Why are patients with diabetic peripheral neuropathy more likely to fall? An examination of the underpinning biomechanical mechanisms of locomotion and the influence of intervention.

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“The noblest pleasure is the joy of understanding.

Therefore, be always curious and observant”

Leonardo Da Vinci

Contents

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Dissemination of study findings

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Submitted articles

Handsaker JC, Brown SJ, Bowling FL, Maganaris CM, Boulton AJM, Reeves NR: Harder, Better, Faster, Stronger: Resistance exercise training increases lower limb speed of strength generation during stair ascent and descent in patients with diabetic peripheral neuropathy. *(Under review at Diabetic Medicine as of 06/02/15)*.

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Published abstracts

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Thesis abstract

The research for this thesis examined the effects of diabetic peripheral neuropathy (DPN) on biomechanical factors related to the risk of falling during locomotor tasks, and the effects of a 16-week multi-factorial intervention on the identified impairments. The speed of ankle and knee strength generation, and muscular activations were measured during stair ascent and descent; and minimum toe clearance, stepping accuracy, and visual gaze parameters were measured during level ground walking. Patients with DPN, diabetes patients with no neuropathy and non-diabetic controls were measured before and after a 16-week intervention consisting of high-load resistance exercises and a visual gaze training task. Patients with DPN displayed slower ankle and knee strength generation during stair ascent and descent than healthy controls ($p<0.05$). Post-intervention, strength was generated faster at the ankle and knee during both tasks ($p<0.05$), which is expected to improve stability during the weight acceptance phase. During level ground walking, patients with DPN displayed a higher minimum toe clearance ($p<0.05$), which is expected to reduce the risk of tripping on smaller, less observable hazards; but displayed a decreased stepping accuracy ($p<0.05$), which may reduce the ability to avoid tripping hazards. Stepping accuracy was improved as a result of the intervention ($p<0.05$), which may originate from improvements in visual gaze strategy and motor control, contributing to reduce the risk of tripping in patients with DPN. Biomechanical impairments during locomotion were observed in patients with DPN; however, the intervention improved these aspects and may reduce the risk of falling in this population.

Chapter 1

Introduction

Background

Diabetes: Definition and global prevalence

Diabetes Mellitus describes a group of metabolic diseases that cause a chronic elevation in blood glucose levels (1, 2). Diabetes develops when adequate glucose cannot enter the cells of the body to be used as fuel, due to impairments in insulin secretion, insulin action, or both (1, 2). There are two different types of diabetes: type 1 and type 2. Type 1 diabetes occurs when the body cannot produce insulin, and accounts for approximately 5-10% of adults with diabetes, whereas type 2 diabetes accounts for 85-95% of all people with diabetes, and is caused by impaired insulin action, which reduces the ability of cells to uptake glucose (1, 2). Type 2 diabetes typically affects patients who are overweight or display a high body fat percentage, a characteristic that has typically caused the initial development of diabetes itself (1).

One in 20 people in the United Kingdom are estimated to have diabetes, with 850,000 of these patients currently undiagnosed (2). Three hundred and forty seven million people worldwide have diabetes, and by 2030, this number is expected to dramatically increase to close to 439 million (3, 4). People with diabetes have approximately twice the risk for cardiovascular disease as those without diabetes, and as a result have an increased risk of mortality (5). The World Health Organisation expects that the number of diabetes related deaths will double before 2030, becoming the 7th leading cause of death worldwide (6). Patients with diabetes require at least two to three times the health-care resources to patients without diabetes, and

approximately 15% of health care budgets are spent on diabetes related care (3, 4). In 2012, diabetes cost the United States of America $245 billion, of which $69 billion was lost due to reduced productivity, and $176 billion was spent on direct medical costs (1).

Consistently high blood glucose levels can lead to a number of secondary complications including retinopathy, nephropathy, cardiovascular disease and neuropathy, which in isolation or combination can seriously impact on a patient's quality of life (7, 8). These complications account for a substantial proportion of the direct health costs, representing 72% of the total costs in the United States of America, and 41% of costs in the United Kingdom (9).

Diabetic foot problems

Problems with the 'diabetic foot' account for more hospital admissions than any other complication among patients with diabetes (10). The term 'diabetic foot' refers to a spectrum of disorders including the ulcerated foot, the foot at risk from ulceration, and the Charcot foot (11). Twenty five percent of patients with diabetes will develop a foot ulcer in their lifetime, which if left untreated, can lead to ischemia and infection, and may consequently require amputation (12, 13). Because of the high risk of foot ulcers and consequential infection in the diabetic population, diabetes is the most common underlying cause of lower extremity amputation in the US and Europe, which is particularly concerning as the three-year survival rate for patients undergoing a major

lower limb amputation is just 24%, compared to 93% in patients who have undergone a minor amputation or none at all (14).

Prolonged and elevated plantar pressures over a bony prominence, (such as a hammer toe or bunion), minor foot-traumas, and neuropathy, are the leading causes of ulceration in patients with diabetes (15-19). Patients with diabetes however typically display a multitude of risk-factors for ulceration, where patients with neuropathy, ischemia, foot deformity calluses, limited ankle mobility and a history of ulcers are at the greatest risk of ulceration (10, 15, 20-24). Foot ulcers often go undetected as a result of sensory neuropathy, leading to a lack of early detection and consequently lead to infection, sepsis, necrosis and gangrene, which ultimately may require amputation (17, 25-27).

Another serious complication of the diabetic foot is Charcot athropathy which is an inflammatory syndrome characterised by varying degrees of bone and joint disorganisation, resulting in the progressive destruction of bones and soft tissue (10, 28). It typically manifests as undetected joint dislocations and pathological fractures of the bones of the feet, due to the neuropathy, which fuse in an un-natural arrangement, altering the architecture and function of the foot (10, 29). Similarly to foot ulceration, Charcot arthopathy typically remains undetected due to the effects of diabetic neuropathy, causing the condition to gradually increase in severity.

Diabetic peripheral neuropathy

Diabetic peripheral neuropathy (DPN) is one of the most common complications of diabetes, affecting up to 50% of sufferers after ten years of having diabetes (30, 31). One in 50 people in the general population of the UK are estimated to have DPN, and 1 in 10 people over the age of 55 are estimated to have DPN to some degree (2).

DPN affects sensory, motor and autonomic nerves, and is caused by neurovascular alterations to the nerve fibres and blood vessels supplying the nerve endings, resulting in reduced or absent nerve conduction (2, 32). Peripheral neuropathy is typically tested by assessing sensory function, using a variety of instruments to identify the patient's ability to detect vibration, temperature, touch and acute pain (31, 33). However, motor neuropathy can also be detected by measuring nerve conduction velocity, and such methods may be a more sensitive measure of DPN than tests of sensorimotor function (34, 35). Diabetic peripheral neuropathy is a predominantly distal condition, primarily affecting the longer nerves of the feet and lower legs in the early stages of the condition, and gradually affecting the more proximal areas of the lower limbs, the hands and distal ends of the lower arms (2, 36). DPN is characterised by the progressive loss of somatosensorial sensitivity, proprioception and muscular function, and can also present as a tingling sensation and pain in some patients (30, 31, 37-39).

Effects of DPN on musculoskeletal structures and gait

The structure and function of skeletal muscles and connective tissues are highly affected by the presence of DPN. Predominantly distal muscle atrophy is common in the lower limbs, which exacerbates reductions in muscle strength (40, 41). Patients with DPN also display a decreased nerve conduction velocity, and impaired contractile properties as a result of non-enzymatic glycation, which in tandem results in a slower muscle response (34, 35, 42). Furthermore, tendon tensile stiffness is increased, limiting the range of joint motion at the ankle and knee (43-45). During locomotion, patients with DPN exhibit delayed peak muscle activations, despite an earlier 'switching on' of muscles, which may lead to decreased motor control during walking (39, 46, 47). Muscle activations during stair negotiation tasks however are less conclusive, with one study identifying earlier peak activations in the lower limb muscles, whilst another observed no differences in comparison to a healthy control group (48, 49).

Patients with DPN display compensatory musculoskeletal mechanisms during locomotion in response to the somatosensorial and motor deficits (39, 47). DPN patients predominantly display a hip strategy during walking. Instead of propelling the leg through the swing phase of gait via rapid plantar flexion of the ankle, the leg is instead 'pulled' forward using the hip flexors (50, 51). This gait strategy causes patients to walk at slower walking speeds, with a lower cadence, a smaller step length, and a wider step width (50, 52, 53). Such gait alterations have been suggested as being the result of subconscious mechanisms to reduce potentially

injurious plantar pressures that may lead to ulceration (52, 53). However, some other studies have identified motor changes to the plantar flexor muscles as being a key component leading to changes in gait (40, 50, 51). When walking on stairs, patients with DPN display a reduced dorsiflexion during ascent, and reduced plantar flexion during descent, as a result of previously described reductions in ankle joint range of movement (41, 49). However, to my knowledge, this is one of only two studies (48, 49) to have examined the effects of DPN on biomechanical characteristics during stair negotiation tasks, with neither examining the effects of underlying muscular activations on characteristics which may influence fall potential.

Fall risk in people with DPN

People with DPN are five times more likely to fall than age-matched controls, with over half of DPN patients reporting at least one fall per year (54-56). Patients with DPN often display a number of factors that may explain an increased risk of falling, however the presence of neuropathy has been identified as an independent risk factor explaining the high risk of falling in the DPN population (55).

Approximately 30% of hospital admissions for traumatic injuries are the result of falls, and are a major cause of severe fatal (40% of injuries) and non-fatal injuries (57, 58). An estimated 73 - 85% of falls occur in the home, with 60% of falls resulting in fractures (59-62). Falls during stair descent account for 60% of all fall-related deaths, and are three times more hazardous than stair ascent, and ten times more hazardous than level ground walking (63-66).

No epidemiological data is currently available that displays the distribution of where and when falls occur in patients with diabetes and diabetic peripheral neuropathy. Despite the absence of this data, most fatal falls occur during stair descent and ascent and level walking (63-66). Furthermore, it is well known that the risk of falling in patients with DPN is higher than is observed in the general population (54-56). Therefore I decided to examine the locomotor paradigms of stair negotiation and level ground walking

Risk factors for falling during walking and stair negotiation

During level ground walking, tripping can occur on observed and unobserved hazards. The incidence of trip related falls is determined primarily by the frequency of tripping, and not the ability to recover from a trip (67). Therefore, the most effective approach to identifying the risk of falling for a particular individual or population is to examine their ability to avoid obstacles before they become a tripping hazard (68, 69). When an obstacle is observed, the patient must co-ordinate an appropriate response to avoid tripping. People with a high risk of falling are less accurate and more variable at stepping onto targets, which may indicate an impaired control of foot trajectory, which may consequently impinge on effective obstacle avoidance (68, 70, 71). However, the potential for tripping on unobserved hazards differs, and is dependent upon the characteristics of normal gait. The variability and absolute minimum of toe clearances during gait have been reported as potential indicators for the risk of tripping during walking in the elderly population (71-73). The more variable

and lower the toe clearances, the higher the risk of the toe catching a smaller, unobserved obstacle during the mid-swing phase of gait.

During stair ascent and stair descent, the physical and sensory demands are greater than during level ground walking. Due to the nature of these stair negotiation tasks, perturbations large enough to cause a loss of balance are almost unrecoverable; therefore the maintenance of a safe and stable locomotor pattern is paramount. During stair descent, the ankle and knee joints are critical to controlling balance with lower extremity joint torques required to be produced to a level much higher than during level walking (74-79). As well as the individual's maximal joint torque capabilities, the speed at which joint torques are produced may also be an important factor in balance maintenance. Bento et al. (80) and La Roche et al. (81) identified the rate of joint torque development (RJTD) as the sole factor indicative of fall risk, observing that people with a history of falling display a significantly slower RJTD at the ankle and knee, than those without a history of falling (80, 81). However, the effects of RJTD on stability during stair negotiation have not yet been examined in a diabetic patient population. To improve the understanding of the study, and the subsequent application of its results by clinicians, the unit of measure 'rate of joint torque development' has been termed 'speed of strength generation' for the following chapters.

Effects of resistance exercise training in patients with diabetes and other high fall risk populations

Type I, and particularly type II diabetes, can be managed by increasing the levels of physical activity performed. Aerobic exercise helps to improve glycaemic control, enhance insulin sensitivity, improve cardiovascular risk factors, and reduce the risk of complications (82). Furthermore, it has been suggested that combining aerobic with resistance exercise may be even more effective for improving glycaemic control than aerobic exercise alone (83-85). Aerobic exercise has also been shown to disrupt and slow the progression of neuropathy, by increasing branching and fibre density of intraepidermal nerves and reducing the decreases in nerve conduction velocity observed over time (86-88).

Resistance exercise training increases muscle strength and volume, as well as altering tendon properties, and helps to control blood pressure (84, 89, 90-93). These adaptations contribute to an increased six minute walking distance, increased walking speed and increased postural stability observed in patients with diabetes following 12 weeks of resistance exercise training (89, 94-97). Resistance exercise also helps to improve psychological well being and the enjoyment of exercise regimens, and may aid the continued performance of exercise in patients with diabetes, which is important for a population whom typically display negative attitudes towards exercise (98, 99). No studies, however, have yet examined the effects of exercise for improving dynamic measures of fall potential such as the ability to rapidly generate strength at the ankle and knee joints, as identified above. Exercise interventions with the specific aim to improve RJTD in an elderly population have previously been suggested to be more effective at reducing the risk of falling than

more generalised exercises, and may therefore also be effective at reducing the risk of falling in patients with DPN (80).

Thesis aim

The purpose of this thesis is to examine the effects of DPN on biomechanical mechanisms of locomotion that may explain an increased risk of falling during level ground walking and stair negotiation. Furthermore, this thesis will examine the effects of a targeted intervention on potential mechanisms of impairment, to examine whether these factors can be improved and potentially contribute to reducing the risk of falling in the DPN population.

Thesis Outline

This thesis will take the form of six chapters, focusing around the presentation of four experimental chapters.

The first two of these experimental chapters (chapters 2 and 3), examine the effects of diabetes and DPN on biomechanical characteristics of stair negotiation, which may impact upon stability, and the effects of an intervention to improve these characteristics. Chapter 2 specifically examines the effects of DPN on speed of strength generation (ability to rapidly develop strength at the joint; RJTD) at the knee and ankle during stair ascent and descent, and the muscular activations that may influence the speed of strength generation observed during these movements. Chapter 3 then examines the effects of a 16-week resistance exercise-based intervention on these characteristics in patients with diabetes and DPN, with the aim to improve stability during stair negotiation.

Chapters 4 and 5 examine factors that may affect the ability of patients to avoid observed and unobserved obstacles during walking, and the efficacy of a targeted intervention to alter these characteristics. Chapter 4 examines the effects of diabetes and DPN on stepping accuracy and minimum toe clearance, which are indicative of the potential for tripping and preliminary measures of visual gaze parameters, which may help to explain the underlying characteristics of stepping accuracy. Chapter 5 then investigates the effects of a targeted multifactorial

intervention on improving stepping accuracy in patients with diabetes and DPN, and discusses the implications of this on the potential for tripping on observed obstacles.

A priori power calculation performed using the parameter of ankle joint torque originally identified requirements for 18 participants in each of the three groups for identification of the pre-intervention between group differences, and 18 participants were also required in each group to identify pre-post intervention within group differences. Post-hoc power calculations were performed where these group numbers were not achieved.

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Chapter 2

A stairway to heaven? Contributory factors to unsteadiness during walking up and down stairs in patients with diabetic peripheral neuropathy

Abstract

Introduction: 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.

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 activation patterns of the ankle and knee extensor muscles were analyzed.

Results: Patients with DPN 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 DPN, 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 ($p<0.05$).

Discussion: 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.

Introduction

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.

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 DPN 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 DPN 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.

Methods

Participants

Sixty-three participants; 21 patients with DPN (Age: 57.6 ± 9.4 years; and BMI: 30.1 ± 5.1 $kg.m^{-1}$; mean ± SD), 21 patients with diabetes but no peripheral neuropathy (Age: 57.5 ± 12.7 years; and BMI: 28.1 ± 3.0 $kg.m^{-1}$) (D) and 21 healthy control participants (Age: 57.6 ± 12.5 years; and BMI: 26.1 ± 3.9 $kg.m^{-1}$)(C) matched for age, gave their written informed consent to participate in this study, which was given ethical approval from the relevant bodies. Patients were recruited through the Manchester diabetes centre, as a result of a local radio show interview, the local newspaper, and through an initiative called Help Beat DiaBEATes. (Patients were recruited through these avenues for all aspects of this thesis). The major exclusion criteria were: open ulcers, requiring the use of a walking aid, a history of any other disorders affecting gait, and a visual acuity of <6/18 (of any aetiology, including retinopathy).

Neuropathy assessment & classification

The presence and severity of neuropathy was measured using separate tests: the Modified Neuropathy Disability Score (mNDS)(Fig. 1)(1, 2), and the Vibration Perception Threshold (VPT)(1, 2) using a neurothesiometer (Bailey Instruments Ltd. Manchester, UK). Patients with no neuropathy (defined by mNDS ≤5 and VPT ≤24) were grouped as D, and those with moderate to severe neuropathy (defined by mNDS ≥6 and VPT ≥25) were grouped as DPN (1, 2).

		Right	Left
VPT 128Hz Tuning fork; apex of big toe; normal = can distinguish vibrating/not vibrating	Normal = 0 Abnormal = 1		
Temperature perception on dorsum of the foot Use tuning fork with beaker of ice/warm water			
Pin prick Apply pin proximal to big toe nail just enough to deform the skin; trial pair = sharp, blunt; normal can distinguish			
Achilles reflex	Present = 0 Present with reinforcement = 1 Absent = 2		
	NDS total out of 10		

Figure 1. The modified neuropathy disability score. Boulton 2004 (1, 2)

Design

Participants ascended and descended a bespoke eight-step staircase with four step-embedded force platforms in the middle four steps of the staircase. A ten-camera motion capture system captured whole body movements (Vicon, Oxford, UK) and ground reaction forces were measured from the step-embedded force platforms (Kistler, Winterthur, Switzerland). Motion and force data were recorded simultaneously at 120Hz and 1,000Hz, respectively. 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 motion analysis preparation methods, creating a 15 segment whole body model, of which the seven segments of the lower body were used in this study (pelvis, thighs, shanks and feet)(4, 14) To ensure the reliability of marker placement, all markers were placed on the participants by myself on bony landmarks and on areas of the body which are least affected by soft tissue movement, such as on the tibia for the shank, for example. 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 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 (knee extensors; KE) and medial gastrocnemius (ankle extensors; AE) 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 if they felt unsafe or unsteady. Trials were disregarded if handrails were used momentarily in trials. The use of handrails was prevented to restrict confounding factors which may affect measurements of speed of strength generation. Handrails can alter the production of joint moments (Reeves 2008), which may then distort the results depending on the strategy of how they are used. In everyday life, whilst they typically will be available, in some situations handrails may not always be present. Therefore, during such scenarios, patients with DPN may be at the highest risk of falling. Participants ascended and descended the staircase until five ascents and five descents were

recorded, and all force plates were contacted by the whole foot, with no part overhanging onto either side of the step.

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 (SoSG) 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 labeled 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 from all four force plates, 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) programme, 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. 2).

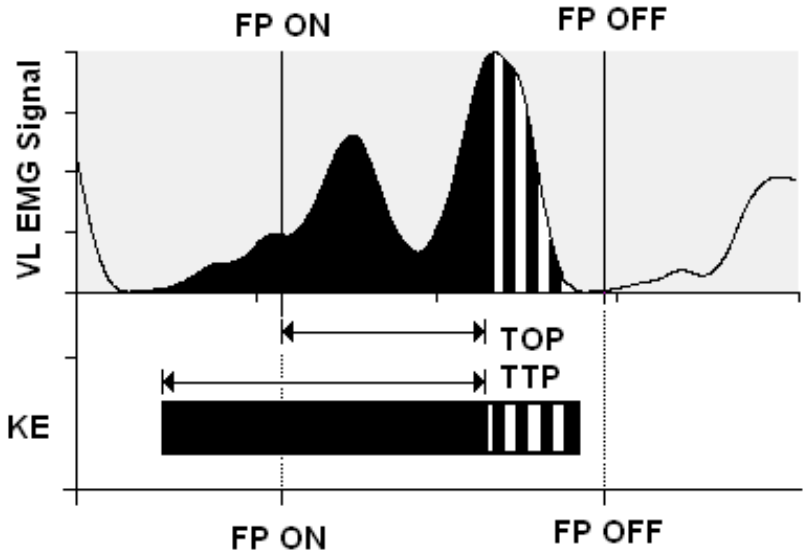

Figure. 2. Example diagram of a stair descent trial from a single participant to illustrate how the muscle activation parameters have been derived from the muscle activation signals (electromyographic activity). The top panel displays the processed muscle activation signals from the knee extensor muscle (KE; measured as vastus lateralis, VL). The corresponding activation bar (lower panel) illustrates 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 measurements of time of peak (TOP) and time to peak (TTP) are illustrated by the arrows above the KE bar.

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 a 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 comparison.

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. 3)

During stair ascent, the D and DPN groups displayed significantly slower ankle and knee strength generation than the C group (Fig. 3). 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.

SoSG 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: 10.7 ± 4.5 $Nm.kg.s^{-1}$; $p<0.05$) during stair ascent and stair descent, compared to level walking, for all groups. An analysis of covariance was also performed using gait velocity as a covariate. The results of this further analysis still showed that patients with diabetes and diabetic peripheral neuropathy generated significantly slower speeds of strength generation compared to controls.

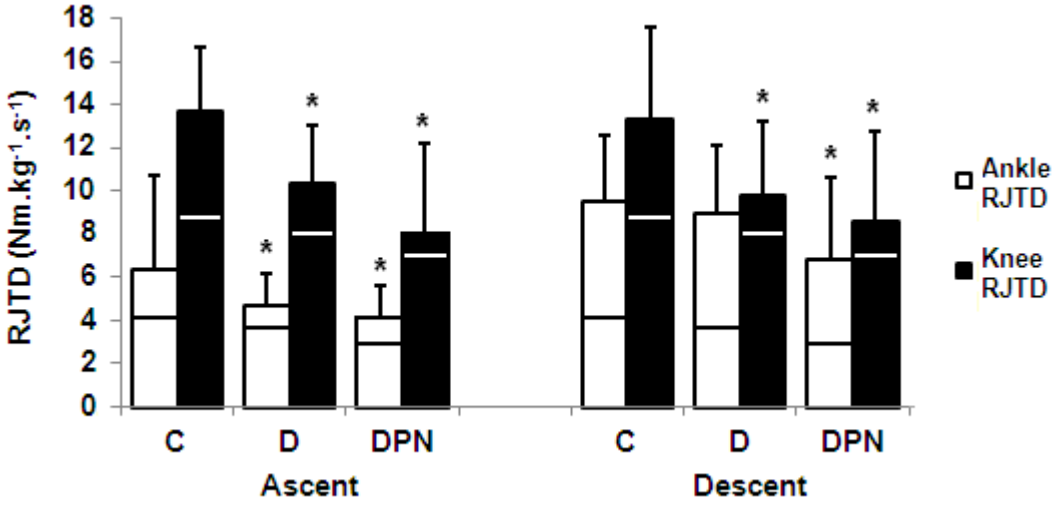

*Figure. 3. Ankle and knee speed of strength generation (rate of joint torque development; RJTD) during stair ascent and stair descent for controls (C; n=21), diabetes patients with no neuropathy (D; n=21) and patients with diabetic peripheral neuropathy (DPN; n=21). The corresponding values obtained 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).*

Muscle activations during stair ascent (Fig. 4)

During stair ascent, the DPN group activated both the knee and ankle extensor muscles significantly later than the C group (Fig. 4). 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 DPN 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. 5)

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. 5). 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 the knee and ankle extensors for significantly longer in total.

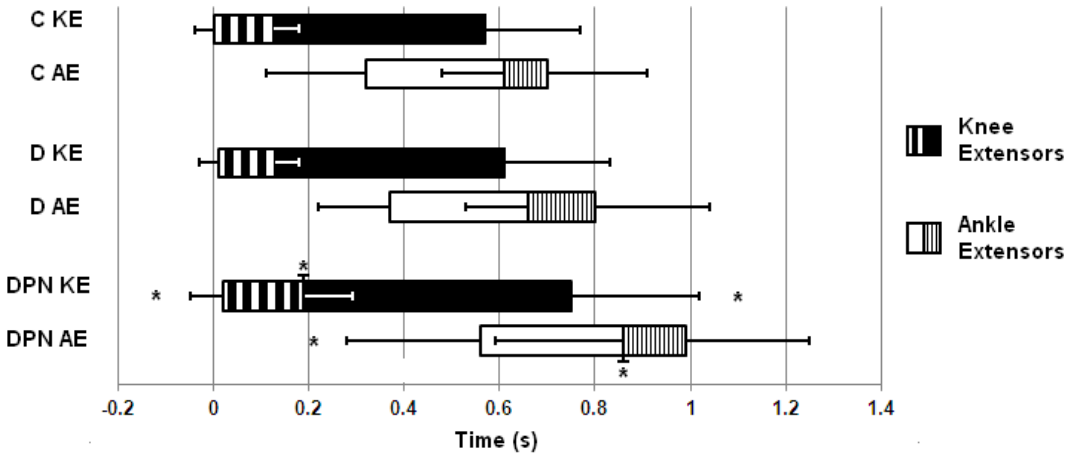

*Figure 4. Periods of activation for the knee extensor (KE; vastus lateralis) and ankle extensor (AE; medial gastrocnemius) muscles with respect to foot-step contact (occurring at time zero) during stair ascent. Values are means and SD for healthy controls (C; n=21), diabetes patients with no neuropathy (D; n=21) and patients with diabetic peripheral neuropathy (DPN; n=21). * 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. 2.*

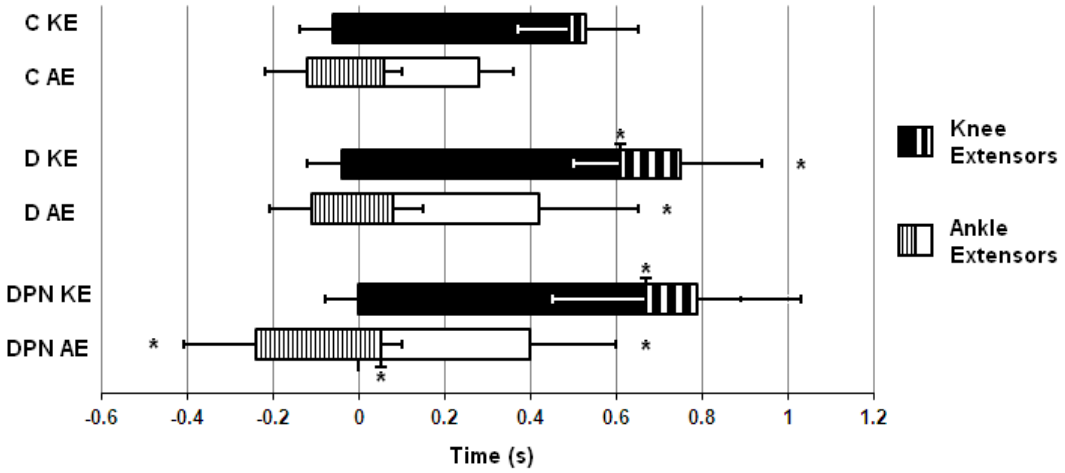

*Figure 5. Periods of activation for the knee extensor (KE; vastus lateralis) and ankle extensor (AE; medial gastrocnemius) muscles with respect to foot-step contact (occurring at time zero) during stair descent. Values are means and SD for healthy controls (C; n=21), diabetes patients with no neuropathy (D; n=21) and patients with diabetic peripheral neuropathy (DPN; n=21). * 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. 2.*

Discussion

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 is 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. 3). Those with diabetes but without neuropathy also displayed slower ankle and knee SoSG during these tasks, but not to the same extent as the patients with moderate-severe neuropathy. The reduced SoSG 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 coordinated 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. 3). A slower SoSG 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 SoSG 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. 2 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 ankle extensors (represented by the GN muscle) by the patients with DPN, may be related to

insufficient sensory feedback, hindering the patient's ability to detect when foot-step contact occurs (Fig. 4). 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. 3). The same may also be applicable to the ankle extensors, however, during stair ascent, the later peak measured from the gastrocnemius 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 ankle extensors with a significantly earlier activation, a longer time to reach peak activation (TTP) and longer duration of activation (Fig. 5). The earlier activation of the ankle extensors 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 ankle extensors 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 present 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 the present 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, I deem that the 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).

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 ankle extensors 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 ankle extensors 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. 3), 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, 27). 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 SoSG in high fall risk populations such as the elderly (28-30). Such training has been shown to reduce the difficulty of performing everyday tasks, decrease the risk of falling, and consequently cut subsequent hospital admissions (29, 31). 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, potentially reducing the risk of falling and improving safety during the everyday task of stair walking.

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Chapter 3

Harder, better, faster, stronger: Resistance exercise training increases lower limb speed of strength generation during stair ascent and descent in patients with diabetic peripheral neuropathy

Abstract

Introduction: Patients with diabetic peripheral neuropathy (DPN) display a slower speed of strength generation (SoSG) at the ankle and knee, which leads to unsteadiness during stair negotiation tasks. This study examines the effects of a 16-week resistance exercise training intervention in patients with DPN on ankle and knee SoSG during stair ascent and descent.

Methods: Forty three participants: 9 patients with DPN; 13 patients with diabetes but no neuropathy (D) and 21 healthy controls (H-CON) ascended and descended a custom-built staircase. The SoSG of the ankle and knee, and muscle activation patterns of the ankle and knee extensor muscles were analyzed before and after a 16-week intervention period.

Results: Ankle and knee SoSG during both stair ascent and descent were significantly higher post-intervention compared to pre-intervention in the diabetes patients who undertook the resistance exercise intervention ($p<0.05$). Although muscle activations were altered by the intervention, there were no observable patterns that underpinned the increases in SoSG.

Discussion: The increased SoSG of the ankle and knee observed after the intervention, are expected to improve stability during the crucial weight acceptance phase of stair ascent and descent, and ultimately contribute towards reducing the risk

of falling. Improvements in strength as a result of the resistance exercise training intervention are expected to be the most influential factor for increasing the SoSG. It is advocated that these exercises could be incorporated into a multi-faceted exercise programme to improve safety in people with diabetes and DPN.

Introduction

Diabetic peripheral neuropathy (DPN) is a chronic complication of diabetes, affecting up to 50% of older patients (1, 2). Patients with DPN are five times more likely to fall than age-matched controls, with over half of patients reporting at least one fall per year (3, 4). Falls whilst walking down stairs account for 60% of all fall-related deaths, making this activity ten times more hazardous than level ground walking (5). Therefore, a means to reduce the number of falls in this population, may reduce the number of patients suffering serious injury, and potentially contribute towards saving lives.

When walking on stairs, and particularly when walking down stairs, it is very difficult to recover balance following a moment of unsteadiness. It is therefore of the utmost importance to reduce this unsteadiness, to prevent a fall occurring on stairs. The speed at which joint strength is produced is an important factor related to unsteadiness, with a slower speed of strength generation (SoSG) indicative of a higher risk of falling (6-8). I have previously shown that during stair ascent and stair descent, patients with DPN display significantly slower SoSG at the ankle and knee upon initial step contact, compared to controls (9). This may therefore lead to unsteadiness during stair walking, and consequently increase the risk of falling during stair ascent and stair descent.

The speed at which joint strength is generated, is the result of muscular forces surrounding the joint. During stair walking, the ankle and knee extensors are the primary muscle groups controlling the motion of the body (10-12). The timing of when, and the speed at which, these muscles are 'switched on' (activated) are therefore key to the safe performance of these movements. I have previously identified that significantly altered muscle activation patterns in patients with DPN may be related to the slower SoSG observed in this population (9). Therefore, if the timing and speed of muscle activations can be positively modified in patients with DPN, the SoSG may consequentially be increased during stair ascent and descent, which may in turn reduce the risk of falling.

Cardiovascular and resistance exercises, have been shown to improve glycaemic control and increase gait speed, six minute walking distance, and daily step counts (13-18). However, whilst a number of studies have looked at the effects of exercise on postural sway during standing and gait characteristics during level ground walking, in patients with diabetes, no studies have yet examined the effects of resistance exercise training on factors affecting unsteadiness during the physically challenging and dangerous tasks of stair ascent and descent. Previous studies have shown that targeted resistance exercise training can improve the speed of strength generation in healthy young and older adults, which is expected to decrease the risk of falling (6, 19, 20). It is hypothesised that such training may therefore increase the speed of ankle and knee strength development in people with diabetes and DPN, potentially

reducing the risk of falling and improving safety during the everyday task of stair walking.

The aim of this study was to investigate the effects of a resistance exercise training intervention on the SoSG at the knee and ankle joints, and muscle activation timings of the knee and ankle extensors in patients with diabetes and DPN. It was hypothesised that improvements in muscle strength and increases in the speed of muscle activations would facilitate a faster SoSG, which would be indicative of a safer, more stable movement pattern during stair ascent and stair descent.

Methods

Participants

Forty three participants; 9 patients with DPN (Age: 57.9 ± 9.5 years; and BMI: 28.1 ± 4.0 $kg.m^{-1}$; mean ± SD) 13 patients with diabetes but no neuropathy [D] (Age: 60.3 ± 10.0 years; and BMI: 28.3 ± 4.1 $kg.m^{-1}$) and 21 healthy controls [H-CON](Age: 66.3 ± 11.5 years; and BMI: 25.1 ± 3.1 $kg.m^{-1}$), gave their written informed consent to participate in this study, which was given ethical approval from the relevant bodies. A healthy non-diabetic control group was included to provide a reference condition, displaying 'optimal' performance and providing a comparison to pre- and post-intervention characteristics of patients with diabetes and DPN. The major exclusion criteria were: open ulcers, requiring the use of a walking aid, a history of any other disorders affecting gait, and a visual acuity of <6/18 (of any aetiology, including retinopathy).

Neuropathy assessment & classification

The presence and severity of neuropathy was measured using two separate tests: the modified Neuropathy Disability Score (mNDS)(1, 2), and the Vibration Perception Threshold (VPT) (1, 2) using a neurothesiometer (Horwell, Nottingham, 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 an mNDS score of ≥6, or a VPT of ≥25 Volts (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 Volts (1, 2).

Study design

Participants ascended and descended a bespoke eight-step staircase with four step-embedded force platforms in the middle four steps of the staircase. A ten-camera motion capture system captured whole body movements (Vicon, Oxford, UK) and ground reaction forces were measured from the step-embedded force platforms (Kistler, Winterthur, Switzerland). Motion and force data were recorded simultaneously at 120Hz and 1,000Hz, respectively. 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

Gait laboratory preparation

Fifty seven retro-reflective markers were attached to the participant's body according to standard motion analysis 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 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 (knee extensors; KE) and medial gastrocnemius (ankle extensors; AE) of both legs.

Stair negotiation

Participants ascended and descended the staircase until at least five ascents and five descents were recorded, with adequate rest between trials. All participants were supported in a harness for safety in case of a fall, and were asked to not use the handrails unless they felt unable to complete the task safely without, in which case light handrail use was permitted. Data were not analyzsed from trials where handrails were used intermittently (and another trial was used for analysis instead).

Resistance exercise training intervention

Diabetes patients were randomly allocated into either the intervention group or a control group (who did not take part in the resistance exercise training) using a random number generator, with a weighting of 2:1 into the intervention and control groups, respectively. Sixteen participants were allocated into the intervention group (splitting into D-INT, n=10; and DPN-INT, n=6 groups for the purpose of data analysis), and six (D: n=3; DPN: n=3) were allocated into the diabetic control group (combined D-CON group for the purpose of data analysis). To determine the adequacy of the group samples in the present study, the statistical power to detect pre- to post-intervention differences (using the parameter knee SoSG during stair

descent) was tested post-hoc for the DPN-INT group (*n*=6). The statistical power was found to be 0.93, indicating the study was well powered to identify true differences with these specific parameters.

Patients in the intervention group attended a weekly, one-hour session for 16 weeks (21, 22), at a private gym dedicated for research studies within the research institute of the university. After the 16-week intervention period, patients repeated the stair negotiation task, and pre- and-post intervention measurements were analysed. The post-intervention test took place within one month of the last intervention session. The intervention comprised of two components, high-load dynamic resistance exercises, and isometric exercises. During the intervention sessions participants were always closely supervised by the lead author. Participants were taught how to use the resistance machines and perform the exercises safely and with the correct technique.

Heavy resistance exercise training

Resistance exercises were based upon those previously performed in other high fall risk groups (23-26). Patients were asked to perform three series of up to twelve repetitions on three different machines; 1) a leg extension (extending the knee from 90˚ to 0˚ flexion to lift the load and flexing to lower under control), 2) a leg press (extending the ankle, knee and hip from a flexed position [knee at >90˚] to a more extended position [knee ending close to full extension] and returning while lowering the load under control), and 3) an ankle press (plantar flexing the ankle from a dorsi

flexed angle and returning to lower the load under control). One repetition consisted of lifting and lowering the load under control in approximately 2 and 3 seconds, respectively. If the participant could perform three series of twelve repetitions or more in any one session, the load was increased for the subsequent week to maintain the training stimulus. If 36 (3 series of 12) repetitions could not be achieved, the load remained the same and the aim for the following week was to achieve more repetitions than the previous week, ultimately working towards three series of twelve repetitions for each load. Participants spent the first two weeks practicing the correct technique and becoming familiarised with the movements of the exercise by using relatively low loads, before progressing towards a suitable load required to yield improvements in strength.

Isometric exercises

With the primary aim of increasing the speed of muscle response of the ankle and knee flexors, 'quasi-isometric' exercises previously applied to improve SoSG in older adults (27) were performed on the same machines as those used for the heavy resistance exercises. Patients performed three series of twelve repetitions on two different machines. On the leg extension machine, the knee was fixed at 90˚ and for each repetition, participants attempted to rapidly extend the knee, activating the knee extensors as quickly as possible, but without knee joint movement due to the immovable load. On the leg press, the ankle was fixed at a neutral angle of 90˚ between the shank and foot and participants attempted to rapidly plantar flex the ankle, activating the ankle extensors as quickly as possible, but without movement of

the ankle joint due to the immovable load. The ankle and knee extensors were activated for half a second (in the respective exercises) followed by a one second rest in between repetitions. One-minute rest was given between series of twelve repetitions.

Data analysis

The reduction in numbers for this chapter and chapter 5 are the result of a number of factors. Participants were recruited from a large geographical area around Manchester, which meant that whilst it was possible for them to attend the initial two sessions, attending training sessions once a week for 16 weeks, as well as attending a further two testing session was infeasible. Furthermore, several participants were lost to injury, typically caused by gait problems related to neuropathy.

Speed of strength generation during stair negotiation

The SoSG at the ankle and knee was measured as the rate of joint torque development (RJTD). A joint torque is the rotational force around the joint, and can both cause and control of movement at the joint.

Individual gait trials were labelled in Vicon Nexus software (Vicon, Oxford, UK) and then exported into Visual3D (C-Motion Inc, MD, USA) for further analysis. Joint torques were normalized to body mass to enable valid between-group and pre-post intervention comparisons. The RJTD of the landing leg was calculated from the gradient of the joint torque-time curve for the ankle and knee proceeding initial step

contact (9). In each stair trial, the joint torque values from each of the four step-embedded plaforms were used and the mean taken, although in some trials not all four values were available (12% of values unavailable), so as many were used as possible. Due to problems with marker visibility and force platforms, two patients within the D-CON group, and one within the D-INT group were unable to provide accurate SoSG data (Data presented for SoSG: DPN-INT: *n*=6; D-INT: *n*=9; and D-CON: *n*=4).

Muscle activation during stair negotiation

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) programme, as detailed previously (9, 22), which identified when muscles were 'switched on and off' (onset and cessation, respectively). The second stage identified muscle activation peaks of each muscle in Visual 3D, as described in detail previously (9). To enable accurate comparisons between groups, the commonly dominant peak was measured. The time to peak (TTP) was measured as the time difference between the onset of muscle activity and the peak of the muscle activation. Due to problems with obtaining muscle activation data (caused primarily by subcutaneous fat attenuating the muscle activation signal),

data could not be obtained for all participants, and only muscle activations of the patients who provided reliable data both pre and post-intervention were included in the results (DPN-INT: n=5; D-INT: n=9; and DCON: n=3).

Statistics

Pre- to post-intervention differences for all variables were tested using a repeated measures Student's t-test. Pre- and post-intervention values in the diabetes groups (D-INT and DPN-INT) were tested for differences with respect to the H-CON group using a one-way analysis of variance (ANOVA) and Bonferroni post-hoc test. Values are presented as means ± SD; significance was set at $p<0.05$.

Results

Speed of strength generation (Fig. 1 & 2)

Stair ascent (Fig. 1)

Ankle and knee SoSG were significantly higher post-intervention compared to pre-intervention in the DPN-INT and D-INT groups ($p<0.01$). The D-CON group displayed no differences pre to post-intervention.

Pre-intervention, the DPN-INT group displayed a similar ankle SoSG to the H-CON group; however, post-intervention, the DPN-INT group displayed a significantly faster SOSG than the H-CON group. Pre-intervention the D-INT group displayed a significantly slower ankle SoSG than the H-CON group. However, post-intervention, no differences between the D-INT and H-CON group were observed. Pre-intervention, SoSG at the knee in both the D-INT and DPN-INT groups was significantly slower than the H-CON group. However, post-intervention, no differences between the diabetes groups and H-CON group were observed.

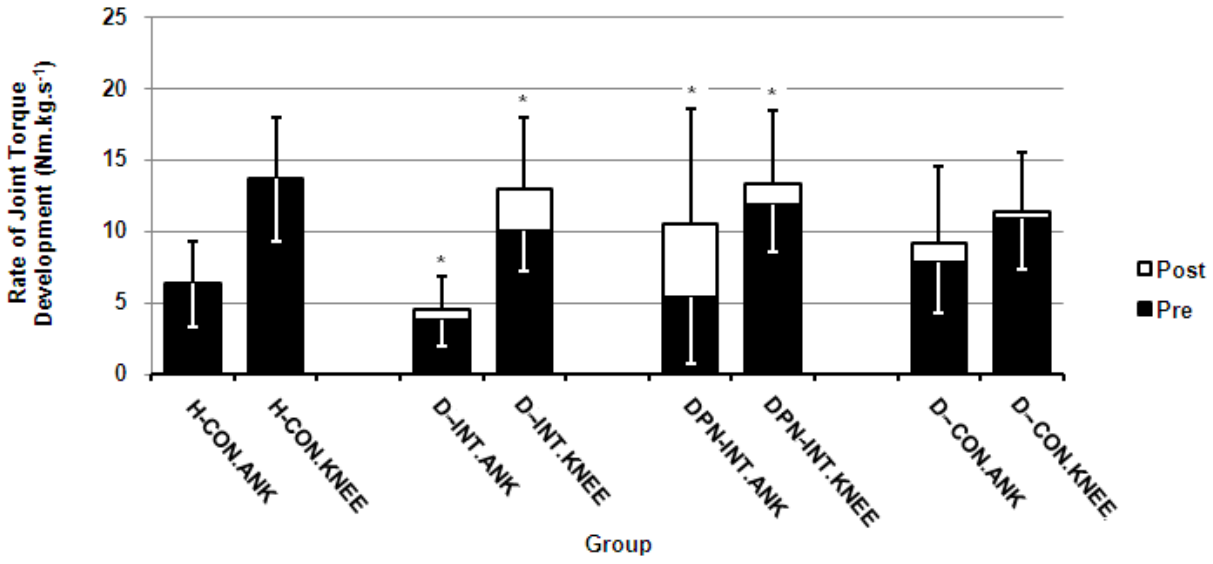

*Figure 1. Ankle (ANK) and knee (KNEE) speed of strength generation (rate of joint torque development; RJTD) during stair ascent. Values are means and SD for healthy controls (H-CON; n=21), and pre- and post-intervention results for the diabetes intervention group (D-INT; n=9), diabetic peripheral neuropathy intervention group (DPN-INT; n=6), and the diabetic control group (D-CON; n=4). Pre-intervention values are displayed as the black bars, and improvements in SoSG post-intervention are displayed as the white bar on top (all post-intervention changes were increased compared to pre-intervention). * denotes significantly different SoSG pre- to post-intervention ($p<0.05$).*

Stair descent (Fig. 2)

Ankle and knee SoSG were significantly higher post-intervention compared to pre-intervention, in the DPN-INT and D-INT groups ($p<0.01$) and the D-CON group ($p<0.05$)

Pre-intervention, SoSG at the ankle and knee in the D-INT group were significantly slower than the H-CON group, but no differences between the groups were observed post-intervention. Pre-intervention, the DPN-INT group displayed a similar SoSG at the ankle and knee to the H-CON group, but displayed a significantly higher SoSG than the H-CON group post-intervention.

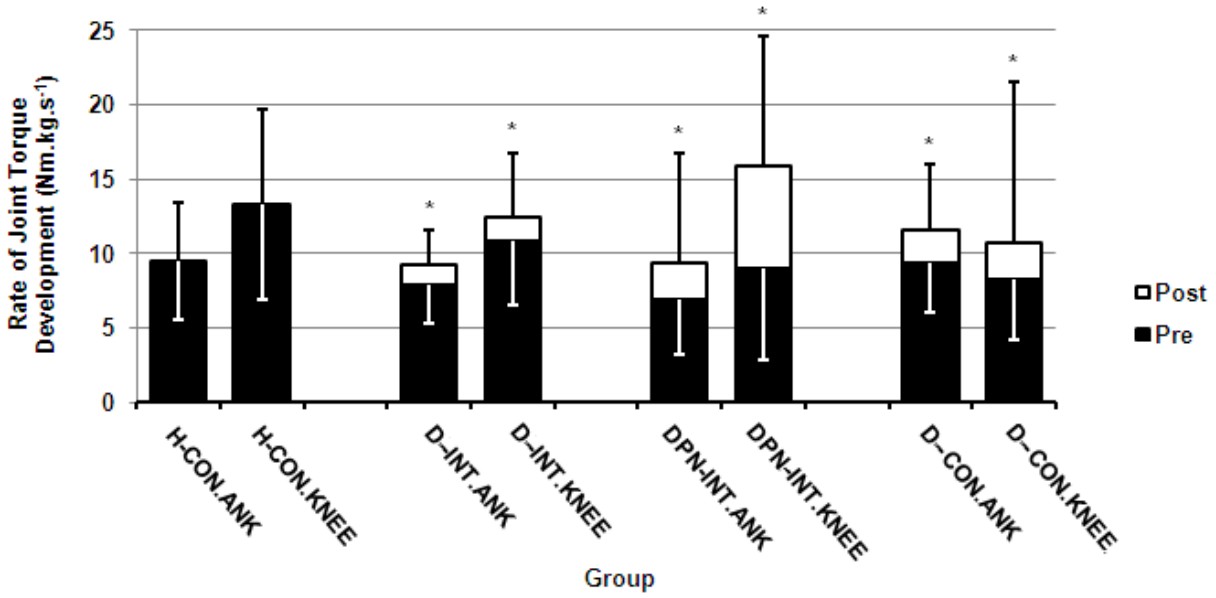

*Figure 2. Ankle (ANK) and knee (KNEE) speed of strength generation (rate of joint torque development; RJTD) during stair descent. Values are means and SD for healthy controls (H-CON, n=21), and pre- and post-intervention results for the diabetes intervention group (D-INT, n=9), diabetic peripheral neuropathy intervention group (DPN-INT, n=6), and the diabetic control group (D-CON, n=4). Pre-intervention values are displayed as the black bars, and improvements in SoSG post-intervention are displayed as the white bar on top (all post-intervention changes were increased compared to pre-intervention). * denotes significantly different SoSG pre- to post-intervention ($p<0.05$).*

Muscle activation timings (Fig. 3 & 4)

Stair ascent (Fig. 3)

The D-INT group activated the knee extensors significantly later, and displayed a slower TTP post-intervention compared to pre-intervention. The DPN-INT and D-CON group activated the ankle extensors significantly later post-intervention compared to pre-intervention, but no other changes were observed.

Stair Descent (Fig. 4)

No changes in the onset of knee or ankle muscle activations were observed in any group. The D-INT and D-CON groups displayed a longer TTP in the knee extensors post-intervention compared to pre-intervention. Pre-intervention, the D-INT TTP of the knee extensors was significantly slower compared to the H-CON group, but no differences existed post-intervention.

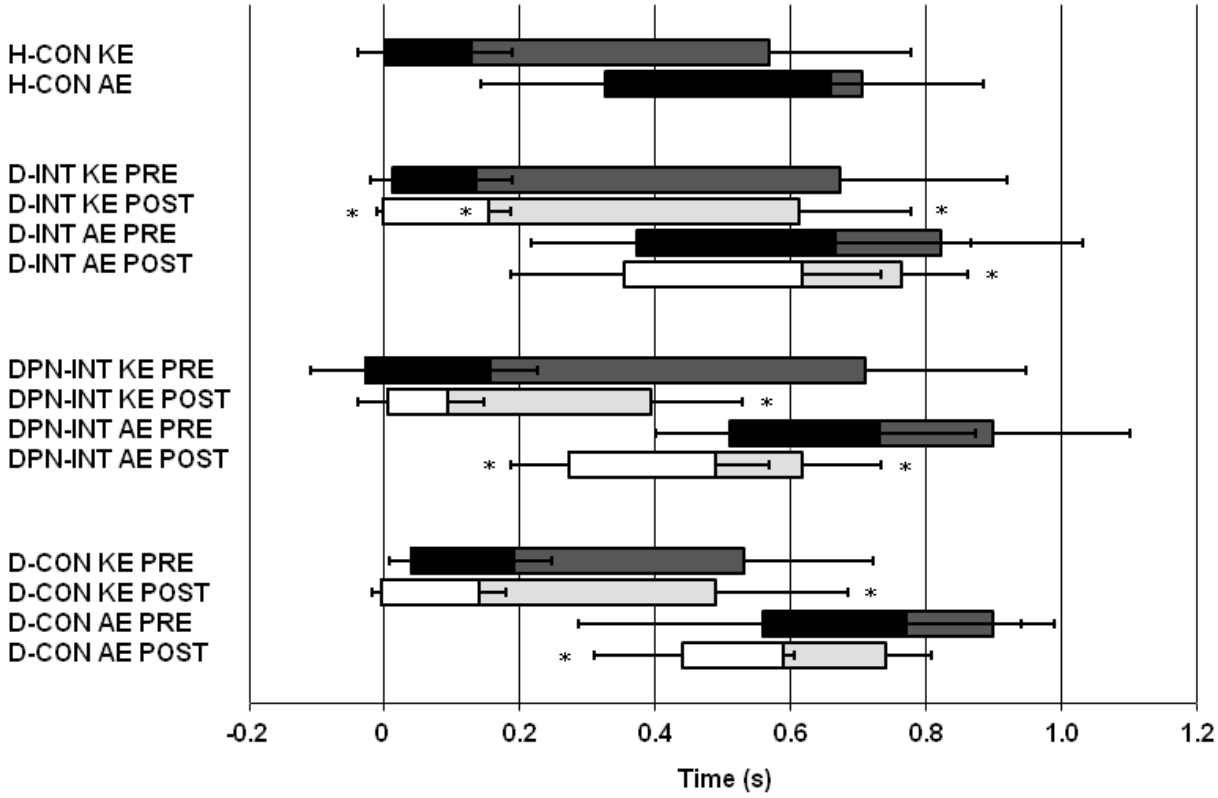

*Figure 3. Periods of activation for the knee extensor (KE; vastus lateralis) and ankle extensor (AE; medial gastrocnemius) muscles with respect to foot-step contact (occurring at time zero) during stair ascent. Values are means and SD for healthy controls (H-CON, n=21), and pre- and post-intervention results for the patients with diabetes but without neuropathy who underwent the intervention (D-INT, n=9), the patients with diabetic peripheral neuropathy who underwent the intervention (DPN-INT, n=5), and the diabetic control group (D-CON, n=3). * denotes significantly different ($p<0.05$) timing between pre- and post-intervention results. Significance is shown for onset (asterisk before bar), time to peak (asterisk after the line within the bar), and duration timings (asterisk after bar).*

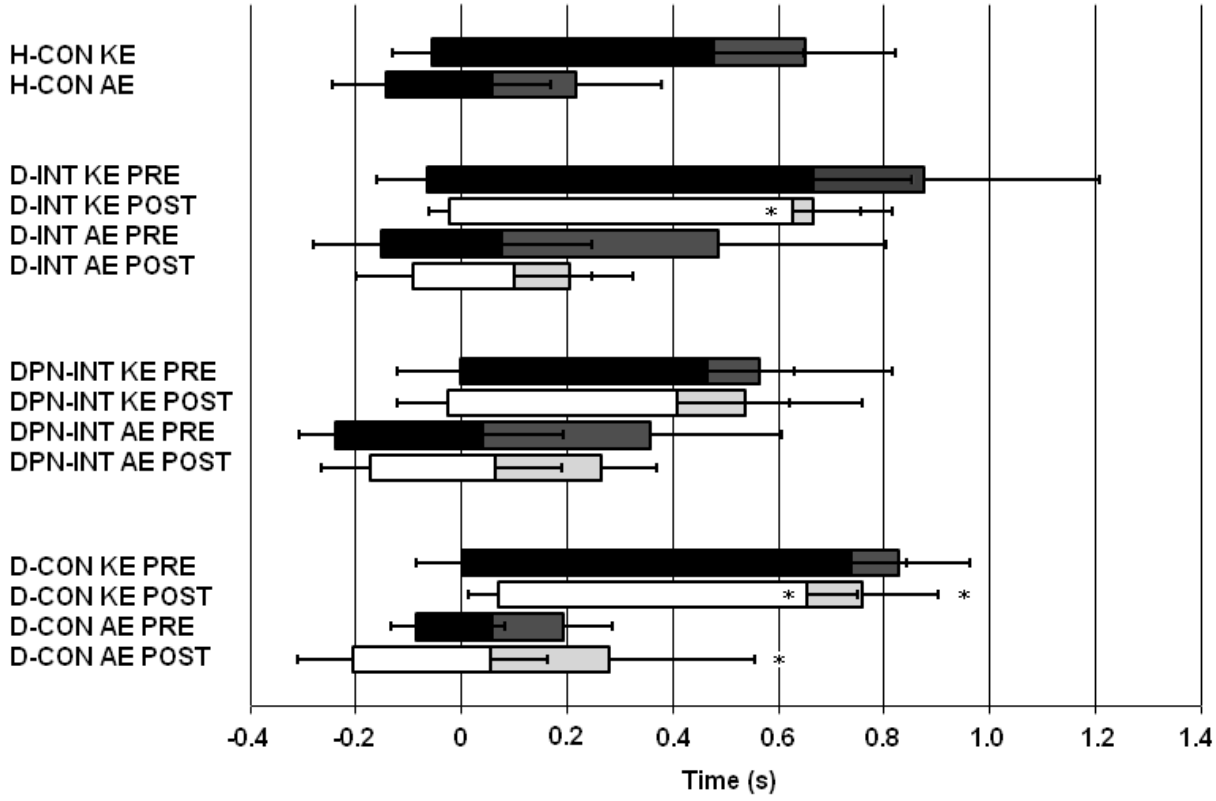

*Figure 4. Periods of activation for the knee extensor (KE; vastus lateralis) and ankle extensor (AE; medial gastrocnemius) muscles with respect to foot-step contact (occurring at time zero) during stair descent. Values are means and SD for healthy controls (H-CON, n=21), and pre- and post-intervention results for the patients with diabetes but without neuropathy who underwent the intervention (D-INT, n=9), the patients with diabetic peripheral neuropathy who underwent the intervention (DPN-INT, n=5), and the diabetic control group (D-CON, n=3). * denotes significantly different ($p<0.05$) timing between pre- and post-intervention results. Significance is shown for onset (asterisk before bar), time to peak (asterisk after the line within the bar), and duration timings (asterisk after bar).*

Discussion

This study shows for the first time how a resistance exercise training intervention can improve the speed of ankle and knee strength generation during stair ascent and descent in patients with diabetes and particularly in patients with DPN. The increased SoSG of the ankle and knee are expected to improve stability during the initial weight acceptance phase of the stair walking tasks, and ultimately contribute towards reducing the risk of falling on stairs. Patients with diabetes, and particularly those with DPN, display a slower SoSG of the knee and ankle during stair negotiation when compared to healthy controls (9). The slower SoSG was suggested to compromise stability during stair walking, and is therefore likely to be an important contributory factor to the high incidence of falls in this population. A method by which SoSG can be increased is therefore of great importance for patients with diabetes and DPN, and the exercises performed in this study successfully improved characteristics indicative of reducing the risk of falling in patients with diabetes and DPN.

Both diabetes intervention groups (D-INT and DPN-INT) displayed significantly faster ankle and knee SoSG post-intervention compared to pre-intervention, generating strength at the ankle and knee at speeds comparable to, and in some cases faster than, a healthy control group (H-CON group) following the intervention (Fig 1). The patients with DPN displayed larger improvements in SoSG as a result of the intervention compared to the diabetes group without neuropathy (D-INT) during both stair ascent and descent, increasing ankle and knee SoSG by 60% and 27%,

respectively during stair ascent (compared to 36% and 19% by the D group), and 35% and 78% (compared to 12% and 24% by the D group) during stair descent, indicating that patients with diabetic neuropathy are highly responsive to resistance exercise training.

During the weight acceptance phase of stair ascent and stair descent strength is rapidly generated to perform an absorptive action, controlling the flexion of the ankle and knee as gravity acts to 'pull' the body down onto the step. During stair descent the landing leg has to quickly stabilise before the trailing leg can move into the swing phase; whilst during ascent, the landing leg has to quickly stabilise the body before propelling it upwards. By generating joint strength quicker, the body is stabilised earlier into the stance phase allowing balance to be more optimally controlled. In the previous study (Chapter 2), I identified that the knee and ankle both performed 'absorptive' roles during ascent and descent, with one joint creating high levels of SoSG to primarily dissipate the ground impact and momentum, whilst the other joint contributed to absorption to a lesser extent and later in the stance phase (9). The DPN-INT group improved the SoSG of the primary 'absorptive' joint by 27% and 35% (the knee during ascent, and the ankle during descent, respectively), whilst the secondary 'absorptive' joint improved by 60% and 78% (the ankle during ascent, and the knee during descent). This may indicate an altered distribution of ground impact absorption, with the secondary absorptive joint playing a relatively greater role post-intervention in supporting and stabilising the body. Furthermore, despite DPN being predominantly a distal disease, similar improvements were observed at the

ankle during stair ascent and descent (35% and 60% respectively) as were observed at the knee during stair descent and ascent (27% and 78% respectively). This highlights that even distal muscles can still be markedly improved by resistance exercise training in patients with DPN.

Muscle activations were altered as a result of the intervention (Fig 2 & 3), but no clear patterns emerged which may explain the increase in SoSG (Fig. 1). Despite SoSG increasing significantly at both joints during stair ascent and descent, the TTP, previously suggested to be closely related to SoSG, varied between groups (slower TTP of the knee extensors in the D-INT and DPN-INT groups during stair descent, and quicker TTP of the knee extensors during ascent) and showed no changes in line with the increases in SoSG that were observed previously (Fig 2 & 3)(9). An increase in muscle strength as a result of the exercise intervention may therefore be the main causative factor for the faster SoSG observed at the ankle and knee, rather than increased speed of muscular activations. Whilst the TTP was unaltered by the intervention, if maximum joint moments were increased, and the time to reach this maximum was unaltered (as indicated by the unaltered TTP), the speed of strength generation would be faster, as was indeed observed. This would indicate that the improvement in strength as a result of the resistance exercise intervention performed may be the most influential factor upon improving SoSG rather than improving the speed of muscle response.

Reduced SoSG in other high-risk populations such as the elderly has been attributed to structural alterations to the muscle and neural changes (20, 29). Resistance exercise training has been identified to be the most effective method of increasing SoSG via improving neural drive and increasing muscle mass, consequently increasing SoSG during dynamic movements and during isolated strength tests (19, 20, 30, 31). In this sample of patients, the muscular adaptations are expected to be more influential than neural adaptations, with the improvements in SoSG observed in patients with diabetes and DPN expected to be predominantly caused by improvements in muscle strength rather than changes in speeds of muscle activation (29). This is a particularly pertinent finding as it may partly explain how patients with DPN can improve SoSG despite presumably irreversible neural damage.

Exercise interventions with the specific aim to improve SoSG in an elderly population have previously been suggested to be more effective at reducing the risk of falling than more generalised exercises (6), yet such studies had not previously been performed in a diabetic patient population. The present study has shown that resistance exercises are an effective way of increasing ankle and knee SoSG, which may translate to improvements in balance and safety during stair ascent and descent. Such exercises should therefore be incorporated into multi-faceted exercise interventions to improve safety in people with diabetes and DPN.

In terms of the clinical and practical implications of the intervention, the exercise session was performed by the patients just once a week and took less than one hour.

The intervention also fitted around the patient's lives, accommodating patients if they missed a session, although patients were required to attend a minimum of 10 of the 16 sessions, and to not miss more than two weeks in a row to be included in the pre-post results (participants attended ~80% of the sessions on average). Patients who missed one or two sessions displayed no decreases in strength for the following week (in terms of training load and number of repetitions performed), raising the possibility that lower limb strength levels may be maintained if the frequency of exercise is reduced to less than once a week. Patients self-reported increased activity levels, and an ability to perform everyday tasks that were previously beyond their capabilities as a result of the increased lower limb strength following the resistance exercise intervention. These self-reported observations should be taken with caution against the main scientific findings, but are in line with previous findings of increased six minute walking distance and daily step counts as a result of exercise (18). The present findings suggest that one hour of resistance exercise training per week may be an effective method of improving factors contributing to the risk of falling and may therefore translate to reducing fall risk in patients with diabetes and DPN.

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Chapter 4

Observed, or unobserved, those are the tripping hazards: Patients with diabetic peripheral neuropathy display a decreased stepping accuracy and increased toe clearance during walking

Abstract

Aims: Patients with diabetic peripheral neuropathy (DPN) are five times more likely to fall than age-matched controls, and approximately 50% of all falls are due to tripping whilst walking. This study examines characteristics of patients with DPN that may be indicative of the potential for tripping on observed and unobserved hazards.

Methods: Sixty two participants; 19 patients with DPN, 22 patients with diabetes but no neuropathy (D) and 21 healthy non-diabetic control participants (C) performed two tests. Accuracy of stepping and visual gaze parameters were measured as participants negotiated a walkway with stepping targets, and minimum toe clearance was measured during level ground walking.

Results: Patients with diabetes and DPN were significantly less accurate at stepping on targets than control participants, and displayed a higher minimum toe clearance during level ground walking ($p<0.05$). Patients with DPN also displayed an altered visual gaze strategy to control participants, however these findings are made from preliminary data from a small cohort of the participants (DPN: 4; D: 4; C: 4).

Conclusions: Patients with DPN display characteristics that indicate they are more likely to trip on observed obstacles than unobserved obstacles. A reduced stepping accuracy may lead to patients with DPN being less able to avoid observed obstacles during walking, whilst an increased toe clearance is expected to be a compensatory

mechanism to avoid obstacles. Visual gaze characteristics indicated an altered visual strategy in patients with DPN compared to controls during stepping, which together with impaired motor control may underlie the changes in stepping accuracy.

Introduction

Diabetic peripheral neuropathy (DPN) is a common complication of diabetes, characterised by sensory loss in the lower limbs, altered joint-position sensation and impaired muscular function, which can result in alterations to gait (1-4). Patients with DPN are five times more likely to fall than age-matched controls, and approximately 50% of all falls are due to tripping whilst walking (5, 6). It has been suggested that the incidence of trip related falls is determined primarily by the frequency of tripping, and not the ability to recover from a trip (7). Therefore, the most effective approach to identifying the risk of falling for a particular individual or population is to examine their ability to avoid obstacles before they become a tripping hazard (8, 9). Tripping can occur as a result of observed and unobserved hazards. When a tripping hazard is observed, the person must initiate and co-ordinate a response to avoid it. However, during level ground walking, some hazards such as an uneven surface may not be observed, and therefore fundamental characteristics of gait may increase or decrease the potential for tripping.

People with a high risk of falling have been shown to be less accurate and more variable at stepping onto defined targets (10, 11). This reduced ability to move the foot where desired may indicate an impaired control of foot trajectory, which could hinder obstacle avoidance, and ultimately increase the probability of tripping on observed hazards (8). Causes for a decreased accuracy of stepping are expected to be multi-faceted, with altered motor control and visual gaze strategies expected to be

contributory factors. Whilst visual gaze strategy has not to my knowledge been evaluated in people with diabetes, it is known that people with a high risk of falling, such as the elderly population, display differing visual gaze strategies to lower risk groups, altering where and when they look during walking (10-12). Previous studies have theorised that visual gaze strategy alters stepping accuracy through taking attention away from the combined positions of the feet and intended targets, but no universal agreement on the exact mechanisms currently exist (10, 11).

Whilst responses can be co-ordinated to avoid observed tripping hazards, the potential for tripping on unobserved hazards are dependent upon characteristics of normal gait. Minimum toe clearance is the minimum height of the toes above the ground during the mid-swing phase of gait, and is a particularly dangerous event due to the low ground clearance and high velocity of the swinging limb during this phase of gait (8). Because of this, minimum toe clearance has been reported as a potential indicator for the risk of tripping and consequential falling during walking in the elderly population (9, 13, 14). The stride-to-stride variability of minimum toe clearance has also been suggested as one of the most important indicators of tripping potential (14). Elderly participants for example, display similar average toe clearances to younger participants, but show an increased variability, which may be one of the major factors explaining an increased risk of falling in the elderly population (14). If patients display a smaller and more variable minimum toe clearance, this may therefore lead to an increased risk of tripping on unobserved hazards.

The aim of this study was to investigate the effects of DPN on stepping accuracy and minimum toe clearance during level ground walking. Furthermore, this study aimed to provide pilot observations of between-group differences in underlying visual gaze strategies, which may affect stepping accuracy. It was hypothesised that patients with DPN would display similar characteristics to other populations at a high risk of falling, displaying a decreased accuracy of stepping, and a lower and more variable minimum toe clearance. Furthermore, patients with DPN were expected to display an altered visual gaze strategy.

Methods

Participants

Sixty two participants; 19 patients with DPN, 22 patients with diabetes but no neuropathy (D) and 21 healthy non-diabetic control participants (C) matched for age and BMI (Table 1) gave their written informed consent to participate in this study, which was given ethical approval from the relevant bodies. Major exclusion criteria were open ulcers, use of walking aids, a history of other disorders affecting gait and a visual acuity <6/18 (of any aetiology, including diabetic retinopathy).

Neuropathy assessment & classification

The presence and severity of neuropathy was measured using two separate tests: the Modified Neuropathy Disability Score (mNDS)(1, 2), and the Vibration Perception Threshold (VPT)(1, 2) using a neurothesiometer (Horwell, Nottingham 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 an mNDS score of ≥6, or a VPT of ≥25 Volts (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 Volts (1, 2)(Table 1).

	C	D	DPN
Age (y)	58.7 ± 12.6	58.1 ± 14	57.7 ± 9.9
BMI ($kg.m^{-2}$)	26.1 ± 4.1	28.4 ± 3	30.2 ± 5.2
Modified neuropathy disability score	1.3 ± 1.4	1.9 ± 1.7	7.5 ± 3 *
Vibration perception threshold (v)	9.4 ± 6.0	9.9 ± 5.5	31.3 ± 9.7 *
Gait velocity ($m.s^{-1}$)	1.37 ± 0.2	1.24 ± 0.2	1.15 ± 0.3 *
Stance time (a)(s)	0.5 ± 0.13	0.48 ± 0.1	0.52 ± 0.1
Stance time (b)(s)	0.59 ± 0.12	0.43 ± 0.1 *	0.49 ± 0.1 *
Visual cycle duration (s)	0.73 ± 0.16	0.53 ± 0.1 *	0.61 ± 0.1 *

*Table 1. Participant demographics, neuropathy scores and temporal gait characteristics for the control (C), diabetes (D) and diabetic peripheral neuropathy (DPN) groups. Values are means ± SD. * denotes significantly different to the control group. Gait velocity was taken during level ground walking. Stance times were taken during the stepping accuracy task, and display results for the whole cohort of participants (a), and the subset that provided visual gaze data (b).*

Procedure

Preparation

Sixteen retro-reflective markers were attached to the participant's feet (8 on each foot) according to standard motion analysis preparation methods. Three dimensional marker positions during both walking tests described below (stepping accuracy task and level ground walking) were recorded by a ten-camera motion capture system recording at 120Hz (Vicon Nexus, Vicon, Oxford, UK). Footwear was standardised across all participants (MedSurg, Darco, Raisting, Germany).

Stepping accuracy task

Participants were asked to walk along a 7m long mat with stepping targets as previously described (15)(Fig. 1) until five trials were captured. Each participant was given the same instructions: "walk at your natural walking speed, stepping on each of the targets as accurately as possible." Participants performed five trials of which three were used for analysis. Kinematic data of foot position, and analogue data of horizontal eye movement were captured from the middle six stepping targets (R4, L4, R5, L5, R6, L6) from a total of eighteen (Fig. 1)(15). Visual gaze direction was obtained using an eye-tracking scanner (ASL 500 mobile gaze tracking system, Bedford, MA, USA) with a sampling frequency of 50Hz, which used corneal and pupil reflections to calculate eye in orbit rotation to an accuracy of one degree.

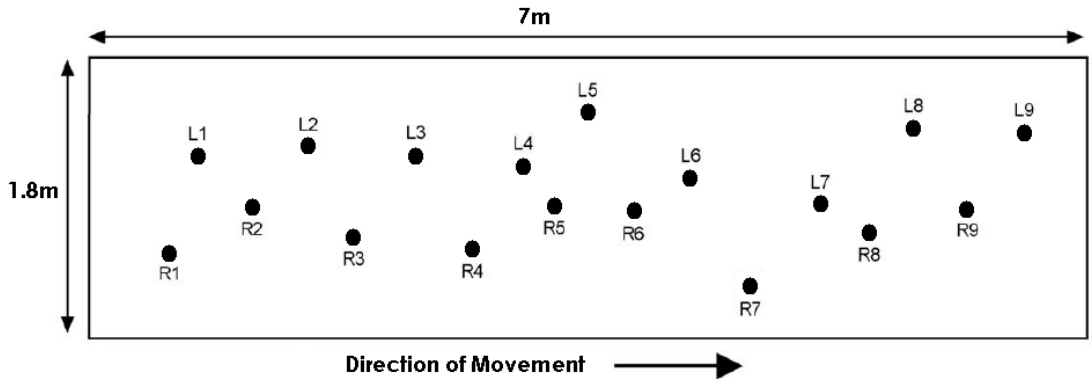

Figure 1. Diagram of the stepping walkway used for the stepping accuracy task. Targets are numbered in order of contact; with 'L' denoting left foot contact and 'R' denoting right foot contact.

Level ground walking

Participants were asked to walk freely (without any stepping targets) at their natural speed along an 8m long walkway until five trials were captured. The middle four strides (two lefts and two rights) were captured. The trajectory of the 2nd Toe marker (placed on the nail of the second phalange of both feet) was captured, and the movement in the vertical axis used for analysis.

Data analysis

Foot stepping accuracy

Thirty six (C: 10; D: 12; and DPN: 14) participants performed the stepping accuracy task. Stepping accuracy was calculated as the difference between the position of the distal aspect of the 2nd metatarsal head (2MH), with respect to the calibrated centre of the targets, at foot-ground contact (measured using the tracked marker coordinates from the motion analysis and the known position of stepping targets within the capture volume). Foot-ground contact was calculated manually as the point at which the trace of the vertical position of the foot reached a fixed minimum height. The co-ordinates of the 2MH at foot-ground contact (medio-lateral: *x* and anterior-posterior: *y*) were subtracted from the co-ordinates of the calibrated target positions to calculate the distance of the 2MH from the target. Using the square root of the two squared distances (*x* and *y*), the hypotenuse of the triangle, the absolute distance between the target and the 2MH, was calculated.

Visual acquisition parameters

Data from twelve participants (C: 4; D: 4; and DPN: 4 [216 saccades analyzed in total: 18 saccades per participant]) were used for analysis of visual acquisition. Data were obtained from a sub-sample of the cohort due to the time-consuming nature of these measurements precluding assessment in all participants; non-spherical corneal shape as the result of surgery in some participants and eyelashes covering the eyes during the tests. Because of the small cohort of participants, the results are presented as preliminary pilot data.

Two points in the horizontal signal of the eye movement trace were identified: the initial visual acquisition of the target (start of visual acquisition), and the point at which gaze was subsequently directed away from the target (visual acquisition end). These events were identified using the second derivative of the eye position signal, i.e. the eye acceleration peak at saccade onset. By using the timing of when each individual target was visually acquired, and when gaze was subsequently directed away, four separate variables were obtained: the time between visual acquisition of the target and foot-target contact; the time between the subsequent saccade away from the target with respect to foot-target contact; the time spent looking at the target (fixation duration); and the time taken to transfer gaze between targets.

Minimum toe clearance

Fifty nine (C: 18; D: 22; and DPN: 19) participants performed the level walking task to obtain minimum toe clearances. Using a bespoke script in Visual3D motion analysis

software (C-Motion Inc, MD, USA), the minimum toe clearance of the second toe was calculated as the lowest point occurring during the swing phase in the trace of the second toe in the vertical axis (9). One minimum toe clearance value was taken from each of the three trials, per participant.

Statistics

Group differences were tested using a one-way analysis of variance (ANOVA) with a Bonferroni post-hoc test, and all significances reported with respect to the control group. Values are presented as means ± SD; significance was set at $p<0.05$. The level of agreement between stance time during the stepping task and visual gaze cycle time was tested using a Pearson's correlation.

Results

Stepping accuracy (Fig. 2)

Patients with diabetes (both D and DPN groups) were less accurate at stepping, and contacted the ground significantly further away from the centre of the target than the C group.

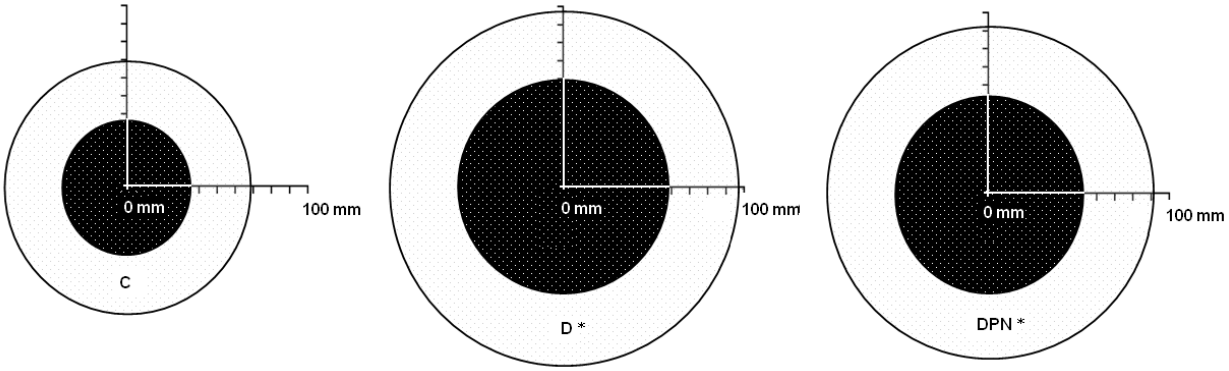

*Figure 2. Group differences in stepping accuracy for controls (C; n=10), patients with diabetes but no neuropathy (D; n=12), and patients with diabetic peripheral neuropathy (DPN; n=14). The black inner circle denotes the mean distance from the centre of the target (0), and the white outer circle denotes the standard deviation. * denotes significantly different group mean accuracy compared to the control group ($p<0.05$).*

Visual acquisition parameters (Fig. 3a & 3b)

In absolute time, patients with DPN visually acquired the targets significantly later, remained looking at the targets until significantly later, and spent significantly less time in total looking at the targets than a control population. The DPN patients also took significantly longer to look between one target and the next. The D group acquired targets significantly later than the control group, but no other changes were observed (Fig. 3a).

Markedly different stance times were observed in the cohort providing visual gaze data (Table 1; stance time (b)), and it was anticipated this may impact on the interpretation of visual gaze results presented in absolute time. Visual cycle duration correlated very highly with stance time of these participants ($r = 0.99$; Table 1.). Therefore, the results have also been presented as a percentage of the visual gaze cycle, to elucidate the visual gaze strategy independent of differences in stance time.

When presented as a percentage of the visual gaze cycle, patients with DPN visually acquired the targets significantly later, and remained looking at the targets until significantly later compared to the control group. The D group also looked away from targets significantly later than the control group, and both D and DPN groups spent significantly less time looking at the target and took significantly longer to look between targets ($p<0.05$) compared to healthy controls (Fig. 3b).

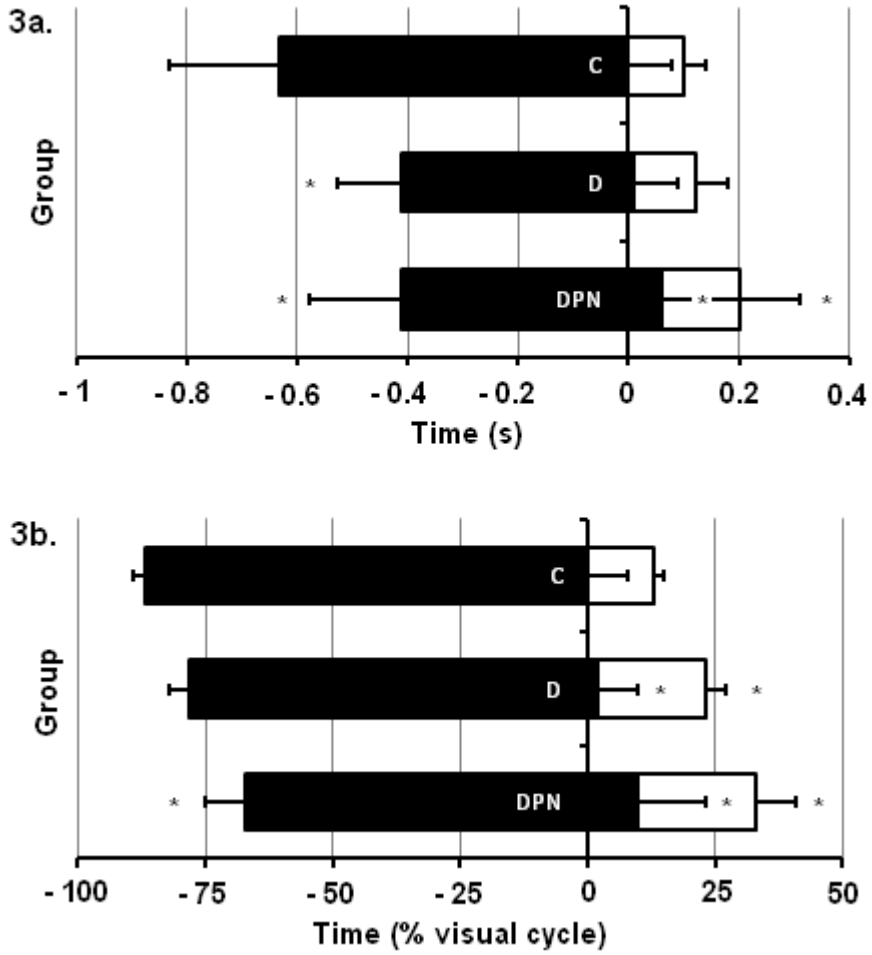

*Figure 3. Target visual acquisition parameters during the stepping task for controls (C; n=4), patients with diabetes but no neuropathy (D; n=4), and patients with diabetic peripheral neuropathy (DPN; n=4). Values are means and standard deviations. 3a displays the results in absolute time and 3b displays the results as a percentage of the entire visual gaze cycle. The black bars denote visual fixation of the target, and the white bars denote the time looking between targets, with the end of the white bar denoting the acquisition of the next target. * denotes significantly different compared to control group ($p<0.05$).*

Minimum toe clearance (Fig. 4)

Patients with diabetes, both with and without neuropathy, displayed a significantly higher minimum toe clearance than the control population during walking. No significant differences in the intra-participant variability of minimum toe clearance were observed between groups.

The minimum toe clearance values may be considered relatively high, but it should be noted that the values presented here include the addition of the toe depth and shoe bed (which is thick by standard shoe dimensions). These factors have therefore contributed to yielding higher toe clearance values than if the participant was barefoot.

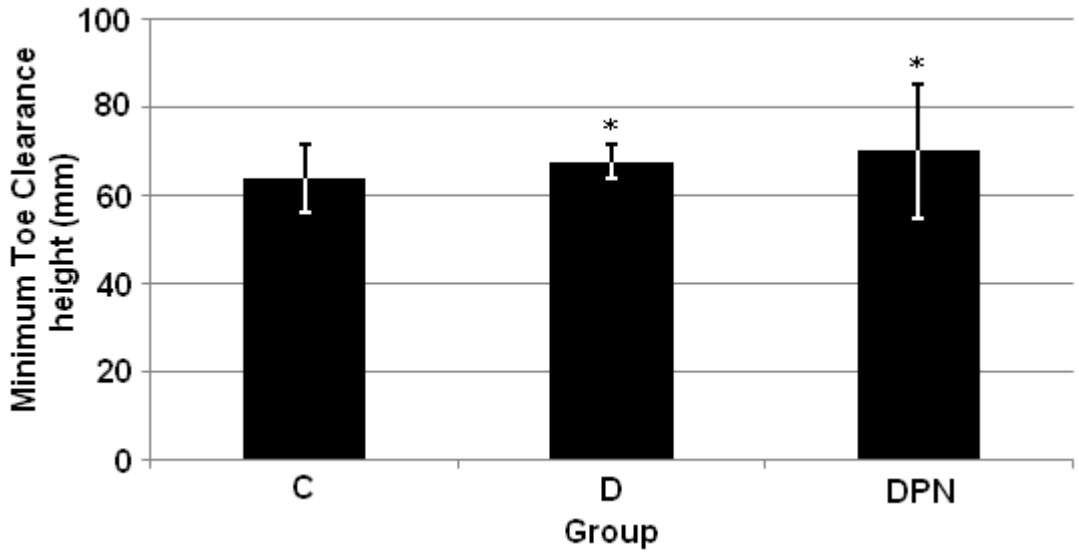

*Figure 4. Minimum toe clearance height for controls (C; n=18), patients with diabetes but no neuropathy (D; n=22), and patients with diabetic peripheral neuropathy (DPN; n=19). Values are means and standard deviations. * denotes significantly different compared to control group (p<0.05).*

Discussion

Patients with diabetes and diabetic peripheral neuropathy (DPN) display gait characteristics that may be indicative of a reduced ability to avoid observed obstacles, but may reduce the risk of tripping on unobserved obstacles. Therefore, larger, more observable, obstacles may be a greater risk to patients with DPN than smaller, less observable hazards such as subtle changes in flooring.

Patients with diabetes and DPN were less accurate at stepping, which may indicate an impaired ability to avoid any potential upcoming obstacles during walking. These preliminary data indicated an altered visual gaze strategy in patients with DPN, which along with impaired motor control, may be an underlying reason for the decreased stepping accuracy. Patients with diabetes without neuropathy also displayed an altered visual gaze strategy, although to a lesser extent than in patients with DPN. This may indicate early adaptations of altered visual gaze and motor control strategies before peripheral neuropathy can be quantified using standard clinical assessments. During level ground walking, patients with DPN displayed higher minimum toe clearances, whilst displaying a similar intra-participant variability to control participants (Fig. 4). An increased minimum toe clearance may in fact be regarded as a safer gait pattern in DPN patients, and is likely a compensatory strategy to lift the toes above any unobserved tripping hazards when walking, therefore reducing the risk of tripping. Although differences in the visual gaze strategy

were clearly evident between groups, these data are considered as preliminary findings due to the small cohorts for this parameter.

The reasons for the decreased stepping accuracy observed in patients with DPN are expected to be multi-faceted, with reduced motor control and altered visual gaze patterns expected to be major contributory factors. The reasons for decreased stepping accuracy in other high fall risk groups have been typically explained by altered visual gaze patterns. Yamada *et al.* identified that the elderly patients' fixation on imminent targets hindered their ability to plan footfall for future targets (10), whilst conversely, Chapman & Hollands concluded that the planning of future movements affected the accuracy of ongoing movements (11). In the present study, patients with DPN displayed a 'hesitant' visual gaze strategy, by continuing to look at targets until after foot-target contact, before re-directing gaze to the next target, possibly in an attempt to ensure foot-target contact (Fig 3a & 3b)(16). This contrasts with the 'confident' visual gaze strategy observed in the C group, who re-directed gaze away to the next target immediately upon foot-step contact, indicating a confidence in their ability to step accurately. Patients with DPN also displayed an increased time interval to look between targets. The combination of looking away from the target later, and taking longer to look between targets, may therefore explain why patients with DPN are slower to initially visually acquire the target, resulting in a decreased total time spent looking at the target. The decreased time available to look at the target during the approach may have hindered co-ordination of an appropriate motor response,

contributing to altered swing trajectories of the lower limbs, and ultimately resulting in a reduced stepping accuracy.

Diabetic controls were even slightly less accurate at stepping than patients with DPN, which is suggested to be due to a less effective specific aspect of the visual gaze strategy than DPN patients. This visual gaze strategy in diabetic controls (looking away from the target sooner after foot-target contact than DPN patients) could perhaps be regarded as an 'over-confident' strategy that seems to have adversely affected their stepping accuracy, since this was significantly worse than in healthy controls, and even slightly less accurate than DPN patients. This may further indicate that diabetic controls displayed some of the altered motor control characteristics of patients with DPN before sensory neuropathy is clinically observed, and before this population are aware of their decreased ability to control trajectory of the swinging leg. The combination of an 'over-confident' visual gaze strategy and altered motor control of the lower limbs may therefore explain the poor accuracy of stepping in this diabetic control population.

Impaired lower limb motor control, likely caused by neural and muscular alterations is also expected to contribute to the reduced stepping accuracy observed in both diabetes groups. Patients with DPN display a reduced nerve conduction velocity, reducing the speed at which movements can be co-ordinated and performed (17, 18). Furthermore, they have a reduced range of movement, decreased strength, and a decreased ability to rapidly develop strength when required (19-21). Whilst these

factors have been observed to affect certain gait characteristics (stride length, cadence and velocity), it is expected that these mechanisms are also important factors for lower limb motor control. The combination of impaired motor control and altered visual gaze strategy are expected to be major factors in reducing stepping accuracy in patients with diabetes, and particularly DPN.

In contrast to the initial hypothesis, patients with DPN displayed larger toe clearances than controls during walking (Fig. 4). When people from the general population are unsure of foot position, such as when carrying a laundry basket, gait velocity is reduced, stride width is increased, and toe clearances are increased (22). Furthermore, when obstacles are present, but not observable, minimum toe clearance has been shown to increase (23). Patients with DPN may therefore employ larger toe clearances as a compensatory mechanism, anticipating potential upcoming obstacles that they may not visually identify. Further explanations may be a flatter trajectory of the foot during gait (i.e., foot remains more parallel to the ground), due to the hip-strategy commonly employed by patients with neuropathy, and the smaller range of movement observed at the knee and ankle joints (24-26). This ‘natural strategy’ may in fact be the safest for DPN patients, allowing a greater chance of avoiding a low tripping obstacle. Variability of toe clearances has been identified as a predominant indicator of tripping potential (14). Patients with DPN however displayed similar intra-participant variability of toe clearances during walking. Therefore, the primary causative factor for tripping during level ground walking may be the

combination of altered visual gaze and motor control strategies rather than an increased variability in toe clearances.

To reduce the potential for tripping in patients with diabetes and DPN, an intervention that aims to modify visual gaze strategy and motor control may improve the ability to observe upcoming obstacles and increase the accuracy of stepping. Previous studies in other (non-diabetic) populations have shown that balance can be improved and visual gaze strategy can be altered using such training, which could improve safety (15, 27). Furthermore, a resistance exercise training-based element may improve control of the foot and ankle during walking, and improve avoidance of any tripping hazards.

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Chapter 5

Walk this way: Effects of resistance exercise and visual gaze training on stepping accuracy in patients with diabetic peripheral neuropathy - implications for the risk of trip-related falls

Abstract

Introduction: Patients with diabetes and diabetic peripheral neuropathy (DPN) are less accurate at stepping than age-matched controls, which may hinder their ability to avoid potential tripping hazards. This study examines the effects of a multi-faceted exercise intervention on stepping accuracy in patients with diabetes and DPN.

Methods: Forty participants; 10 patients with DPN, 20 patients with diabetes but no neuropathy (D) and 10 healthy controls (H-CON) took part in the study. Accuracy of stepping was measured pre- and post-intervention as participants walked along an irregularly arranged stepping walkway. Participants in the intervention group attended a one-hour session, once a week, for sixteen weeks, involving high-load resistance exercise and visual-motor training.

Results: Patients who took part in the intervention significantly improved stepping accuracy ($p<0.05$). The diabetic control group did not display any significant differences in stepping accuracy pre- to post- the intervention period.

Discussion: The improved stepping accuracy observed in patients with diabetes and DPN as a result of the intervention is expected to translate to an improved ability to co-ordinate the appropriate response to avoid a potential tripping hazard. The improvements in stepping accuracy are expected to be the result of improvements in motor control and visual gaze strategy. A multi-faceted intervention such as the one

performed in this study could be incorporated into a clinical treatment programme to improve the general health and safety of patients with diabetes.

Introduction

Patients with diabetic peripheral neuropathy (DPN) are five times more likely to fall than age-matched controls, and approximately fifty percent of all falls are due to tripping whilst walking (1,2). Falling can result in serious injury, and in extreme cases even death (3,4). Further to the physical consequences of falling, is the considerable economic burden to national health bodies. Therefore, a means by which the number of falls in this population can be reduced is of great interest, not only to patients with DPN, but also to national health authorities, employers and the general population.

The frequency of tripping has been shown to be a major contributory factor to the probability of falling (5,6). Therefore, if the frequency of tripping can be reduced, then theoretically, so will the risk of falling. A key approach to reducing the risk of tripping is to improve a patient's ability to avoid obstacles before they become a tripping hazard. In the previous chapter I investigated two different aspects of gait in diabetes patients, which were suggested to relate to the risk of tripping on observed and unobserved obstacles (Chapter 4). Whilst it was found that patients with DPN displayed an increased minimum toe clearance, which would reduce the risk of tripping on smaller, unobserved hazards; stepping accuracy was decreased, which is indicative of a reduced ability to avoid observed obstacles. This impaired ability to move the foot where desired is thought to be caused by decreased motor control of the lower limbs and an altered visual gaze strategy. Therefore it was hypothesised that if the motor control and visual gaze strategies can be altered to resemble those

employed by the non-diabetic healthy population, stepping accuracy may therefore be consequently improved.

Resistance training to increase lower limb muscle strength is expected to improve motor control, and therefore increase the accuracy of stepping (6-10). Previous studies in diabetes patients have shown that resistance and balance training can improve gait speed, muscle strength, postural sway, joint strength and activity levels (11-13), but no studies have yet looked at the effects on stepping accuracy in diabetes patients. Furthermore, patients with cerebellar and vestibular dysfunction and healthy young adults have displayed improvements in gait velocity, postural stability and stepping accuracy in response to visual gaze-based training (14-16). Therefore, it is hypothesised that the combination of such training programmes (resistance exercise and visual gaze training) may be beneficial for stepping accuracy in patients with DPN. This study therefore examines the effects of a multi-factorial intervention on stepping accuracy in patients with diabetes, both with and without DPN. Resistance-based exercises were performed to increase ankle and knee extensor strength, with the aim to improve motor control of the lower limbs and consequently improving the accuracy of foot swing trajectories during stepping. Visual gaze exercises were performed with the aim to alter visual gaze strategy, teaching patients to visually plan their stepping route before walking, with the aim to encourage patients to use vision more for ‘feedforward’ planning, as well as their current use for ‘feedback’ of foot position (6). It is hypothesised that such exercises

will improve the use of vision during walking, and motor control of the lower limbs, leading to an increased stepping accuracy.

Methods

Participants

Forty participants: 10 patients with DPN (Age: 56.8 ± 9.6 years; and BMI: 28.9 ± 4.6 $kg.m^{-1}$; mean ± SD), 20 patients with diabetes but no neuropathy [D](Age: 58.9 ± 11.7 years; and BMI: 27.2 ± 3.8 $kg.m^{-1}$) and 10 healthy controls [H-CON](Age: 66.3 ± 11.5 years; and BMI: 25.1 ± 3.1 $kg.m^{-1}$) gave their written informed consent to participate in this study, which was given ethical approval from the relevant bodies. A healthy control group was included to provide a reference condition, displaying 'optimal' performance, providing a comparison to pre- and post-intervention characteristics of patients with diabetes. 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 & classification

The presence and severity of neuropathy was measured using two separate tests: the modified Neuropathy Disability Score (mNDS) (17,18), and the Vibration Perception Threshold (VPT) (17,18) using a neurothesiometer (Horwell, Nottingham 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 an 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 (17,18).

Pre- and post-testing procedures

Sixteen retro-reflective markers were attached to the participant's feet (8 on each foot) according to standard motion analysis preparation methods. Three-dimensional marker positions were then tracked during the stepping accuracy task described below, by a ten-camera motion capture system recording at 120Hz (Vicon Nexus, Vicon, Oxford, UK). 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.

Participants were asked to walk along a 7m long mat with stepping targets designed to specifications previously described by Marple-Horvat & Crowdy (19)(Fig. 1) until five trials were captured. Each participant was given the same instructions: "walk at your natural walking speed, stepping on each of the targets as accurately as possible." Participants performed five trials of which three were used for analysis. Kinematic data of foot position were captured from the middle six stepping targets from a total of eighteen (R4, L4, R5, L5, R6, L6)(19)(Fig. 1).

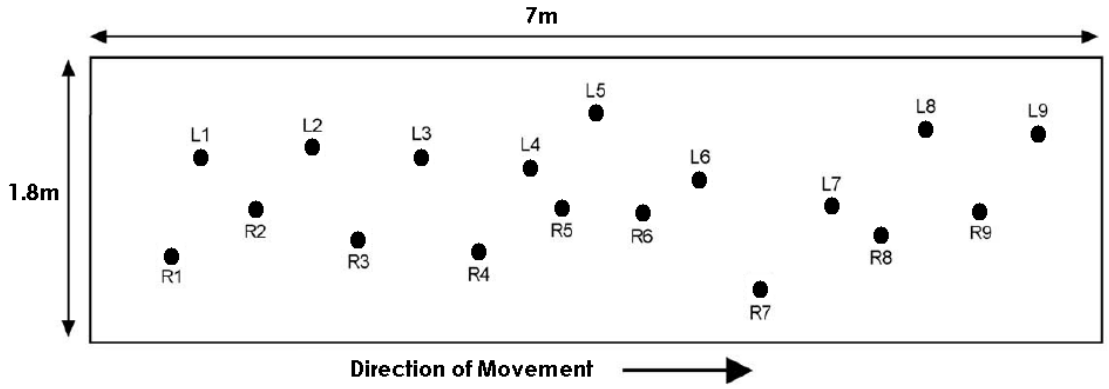

Figure 1. Diagram of the stepping walkway used for the stepping accuracy task. Targets are numbered in order of contact; with 'L' denoting left foot contact and 'R' denoting right foot contact.

Multi-factorial intervention

Diabetes patients were randomly allocated into either the intervention group or a control group (who did not take part in the resistance exercise training) using a random number generator, with an expected weighting of 2:1 into the intervention and control groups, respectively. Twenty four participants were allocated into the intervention group (D-INT, *n*=17; and DPN-INT, n=7), and seven (D: *n*=4; DPN: *n*=3) were allocated into the control group. Due to the relatively small number of patients within the diabetes control group, data from D and DPN patients were grouped together and presented as a single diabetic control group (D-CON; *n*=7). Sample size was considered sufficient to analyse the intervention group data separately as D and DPN groups (D-INT and DPN-INT). To determine the adequacy of the group samples in the present study, the statistical power to detect pre-to-post intervention differences in stepping accuracy were tested for the DPN-INT group post-hoc (*n*=7). The statistical power was found to be 0.81, indicating the study was well powered to identify true differences with these specific parameters.

Patients in the intervention group attended a weekly, one-hour session, at a private gym within the research institute (used for research purposes only), for a 16-week period. Within this session, a series of resistance training exercises and visual gaze training strategies were performed (see relevant sections below for further details) with the aim to improve the visual and motor limitations previously observed in patients with diabetes and DPN (Chapter 4). During the intervention sessions, participants wore un-restrictive clothes and their own footwear. After the 16-week

intervention period, patients in both control and intervention groups repeated the stepping accuracy task as described above. The post-intervention test took place within one month of the last intervention session.

Visual gaze and motor control training

A visual gaze and motor control training task was performed in which participants negotiated a small stepping walkway, comprised of six stepping targets. The arrangement of these stepping targets was randomised each week to avoid any learning of the stepping pattern, but was in principal similar to the stepping walkway used pre- and post-testing described above (irregularly placed targets, with steps of different lengths). Patients walked in both directions on the walkway used during the intervention, to reduce any learning effects of the stepping pattern. Before participants began each walkway negotiation and while standing at the start, they were instructed to trace their upcoming walk with their eyes three times before they actually walked through the stepping task. This was performed in an effort to improve visual gaze strategy by encouraging patients to look at targets in advance of stepping onto them, promoting optimal use of a 'feedforward' strategy of visually planning their route. The stepping task (with the necessary visual trace) and walk were performed five times in each direction.

Resistance exercise training

Resistance exercise training sessions were always closely supervised by the lead researcher. Participants were taught how to use the resistance machines and

perform the exercises safely and with the correct technique. Participants spent the first two weeks practicing the correct technique and becoming familiarised with the movements of the exercise by using relatively low loads, before progressing towards a suitable load required to yield improvements in strength. In the first session following the initial two-week period, patients gradually increased the load until it was sufficiently challenging to perform no more than ten repetitions. One repetition consisted of lifting and lowering the load under control in approximately 2 and 3 seconds, respectively. In the following fourteen weeks, patients were asked to perform three sets of up to twelve repetitions on three different machines; a leg extension (extending the knee from 90˚ to 0˚ flexion to lift the load and flexing to lower under control), a leg press (extending the ankle, knee and hip from a flexed position [knee at >90˚] to a more extended position [knee ending close to full extension] and returning while lowering the load under control), and an ankle press (plantar flexing the ankle from a dorsi flexed angle and returning to lower the load under control). If the participants could perform three sets of twelve repetitions or more in any one session, the load was increased for the subsequent week to maintain the training stimulus. If 36 (3 x 12) repetitions could not be achieved, the load remained the same and the aim for the following week was to achieve more repetitions than the previous week, ultimately working towards three times twelve repetitions for each load.

Data analysis

Foot stepping accuracy

Twenty nine participants (DPN-INT: 5 [mean ± SD age: 58.8 ± 10.2 years; BMI: 26.8 ± 2.9 $kg.m^{-1}$]; D-INT: 8 [age: 63.4 ± 9.8 years; BMI: 29.4 ± 3.2 $kg.m^{-1}$]; D-CON: 6 [age: 54.5 ± 7.8 years; BMI: 28.2 ± 5.6 $kg.m^{-1}$] and H-CON: 10 [age: 66.3 ± 11.5 years; BMI: 25.1 ± 3.1 $kg.m^{-1}$]) performed the stepping accuracy task, pre- and post-intervention. Eleven participants from the intervention groups (D: 9; and DPN: 2) were tested pre-intervention but withdrew from the process during the intervention period because of reasons unrelated to the study. Stepping accuracy was calculated as the difference between the position of the distal aspect of the 2nd metatarsal head (2MH), with respect to the calibrated centre of the targets, at foot-ground contact (measured using the tracked marker coordinates from the motion analysis and the known position of stepping targets within the capture volume). Foot-ground contact was calculated manually as the point at which the trace of the vertical position of the foot reached a fixed minimum height. The co-ordinates of the 2MH at foot-ground contact (medio-lateral: *x* and anterior-posterior: *y*) were subtracted from the co-ordinates of the calibrated target positions to calculate the distance of the 2MH from the target. Using the square root of the two squared distances (*x* and *y*), the hypotenuse of the triangle, the absolute distance between the target and the 2MH, was calculated.

Statistics

All statistical tests were performed on SPSS statistical package (SPSS v18, Chicago, Illinois) with significance set at $p<0.05$. Pre- to post-intervention differences were statistically tested using a repeated measures Student's *t*-test. Between group differences were performed using a one-way ANOVA, with a Bonferoni post-hoc test, with significances reported with respect to the H-CON group. Values are presented as means ± SD.

Results

Neuropathy scores

Patients within the DPN-INT group displayed significantly higher mNDS (DPN-INT: 6.2 ± 2.6; D-INT: 2.4 ± 2.1; D-CON: 4.8 ± 4.5; and H-CON: 2.0 ± 1.4; $p<0.05$) scores than the D-INT and H-CON groups, and significantly higher VPT (DPN-INT: 31.0 ± 5.9 V; D-INT: 8.5 ± 2.7 V; D-CON: 11.8 ± 6.0 V; and H-CON: 11.9 ± 7.0 V; $p<0.05$) scores than the D-INT, D-CON and H-CON groups.

Stepping accuracy (Fig. 2)

Patients within the DPN-INT and D-INT groups were significantly more accurate at stepping post-intervention compared to pre-intervention, contacting the ground significantly closer to the centre of the target (pre- *vs* post-Intervention – DPN-INT: 57 ± 33 *vs* 31 ± 15 mm [45% increase in accuracy]; and D-INT: 64 ± 29 *vs* 41 ± 14 mm [36% increase in accuracy]). In contrast, the stepping accuracy of the D-CON group was unchanged pre- to post-intervention (pre- *vs* post-Intervention – D-CON: 33 ± 9 *vs* 35 ± 7 mm [7% decrease in accuracy]; $p>0.05$).

Pre-intervention, the DPN-INT and D-INT groups were significantly less accurate at stepping than the H-CON group ($p<0.05$), whereas the D-CON group displayed a similar level of stepping accuracy (DPN-INT: 57 ± 33; D-INT: 59 ± 28; D-CON: 33 ± 9; and H-CON: 38 ± 31 mm). Post-intervention, no differences in stepping accuracy

were observed between the groups (DPN-INT: 31 ± 22 mm D-INT: 41 ± 24mm; D-CON: 35 ± 20 mm; and H-CON: 38 ± 31 mm; $p>0.05$).

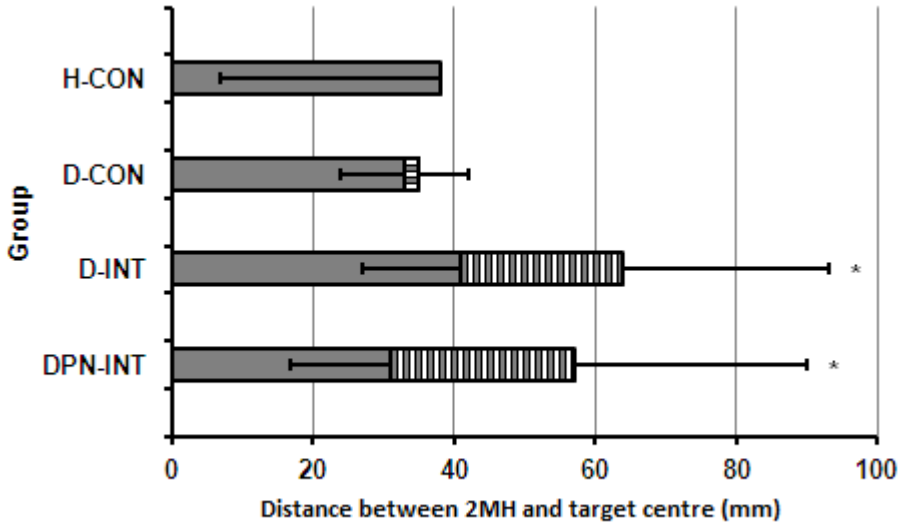

*Figure 2. Pre- and Post-intervention results for stepping accuracy (distance between 2MH and the target centre) for diabetic controls (D-CON; n=6), diabetic intervention (D-INT; n=8), and diabetic peripheral neuropathy intervention (DPN-INT; n=5) groups. The H-CON bar shows the results without any intervention for the healthy control group (H-CON; n=10) as a reference for comparison against the diabetes groups. For the D-CON bar, the grey section shows the pre-intervention results, and the additional horizontal striped section shows the increase in distance (i.e., reduced accuracy post-intervention) post-intervention. For the D-INT and DPN-INT bars, the grey bar shows the post-intervention distance, and the vertical striped bar in addition to the grey bar shows the pre-intervention distance (i.e., improved accuracy post-intervention). Values are mean distances and SD; * denotes significantly different distance post-intervention compared to pre-intervention ($p<0.05$).*

Discussion

This study shows for the first time that resistance exercise and visual gaze training can increase stepping accuracy during walking in patients with diabetes and DPN. This is expected to translate to an improved ability for patients with diabetes, and particularly DPN, to avoid observed obstacles during walking, and may result in a reduced risk of tripping and subsequent falling, in this population.

Accurate stepping is dependent upon the combined use of vision and motor control, to visually identify the intended position of future foot placement, and subsequently control the swing trajectory of the lower limb. Motor control of the lower limbs is highly affected by neuropathic damage, as DPN affects not only cutaneous sensation and muscle response, but also proprioception of lower limb position, often resulting in a reduced postural stability (20, 21). Patients with DPN, as a result of decreased proprioception, also display a decreased sense of joint position, which is therefore likely to impact upon knowledge of lower limb position and orientation during stepping, as well as the swing limb velocity (20). Another important element of motor control is the ability to accurately and consistently develop an appropriate level of muscle force, to control joint movement. Whilst no research into the effects of diabetes or DPN on muscle force steadiness has yet been performed, older adults, another population at a high risk of falling, are less steady during submaximal isometric contractions (22). This is particularly important during the swing phase of stepping where ankle and knee joint moments are very low compared to during the

stance phase of gait (23). Furthermore, variability in lower limb motor performance during low and medium effort tasks is exacerbated by increased cognitive demand (24). The stepping task is likely to increase cognitive demand and is expected to notably affect patients with DPN, who use vision for both 'feed-forward' planning, as well as feedback of foot position, during walking. Furthermore, in the event of a potential tripping hazard being presented, cognitive demand would rapidly increase, which may therefore affect lower limb performance and subsequent ability to perform an avoidance strategy.

Strength training has previously been shown to improve force accuracy and steadiness in elderly patients, increasing maximal strength as well as control of submaximal strength (25). It also reduces force fluctuations, which are expected to improve force steadiness and consequential motor control (26). It is therefore expected that as well as increasing maximal strength of the ankle and knee flexors, the resistance training exercises may have improved force steadiness and increased the control of submaximal muscle force during dynamic tasks, resulting in an improved control of joint position and lower limb orientation.

In addition to improvements to motor control, visual gaze strategy is also expected to have been altered by the visual gaze training task. Previous studies have shown positive responses to visuomotor training by improving postural stability, dynamic visual acuity, and stepping accuracy in both healthy young and elderly populations (14, 16, 19, 27). The visual gaze training task performed over the 16-week

intervention in the present study required participants to visually map the route before stepping onto the irregularly placed stepping targets. This was expected to encourage a 'feed-forward' planning of the stepping route, which during walking would cause patients to continuously survey the upcoming environment, allowing patients to observe and subsequently avoid potential tripping hazards. This would allow participants to consider the location of upcoming targets as well as the next immediate target, allowing more time to co-ordinate appropriate responses for the future (28). Using the same methods as those presented in Chapter 4, the effects of the visual gaze intervention on visual gaze parameters were measured in a subset of intervention patients (*n*=3; D-INT=2 and DPN-INT=1), who improved stepping accuracy by a mean average of 173%. Visual gaze timings were altered as a result of the intervention, with patients looking away to the subsequent target earlier, and taking less time to look between targets, consequently resulting in patients acquiring the next target earlier (Fig. 3). These visual gaze characteristics indicate that patients were able to spend longer assessing the target position on approach, and may at least in part, have contributed to the improved stepping accuracy observed. These are, however, only preliminary observations in a small sample size, but the consistent and clear direction of the changes at least provide some insight into the potential mechanism for the improved stepping accuracy and a stimulus for further research.

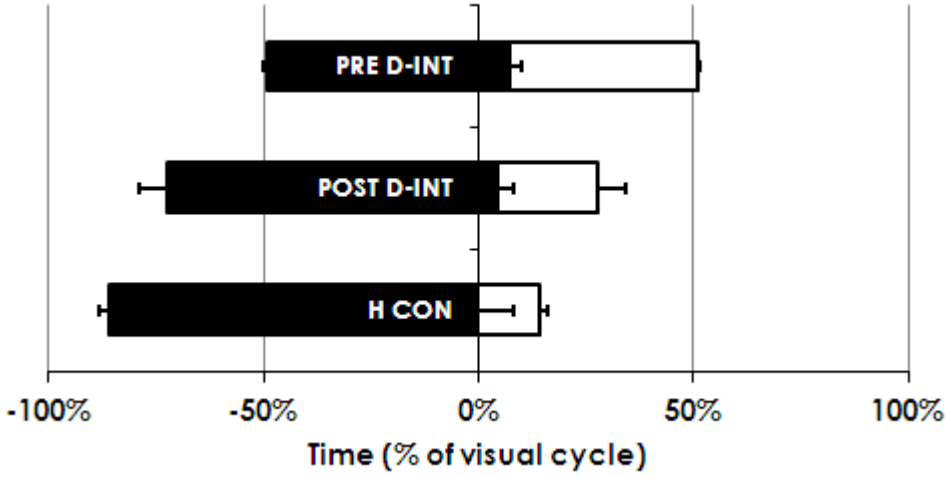

Figure 3. Target visual acquisition parameters during the stepping task, pre- (PRE D-INT) and post-intervention (POST D-INT) for the combined diabetic patient intervention group, and shown in comparison to healthy controls (H-CON) as a reference. Values are means and standard deviations as a percentage of the visual gaze cycle. The black bars denote visual acquisition of the target, the white bars denote the time looking between targets, and the end of the white bar denotes the acquisition of the next target. Foot-ground contact occurs at 0%.

This study has shown that stepping accuracy can be improved through high-load resistance exercise and visual gaze training. Future studies should look to elucidate the separate effects of the high-load resistance exercise and visual gaze training components on motor control and visual gaze strategy. Such work may help to further focus exercise regimens and aid the production of an all encompassing, yet short and enjoyable intervention regimen that patients with diabetes and DPN can perform to improve their safety in a real-world environment. Furthermore, I theorise that the observed increases in stepping accuracy are indicative of an increased ability to avoid tripping hazards, and therefore this specific hypothesis should be tested experimentally by future studies. The findings of this study provide further evidence of resistance exercise training being beneficial to patients with diabetes and DPN, and in combination with visual gaze training, the performance of these training tasks may reduce the risk of tripping on observed obstacles. This multi-faceted intervention could be considered as part of a clinical treatment programme to improve the general health and safety of patients with diabetes.

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Chapter 6

Conclusions and future directions

Summary of main findings

The central aim of this thesis was to examine why patients with DPN are more likely to fall than age-matched controls, and to examine the efficacy of a multifaceted intervention on reducing the risk of falling in this population. The general finding of the work from this thesis was that a targeted multifaceted intervention improves factors that have been linked to an increased risk of falling in patients with diabetes and DPN.

In chapter two it was observed that patients with DPN are slower at generating strength at the ankle and knee than control participants during stairs ascent and stair descent. These changes were theorized to be caused by altered activations of the extensor muscles which may increase the likelihood of instability. In chapter three it was then found that the performance of resistance exercises, once a week for sixteen weeks, resulted in increases in SoSG of the ankle and knee. This is expected to improve stability during the crucial weight acceptance phase of stair ascent and descent, and ultimately contribute towards reducing the risk of falling. Improvements in strength as a result of the resistance exercise training intervention are expected to be the most influential factor for increasing the SoSG.

In chapter four, it was found that patients with DPN display a reduced stepping accuracy, which may lead to patients with DPN being less able to avoid observed obstacles during walking. However, patients also displayed an increased toe clearance, which is expected to reduce their likelihood of tripping on smaller, less

observable potential trip hazards. Preliminary analysis of visual gaze characteristics indicated an altered visual strategy in patients with DPN compared to controls during stepping, which together with impaired motor control may underlie the changes in stepping accuracy. In chapter five I demonstrated that the performance of an intervention consisting of resistance and visuomotor exercises improved stepping accuracy in patients with diabetes and DPN. This is expected to translate to an improved ability to co-ordinate the appropriate response to avoid a potential tripping hazard. The improvements in stepping accuracy are expected to be the result of improvements in motor control and visual gaze strategy.

Both aspects of the intervention, the high load resistance and visual gaze training elements, are expected to have contributed to improvements in biomechanical characteristics indicating a reduced risk of falling. The visual gaze exercise performed by participants is a novel technique, unusual to the area of diabetes, and appears to contribute to increasing stepping accuracy in patients with diabetes and DPN. Whilst the data presented was preliminary due to the small cohort examined, the results are promising, and appear to indicate an altered visual gaze strategy, approaching that used by healthy controls. It is expected that these observations would be reinforced in a larger cohort, and it is therefore suggested that future studies should look at the sole effect of visual gaze training on stepping accuracy, in the absence of other training methods such as resistance exercise.

Resistance training was suggested to potentially be the most important component of the intervention, by improving muscle strength, which contributes to improvements in SoSG and motor control during stair negotiation and level ground walking, respectively. Therefore, resistance training may be the key exercise for patients with diabetes, and particularly those with DPN, by helping to improve markers indicative of fall risk, walking ability, and postural stability.

Further findings of interest

An interesting and unexpected finding was the apparent ability of patients to retain strength over a two-week period. On the rare occasions where patients were unable to attend a session for a given week, they were able to retain the same level of strength (indicated by the ability to perform the resistance exercises using the same weight as the previous week) on their return, as discussed in chapter 3. One of the potential reasons for this could be the increased self-reported activity; as by improving muscle strength, patients were able to be more active, which therefore contributed to further improvements in fitness. These findings may indicate that patients may only need to exercise for one hour, twice a month, to retain levels of strength beneficial to reducing the risk of falling during locomotor tasks.

In addition to this, and contradictory to the typical approach to weight loss, I speculate that resistance training may also be a beneficial approach to reducing weight and improving metabolic control in patients with diabetes and DPN. Whilst it

was not measured in this thesis, previous studies have identified a number of factors, which in combination, lead me to this concept. Resistance training improves muscle quality and muscle volume, and has previously been shown to improve glycaemic control and control blood pressure (1-5). Furthermore, as observed in the patients who undertook the intervention, improvements in muscle strength encouraged and allowed patients to increase activity levels, which may lead to further weight loss. Such training has also been identified as a more enjoyable form of exercise, and may provide a method of getting more patients exercising than if solely aerobic exercises were prescribed (6). Therefore, resistance exercise may be the 'holy grail' for patients with diabetes and DPN, allowing improvements in a number of important areas which may improve safety, health and well being.

Clinical Implications

As stated in the background of this thesis, secondary complications are common in patients with diabetes. Whilst DPN is the most common of these complications, it is not necessarily always the main concern of patients and clinicians. Retinopathy, nephrology, and cardiovascular diseases are often observed in patients who have had diabetes for a long period of time. Therefore the management of neuropathy must be something that is considered alongside other treatments.

As stated in the previous section, resistance exercise may be the 'holy grail' for patients with neuropathy. Not only allowing the improvements in safety, but also

facilitating potential important increases in activity levels and subsequent improvements in weight and blood pressure control. The design of this study to make the results as real-world applicable as possible means that the results observed are expected to be directly reproducible by clinicians and physiotherapists. The length and frequency of the sessions mean that they are as manageable as possible for people of all ages and conditions, and for patients of all levels of employment. The small number of resistance exercise machines required, and the fact that they are common machines found in commercial gyms, as well as clinically based gyms, means that patients of all levels of diabetes and neuropathy will be available to perform such exercises. If performed in a clinical setting, it is important that the gym environment created is different to that typically experienced in commercial gyms. A friendly and more enjoyable approach to exercise should be developed. Trainers and physiotherapists should build bonds with patients to gain their trust and hopefully develop their patients understanding of how resistance exercise and increased activity levels can improve their lives and diabetic condition. Motivation is crucial in patients who in a large number of cases will have developed diabetes through inactivity and a sedentary lifestyle.

An important side effect of the intervention is the increase in self-reported activity. Previously, sedentary individuals were unable to walk for long distances and perform normal everyday tasks, expectedly as a result of reduced muscle strength. This meant that muscle strength could not be increased and therefore created a cycle of inactivity. The increases in muscle strength as a result of the intervention meant that

patients were able to walk for longer, play with grandchildren and go shopping with friends and family. All of these activities were manageable, and patients felt that they could then maintain the performance of these activities without the performance of the intervention exercises after the 16-week period. This is particularly important as this may mean that patients with diabetes can build muscle strength over a three month period to build 'base' muscle strength, which can then be maintained through a more active lifestyle consisting of low intensity everyday tasks typical to everyday life in the general population. This may imply that the intervention is a cost-effective proposition to national health bodies. However, it should be noted that the cost-effectiveness of the intervention used in the present study was not investigated, hence, it is hoped that this will be examined in future studies.

An important aspect of the intervention was that typically, only the more motivated patients chose to take part, which could be observed as contributing to why such large improvements post-intervention in SoSG and stepping accuracy were observed. However, this is also reflective of real-life where only the more motivated patients who want to improve their condition will perform the exercises. It is hoped that the presentation of our results may be a 'carrot' to patients and that positive results from friends and family who undertake an intervention may be persuasive for them to also take part. Whilst not a 'quick-fix', the intervention is non-pharmacological, non-invasive and manageable, which to a lot of patients may prove an attractive proposition. Furthermore, this means that it will not conflict with any medication taken to control other aspects of diabetes and its complications.

Risk of ulceration and management of ulceration are important considerations for any patients performing these exercises. Unlike cardiovascular exercises that are typically load bearing and cause the feet to be repetitively in contact with a surface for prolonged periods of time, resistance exercises require only short bursts of contact with a surface, and when performed using the correct technique, pressure should be distributed across the feet. Feet should be checked before and after exercise, and correctly fitted trainers should be worn at all times. Furthermore, if any signs of ulceration, or a potential risk for ulceration are observed then exercises should not be performed and medical advice should be sought.

Even if patients are not able to perform the exercises proposed by this study, certain strategies and considerations can be made which would improve their safety during everyday life. Where possible, handrails should be used when negotiating staircases, and stairways should be brightly lit (as it is assumed that these factors will improve safety). Where this is not possible, patients should take more care in maintaining a safe and stable pattern of locomotion, although neuropathy may considerably hinder this.

My advice for doctors and clinicians would be to prescribe the resistance exercise program presented in chapters three and five to patients who are currently unstable and at a high risk of falling, but who are also driven to improve their condition. Such

exercise is expected to be multi-faceted in helping to improve patients' safety and day-to-day life.

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