edited the manuscript. N.R. conceived the study, contributed to the results and discussion, and reviewed/edited the manuscript.

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Figure and Tables

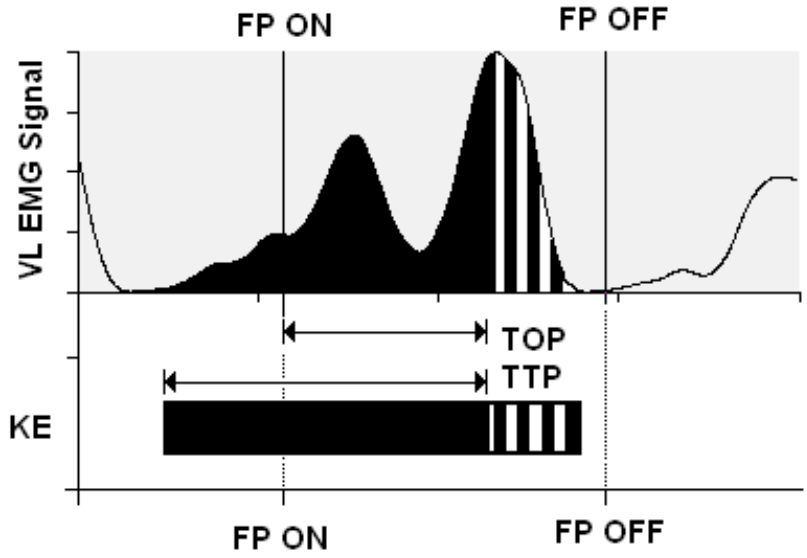

Figure. 1. Example diagram of a stair descent trial from a single participant to illustrate how the muscle activation parameters have been derived from the muscle activation signals (electromyographic activity). The top panel displays the processed muscle activation signals from the knee extensor muscle (KE; measured as vastus lateralis, VL). The corresponding activation bar (lower panel) illustrate how activation parameters are derived for the results: the start of the bars show the muscle onset, the change in colour indicates the point at which the peak activation occurs and the end of the bars denotes the muscle cessation. The measurement of TOP and TTP are illustrated by the arrows above the KE bar.

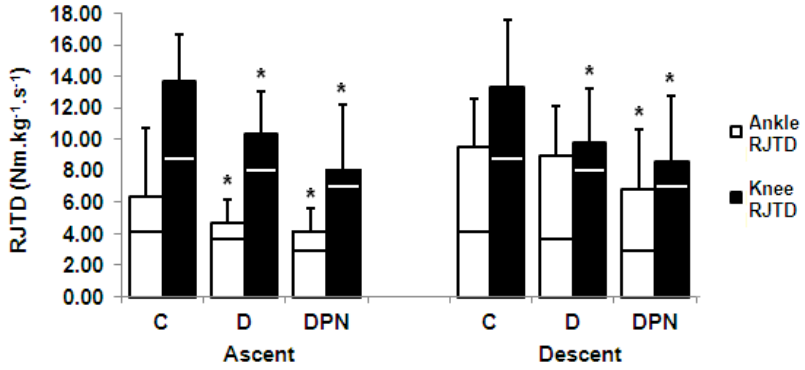

*Figure. 2. Ankle and knee speed of strength generation (rate of joint torque development; RJTD) during stair ascent and stair descent for controls (C), diabetes patients with no neuropathy (D) and patients with diabetic peripheral neuropathy (DPN). The corresponding values obtained for level ground walking are indicated on each bar by the horizontal white/black lines. Light grey bars show the mean ankle speed of strength generation and dark grey bars the mean knee speed of strength generation. Values are means and standard deviations. * denotes significantly different compared to control group ($p<0.05$).*

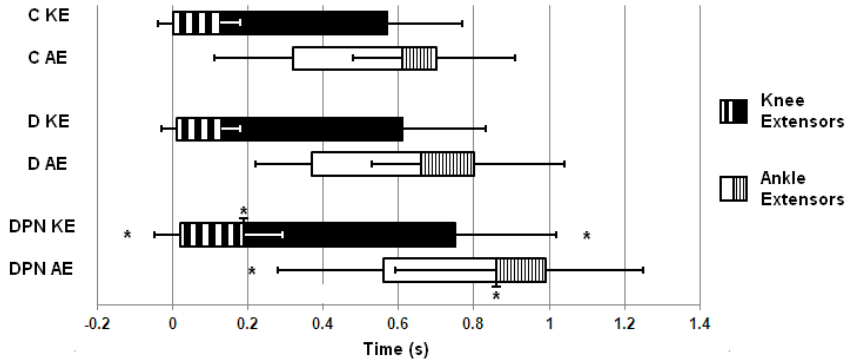

*Figure 3. Periods of activation for the knee extensor (KE; vastus lateralis) and ankle extensor (AE; medial gastrocnemius) muscles with respect to foot-step contact (occurring at time zero) during stair ascent. Values are means and SD for healthy controls (C), diabetes patients with no neuropathy (D) and patients with diabetic peripheral neuropathy (DPN). * denotes significantly different ($p<0.05$) timings compared to control group. Significance is shown for onset (asterisk before activation), time to peak (asterisk above/below point of peak), and duration timings (asterisk after activation). For definition of the measured parameters see Fig. 1.*

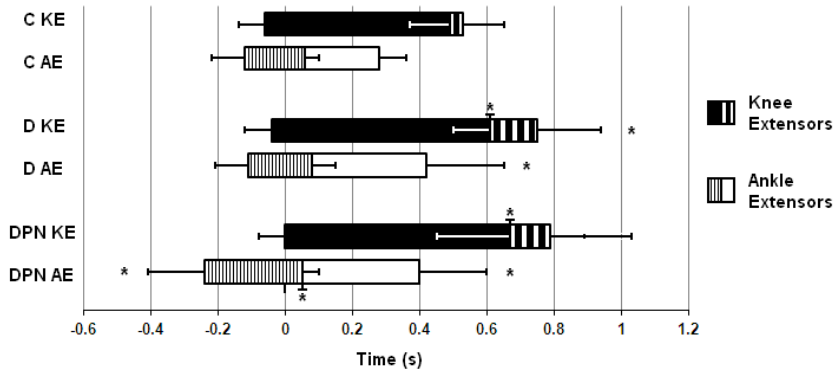

*Figure 4. Periods of activation for the knee extensor (KE; vastus lateralis) and ankle extensor (AE; medial gastrocnemius) muscles with respect to foot-step contact (occurring at time zero) during stair descent. Values are means and SD for healthy controls (C), diabetes patients with no neuropathy (D) and patients with diabetic peripheral neuropathy (DPN). * denotes significantly different ($p<0.05$) timings compared to control group. Significance is shown for onset (asterisk before activation), time to peak (asterisk above/below point of peak), and duration timings (asterisk after activation). For definition of the measured parameters see Fig. 1.*