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Gait Variability and Kinematic Alterations in People with Diabetes Mellitus and Peripheral Neuropathy

A dissertation in submission for partial fulfilment of a

professional doctorate in Podiatric Medicine

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by

Frank L. Bowling

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Reeves, N.D., Brown, S.J., Handsaker, J.C., **Bowling, F.L.,** & Boulton, A.J.M., (2013). Are shear forces elevated at the foot-ground interface during gait in patients with diabetic neuropathy? Proceedings of the 11th Meeting of the Diabetic Foot Study Group, Sitges Spain, p. 25.

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Handsaker, J.C., Boulton, A.J.M., Brown, S.J, Maganaris, C.N., Cooper, G., **Bowling, F.**L., & Reeves, N.D.,(2013). Effects of Diabetic Peripheral Neuropathy

on Muscular Activations during Stair Descent. Proceedings of the Physiological Society, PCA252.

Brown, S.J., Handsaker, J.C., Boulton, A.J.M., Maganaris., C.N., **Bowling F.L.,** & Reeves, N.D.(2013). Influence of Diabetes and Diabetic Peripheral Neuropathy on Lower Limb Joint Moment Distribution During Stair Negotiation. Proceedings of the Physiological Society, PCA253.

Handsaker, J.C., Boulton, A.J.M., Brown, S.J., Maganaris, C.N., Cooper, G., **Bowling, F.L.,** & Reeves N.D. (2013). Diabetic peripheral neuropathy alters muscle activation strategy and the rate of joint torque development during stair descent. Proceedings of the Staffordshire Clinical Biomechanics Conference, p.5-6.

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Reeves, N.D., Brown, S.J., Handsaker, J.C., Maganaris, C.N, **Bowling, F.L**., & Boulton,A.J.M. (2012). Foot-ground interaction during walking and stair negotiation in people with diabetes and peripheral neuropathy. Proceedings of the 10th Meeting of the Diabetic Foot Study Group, Berlin Germany, p. 39.

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List of Abbreviations

AGEs	Advanced Glycation End Products
AR	Aldose Reductase
ATP	Adenosine Triphosphate
BMI	Body Mass Index
CO_2	Carbon Dioxide
CCM	Corneal Confocal Microscopy
COM	Centre of Mass
Ctl	Control
DCCT	Diabetes Control and Complications Trial
DESMOND	Diabetes Education and Self-Management for Ongoing and Newly-Diagnosed (type 2 diabetes)
DFUs	Diabetic Foot Ulcers
DH	Department of Health
DM	Diabetes Mellitus
DNA	Deoxyribonucleic Acid
DPN	Diabetic Peripheral Neuropathy
EMG	Electromyogram
EURODIAB	European Diabetes Prospective Complications Study
EURODIALE	European Diabetes Study Group on Diabetes and the Lower Extremity
$FADH_2$	Flavin Adenine Dinucleotide

GLUTs	Glucose Transporter Molecules
GP	General Practitioner
HbA1c	Glycated Haemoglobin
HSCIC	Health and Social Care Information Centre
IDDM	Insulin Dependent Diabetes Mellitus
IDF	International Diabetes Federation
IWGDF	International Working Group on the Diabetic Foot
K^+	Potassium Ion
MDF	Medium Density Fibre
Na^{2+}	Sodium Ion
NAD	Nicotinamide Adenosine Dinucleotide
NADP	Nicotinamide Adenosine Dinucleotide Phosphate
NCS	Nerve Conduction Studies
NDS	Neuropathy Disability Score
NHS	National Health Service United Kingdom
NICE	National Institute for Clinical Excellence
NIDDM	None Insulin Dependent Diabetes Mellitus
NSF	National Services Framework
PN	Peripheral Neuropathy
RAGE	Receptor (for) Advanced Glycation End Product
ROM	Range of Motion
3D	Three-dimensional

UK   United Kingdom

UKPDS   United Kingdom Prospective Diabetes Study

USA   United States of America

VPT   Vibration Perception Threshold

WHO   World Health Organisation

Thesis Outline

The consequences of diabetes for the human body are initiated at a molecular and cellular level, which promotes the widespread dissemination of cell dysfunction. Peripheral neuropathy is a clinical manifestation of altered cell function, and, therefore, the mechanisms of dysfunction in diabetes are presented to demonstrate the materialisation/conversion of hyperglycaemia into Diabetic Peripheral Neuropathy (DPN). Normal gait in humans will be summarised in order to create a background for a review of disruptions in gait that can lead to falls. The current evidence base for altered gait patterns and the potential for this to increase falls risk is reviewed. Finally, data as it relates specifically to diabetes is discussed before presenting the study. The hypothesis is that people with diabetic peripheral neuropathy will exhibit significant differences in joint range of motion and gait variability during three gait tasks (stair ascent, stair descent, and level walking) compared to people without diabetes-related peripheral neuropathy, and healthy controls. The differences between the groups will become more evident as the gait tasks become more challenging.

Abstract

Background: People with diabetes and peripheral neuropathy have been reported to show alterations in lower limb joint function compared to healthy non-diabetic people. Specifically the maximum angular movement available at certain joints can be reduced during static, non-weight bearing tasks. Limited joint range of motion has the potential to compromise balance and stability thereby increasing the risk of falling. It is unclear whether a reduction in the extent of movement available at the joints is reflected by a reduction in the amount of angular movement actually utilised during a functional task such as stair negotiation. The aim of this study was to determine if people with diabetes show reduced dynamic range of motion at the ankle, knee and hip joints during stair ascent and descent in comparison to controls. Falls risk during stair negotiation was calculated by measuring the degree of variability in dynamic joint range of motion. **Methods:** Data were generated from three groups: subjects with diabetes and peripheral neuropathy (DPN), diabetes without peripheral neuropathy (DM), and healthy controls (Ctl). The study was conducted in a gait laboratory using motion capture and related 3D software for analysis. Joint range of motion for the ankle, knee, and hip were captured during level walking, stair ascent, and descent. A seven step, bespoke staircase was fabricated for this purpose. Analysis of Variance (ANOVA) and Newman-Keuls tests were used to analyse the data. **Results:** Significantly reduced ankle range of motion, in the sagittal plane, was observed in the DPN group during stair ascent when compared to the controls. For stair descent, the DPN group demonstrated a

significant increase in knee and hip ROM in the frontal plane, and also hip ROM in the transverse plane. No significant differences between the groups were identified for joint variability. **Conclusions:** People with DPN demonstrate alterations in dynamic range of motion at the lower limb joints during stair ascent and descent. The degree of angular movement utilised for both stair tasks was decreased at the ankle joint and this has the potential to undermine balance and stability. In contrast, angular movement at the knee and hip joints was increased in the frontal and transverse planes. This may compensate for impaired balance and stability by increasing the base of support to maintain balance and assist in foot clearance and placement. The specific combination of increased angular movement at the knee and hip may represent a compensatory stair gait strategy in response to reduced angular movement at the ankle joint.

Declaration

No portion of the work referred to in this dissertation has been submitted in support of an application for another degree or qualification of this, or any other, University or other institution of learning.

Disclaimer

I, Frank L. Bowling, performed all database construction and the majority of data acquisition, as well as all data analysis and writing. A number of individuals, notably Karen Ousey, John Stephenson, Wesley Vernon, Mark Tagoe, Andrew Boulton, Neil Reeves, and the diabetes team, participated in the acquisition of data and/or evaluation of the final dissertation.

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5. Further information on the conditions under which disclosure and exploitation may take place is available from the Head of the Division of Podiatry and Clinical Sciences, Department of Health Sciences, School of Health Sciences, University of Huddersfield.

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The Author

Frank Bowling graduated with an Honours Degree in Podiatry from the University of Salford. Following graduation, he consolidated his skills, knowledge, and experience through clinical practice. He was keen to progress practice through research, and his research interests have focused on a broad spectrum of lower limb complications. In order to advance his clinical practice, he undertook a Master of Science degree in Podiatric Surgery at the University of Huddersfield. He continued his academic career pathway at the University of Manchester, where he completed a Doctor of Philosophy (Medicine) in the Faculty of Postgraduate Medicine. He currently works in both in a clinical capacity (Trainee in Podiatric Surgery at West Middlesex University Hospitals), and in a research capacity (Clinical Research Fellow at the University of Manchester, Manchester Royal Infirmary). Since graduation, he has authored and co-authored over fifty-four peer-reviewed publications in a range of medical journals, including book chapters in Pharmacology, Disease Management, Diabetic Neuropathy, Charcot Foot, and New Frontiers in Research. He regularly undertakes peer reviews for national and international journals. More recently, he was awarded the Top Clinical Abstract Prize at the Symposium of Advanced Wound Care (SAWC), and was also awarded the Chairman's Research Prize Scholarship, Manchester Royal Infirmary. Frank was part of the four-strong team that won the highly prestigious BioKnow AstraZeneca award for medical innovation in 2012.

Contents

Chapter One

Introduction

Introduction to Diabetes Mellitus

Diabetes mellitus is a serious chronic endocrinological disease characterised by abnormal metabolism of lipids and sugars. Chronic hyperglycaemia, if left unchecked, has a detrimental effect on multiple physiological systems. The complications associated with the hyperglycaemic state include peripheral vascular disease, cardiovascular diseases (Juutilainen, Lehto, Ronnemaa, Pyorala & Laakso, 2005), retinopathy, nephropathy, and peripheral neuropathy (Fowler, 2008). The clinical manifestations of diabetes-related complications include tissue breakdown in the peripheral limbs due to vascular insufficiency, claudication pain, myocardial infarction, cerebrovascular attack, renal failure, visual impairment, neuropathic lower limb pain, and diabetic foot ulceration (Chaturvedi, 2007).

Management of conditions arising from diabetes is guided by the National Service Framework for Diabetes (Department of Health, 2001), and National Institute of Healthcare Excellence (NICE) clinical guidelines (CG66) (NICE, 2008), with the aim of providing structured, evidence-based care. Podiatry has a high profile in managing the diabetic foot as recommended by clinical guideline 10, type 2 diabetes: prevention and management of foot problems (NICE, 2004). One of the key themes of this guideline is prevention of foot complications due to high rates of morbidity and mortality associated with infections in the diabetic foot (Davis, Norman,

Bruce & Davis, 2006; Ghanassia et al., 2008). Peripheral neuropathy plays a significant part in the causal pathway to foot ulceration, as loss of sensation prevents the foot from responding appropriately to the presence of abnormal pressures and shear forces (Veves, Murray, Young & Boulton, 1992), whilst simultaneously diminishing foot sensitivity to trauma. A breach in the protective epithelium of the foot can be the first step towards formation of a diabetic foot wound, and once an ulcer is established, it can transform into a chronic, non-healing wound with ease. This process is assisted by a prolonged inflammatory response (Stegenga et al., 2008), decreased perfusion (Apelqvist et al., 2011), and altered immune response (Rubinstein, Genaro,Motta, Cremaschi & Wald, 2008). The risk of infection in a diabetic foot wound is high at 58%, and infection is often the precursor to lower limb amputation (Prompers et al., 2007). A large prospective study (n=3,018) involving 97 hospitals across the United States examined risk factors and outcomes in patients with a diabetic foot ulcer and identified that over one fifth of these patients required a lower extremity amputation (Lipsky, Weiglet & Sun, 2011). According to the National Diabetes Audit (Health and Social Care Information Centre), between 2010 and 2012, 1.96 million people in the UK were living with diabetes in England and Wales. Major lower limb amputations were carried out for 3,319 of these people as a result of their diabetes. However, type 1 and type 2 diabetes were pooled, and there are no statistics available according to type of diabetes. Nevertheless, given such poor outcomes, it is essential to reduce the risk of developing a diabetic foot ulcer, which necessitates attempting to interrupt the chain of events that cause

ulceration. Diabetic Peripheral Neuropathy (DPN) is at the centre of the pathway to ulceration due to the associated loss of protective sensation, but the peripheral nerves of the lower limb are also involved in locomotion. Sensorimotor function enables humans to mobilise whilst remaining upright, and in the absence of this information, balance will be lost, which can culminate in a fall. It is physiologically feasible that DPN places patients with diabetes at risk of falls due to the inherent loss of sensation.

1.1 The Diabetes Epidemic

According to the World Health Organisation (WHO), in 2013, there were approximately 347 million people living with diabetes mellitus worldwide, and this is predicted to increase to almost 552 million people by 2030 (World Health Organisation, 2013). Type 2 diabetes mellitus accounts for 85% to 95% of cases in high-income regions such as the United States of America (USA) and Europe (International Diabetes Federation [IDF], 2013). Diabetes is characterised by sustained elevation of blood glucose levels, as measured by glycated haemoglobin, or HbA1c, but, with strict glycaemic control, type 2 diabetes can be reversed (United Kingdom Prospective Diabetes Study, UKPDS, 1990; Dufor, Befroy, Lehrke & Schulman, 2005). Type 1 diabetes requires treatment with regular replacement of insulin, usually in the form of sub-cutaneous injection. However, achieving stable blood glucose is notoriously difficult (Govan, Wu & Brigg, 2011). This is largely

attributable to pharmacological limitations that result in highly variable rates of absorption, in addition to peaks and troughs in insulin levels leading to hypo- and hyperglycaemic episodes (Heinemann, 2002).

Sustained and uncontrolled fluctuations in blood sugar levels are at the centre of diabetes-related complications such as retinopathy, neuropathy and nephropathy. This relationship was demonstrated in the European diabetes (EURODIAB) study of Insulin Dependent Diabetes Mellitus (IDDM) by Tesfaye et al. (1996), whereby diabetic peripheral neuropathy was linked to glycaemic control and duration of disease. This is one of the largest prospective, longitudinal studies available, and included health centres across European countries. Hence, the data is highly relevant to the current study. Over a seven-year follow-up period from baseline measurements, almost one quarter of patients developed diabetic peripheral neuropathy, or DPN (Tesfaye, 2005).

People with diabetes are estimated to have a twofold excess risk of developing cardiovascular complications such as ischaemic heart disease, cerebrovascular disease, peripheral arterial disease, and heart failure. Cardiovascular disease is the most common cause of death in individuals with both type 1 and 2 diabetes mellitus, suggesting an inextricable link between the two diseases (Buse et al., 2007; Sarwar et al., 2010).

Medical management of this array of conditions is costly. In 2011 the global spend for the provision of diabetes-related healthcare amounted to $465 billion, constituting a considerable financial burden (IDF, 2013). The projected estimates of increases in world population and diabetes prevalence will see this magnified in future years, and the IDF have calculated a global spend of $595 billion for the year 2030 (IDF, 2013). The effects of the increased demand will be felt by all healthcare providers, including the National Health Service (NHS) in the UK. Increased prevalence of diabetes has been mirrored by increased expenditure in European countries such as France, Italy, Germany and Spain. A report from the London School of Economics (Kanavos, van den Aardweg & Schurer, 2012) calculated that total healthcare expenditure between 2004 and 2008 had increased by 49% in France, 22% in Germany, 48% in Italy, 111% in Spain, and 45% in the UK. These increases in expenditure correlated strongly with increased prevalence of diabetes in each country, most notably Spain. Within the UK, expenditure on type 2 diabetes far exceeds that of type 1, expenditure on the former being £11.9 billion per year versus £1.8 billion per year on the latter. The National Diabetes Audit, 2012 - 2013, (Health and Social Care Information Centre [HSCIC], 2014) found the majority of this spending went on in-patient care due to diabetes-related complications, including diabetic foot disease.

The need to deliver high quality care with maximum efficiency has prompted fundamental changes in practice in many aspects of medicine, and diabetes is no exception (Department of Health, [DoH], 2001; 2010). The range of complications

associated with diabetes, and the interactions between them, can produce a complex clinical picture making it difficult to determine the specific influence of any contributing factors. However, an appreciation of the metabolic processes driving the physiological changes helps to illustrate how and why DPN might be linked with gait disorders. The following section will explore the physiology underlying DPN whilst also examining the molecular and cellular level changes that produce neuropathy. The effects on nerve function will be considered with a view as to how this may link to gait changes.

1.2 The Pathophysiology of Diabetes Mellitus

The aim of this section is to demonstrate how the molecular changes that arise as a result of diabetes disturb cell function throughout the human body. Diabetes mellitus is an endocrinological disease characterised by abnormal glucose metabolism. Type 1 diabetes accounts for between 5% and 10% of all cases worldwide, and usually presents in childhood or early adolescence (WHO, 2013). It is an auto-immune regulated disease, resulting in the targeted destruction of pancreatic beta (β) cells, the cause of which is a complex interplay between genetic and environmental factors. There are a number of immunological indicators of type 1 diabetes, including the presence of islet cell antibodies, auto-antibodies to insulin, glutamic acid, decarboxylase, and tyrosine phosphates (Pfluger et al., 2011). At the point where insulin secretion is minimal or absent, levels of plasma c-peptide become

undetectable. However, at this stage in the disease process, the patient will have clinical signs of uncontrolled diabetes that are life-threatening, such as ketoacidosis. Long-term insulin therapy is essential for the health and survival of patients with type 1 diabetes, but glycaemic control can be difficult to achieve due to hypoglycaemic responses (Perez-Maraver et al., 2013). In contrast, type 2 diabetes is an obesity-driven abnormality in glucose metabolism (Khan, 2006) resulting in increased resistance to insulin activity, and subsequent inadequate insulin secretory response.

1.2.1 Glucose Homeostasis

In healthy humans, plasma glucose is derived from two main sources: through diet via ingestion, and through metabolism of glycogen in the liver. Ingestion of glucose results in increased plasma glucose levels which initiates the release of insulin by pancreatic β cells (Henquin, 2000). Normal levels of blood glucose before a meal should be between 3.5 and 5.5 millimoles per litre (mmol/l), and less than 8 mmol/l after a meal (WHO, 2006). Staying within these parameters is dependent upon maintaining a balance between insulin action and insulin secretion. Healthy β cells are highly flexible and adapt to altered insulin levels accordingly. Thus, a decrease in insulin action can be balanced by an upregulation of insulin secretion.

Insulin plays a major role in glucose regulation through the acceleration of glucose transport to insulin sensitive cells, and by facilitating glycogenesis and lipogenesis

for energy storage (Wright et al., 2007). In addition to insulin, the hormone glucagon is involved in glucose homeostasis, as it is secreted in response to hypoglycaemia. Glycogenesis and glucogenesis are both enhanced by glucagon, thereby increasing glucose levels and returning to normoglycaemia. After a meal, glucagon secretion is inhibited under normal conditions by hyperinsulinaemia, which assists in suppressing hepatic glucose production (Ramnanan, Edgerton, Kraft & Cherrington, 2011), thereby assisting in maintaining normal glucose levels. Target sites for glucose transport include adipose, muscle, cardiac, brain and liver tissues. Permeability of target cell membranes is achieved with the assistance of glucose transporter molecules (GLUTs) (Baloh, 2008), which allow the passage of glucose via an aqueous pore into the cytoplasm (Joost & Thorens, 2001).

Utilisation of glucose begins with the enzyme-mediated reduction of glucose to pyruvate via glycolysis. Oxidative phosphorylation sees pyruvate oxidised to acetyl coenzyme A, which then enters the Krebs cycle to combine with oxaloacetate forming citrate. Throughout the process, a series of redox reactions generate Adenosine Triphosphate (ATP), Nicotinamide Adenosine Dinucleotide Phosphate (NADH), Flavin Adenine Dinucleotide ($FADH_2$), and carbon dioxide (CO_2). Electrons are then transported down the electron transport chain via an energy gradient until accepted by oxygen, which is the terminal acceptor of electrons. As electrons move down the chain, four protein complexes (Sperlagh & Vizi, 1996) assist in the donation and acceptance of electrons, which creates a proton gradient of potential

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energy. The relative impermeability of the cell membrane maintains stability of the gradient whilst the enzyme ATP synthase allows protons to flow back down the gradient and cross the membrane, thereby generating ATP (Starkov & Fiskum, 2003).

Nerve cells have high requirements for ATP in the formation of cell units, and maintenance and generation of action potentials (Viader et al., 2011). The propagation of electrical signals along the length of axons is driven by the sodium and potassium ion pump. The pump builds up a concentration gradient, thus creating the resting potential of the cell and, when stimulated, an action potential is generated allowing the inflow of sodium across the cell membrane. This opens a gated channel for potassium ions (K+) to leave the cell. The sodium in-flow also stimulates the opening of sodium channels on the next axon thereby propagating the signal. This pattern of neuro-electrical signalling underpins the peripheral and central nervous systems both of which utilise glucose for energy generation.

1.2.2 Glucose Metabolism in Diabetes Mellitus

Diabetes mellitus is characterised by hyperglycaemia, which initiates the diversion of glucose away from glycolysis towards alternative metabolic pathways with noxious implications for nerve cells. The polyol pathway was first described by Hers (1956,

cited in Oates, 2002,) as the enzymatic reduction of glucose to sorbitol, producing fructose as the end product. Glucose is converted to sorbitol in nerve cells, leading to the accumulation of sorbitol in the cytoplasm. Sorbitol synthesis assists cells in buffering high interstitial osmotic pressures, but in the presence of high levels of glucose, the accumulation alters osmolarity in the cytoplasm, which in turn drains other osmolytes normally involved in regulating cell osmolarity (Kinoshita & Nishimura, 1988). The consequences for cells involved in this process are direct tissue toxicity or a rapid increase in cell volume due to water influx (Suzuki et al., 1999).

The enzyme Aldose Reductase (AR) plays a key role in the polyol pathway, and high levels of AR have been found in Schwann cells of myelinated nerve fibres (Brownlee, 2005), percicytes, and smooth muscle cells. Increased AR activity, and subsequent increased flux through the polyol pathway, utilises and reduces levels of co-enzyme Nicotinamide Adenine Dinucleotide Phosphate (NADPH) whilst increasing nitric oxide synthase (Kamiya et al., 2003), as this would normally combine with NADPH under normoglycaemia. The resulting decrease of nitric oxide in nerve tissue disturbs endothelial function, thus reducing perfusion of nerve tissue (Tomlinson et al., 1998). The polyol pathway is also implicated in reduced neurotrophin secretion leading to degeneration of nerve cells (Suzuki et al., 2004). Aldose reductase is challenged by the enzyme glutathione reductase under normal physiological conditions. However, increased levels of AR result in over-use of glutathione, whose

subsequent inhibition leads to increased free radical generation and oxidative stress (Yagihashi, Mizukami & Sugimoto, 2011).

Oxidative stress is a further glucose-driven mechanism promoting cell toxicity through the generation of free radicals and reduced free radical scavenging. Increased hydrogen peroxide levels, due to polyol-related activities, allow hydrogen peroxide to join a reaction that produces superhydroxyl radicals, thus increasing free radicals and oxidative stress. Glycolysis is slowed down due to oxidative stress-induced DNA strand breakage and activation of poly polymerase, which reduces NAD concentration to drive glycolysis. The metabolism of glucose via glycolysis is therefore slowed, the electron chain becomes inefficient and ATP is reduced, as observed in Schwann cells by Obrosova and colleagues (2005). Oxidative stress can also cause decreases in nerve conduction velocity, and decreased nerve blood flow (Cameron, Cotter, Archibald, Dines & Maxfield, 1994). Axonal regeneration of peripheral nerves can be disrupted by oxidative stress with the degree of impairment being inversely proportional to length of time with diabetes (Kennedy & Zochodne, 2000). Biopsies of sural nerves have shown virtually no regeneration (Malik, 2005).

Advanced Glycation End Products (AGEs) are formed by non-enzymatic protein glycation via the Maillard reaction, resulting in a group of molecules that can disturb the structure, function and integrity of a cell (Munch & Westcott, 2012). Amino acids of proteins with side chains of lysine or arginine react with carbonyl compounds

whose reactivity has been enhanced by increased levels of glucose. A Schiff-base is formed and rearranged into a protein-bound Amadori product which undergoes a series of oxidations and dehydrations until a broad range of fluorescent and yellow-brown molecules result. AGE products can form irreversible cross-links with neurofilament proteins involved in axonal regeneration leading to atrophy of axons (Duran-Jimenez et al., 2009). Activity of $Na^{2+}K^{+}$ ATPase is impaired by AGE products, resulting in axonal dysfunction, but more direct nerve fibre loss can be initiated by AGE product-activated apoptosis (Ota et al., 2007). Basement membrane hypertrophy is influenced by AGE products' interaction with extracellular matrix proteins (collagen, fibronectin and laminin) and endothelial cells, thereby disturbing microvascular structure and function at the blood-nerve barrier (Yao et al., 2010).

RAGE is the receptor for AGEs and is classified with the immunoglobulin family of cell surface receptors. It has been identified as present in dorsal root ganglion, Schwann cells and peripheral nerves of diabetic mice (Toth et al., 2008). Cell damage arises from the activation of nuclear factor kappa beta (NF-kB), stimulation of NAD(P)H oxidase and protein modification. Activation of NF-kB increases gene expression of cytokines, which can prolong and maintain the pro-inflammatory response, whilst sustained activation irreversibly alters gene expression and causes upregulation of RAGE (Haslbeck et al., 2007).

1.3 Diabetic Peripheral Neuropathy

The consequences associated with the metabolic processes instigated by hyperglycaemia are diverse, and are implicated in diabetes-related complications such as retinopathy, nephropathy and cardiovascular dysfunction (Goh & Cooper, 2008). DPN encompasses the clinical manifestations of the processes that drive changes in nerve cell structure and function. Electromicroscopy of neuropathic peripheral nerves demonstrates axonopathy of small distal unmyelinated fibers (Ørstavik et al., 2006) with skin denervation, reported as the DPN progresses (Shun et al., 2004). Wallerian degeneration and segmental demyelination are also characteristic of DPN (Kennedy & Zochodne, 2005) and can affect larger fibres which already demonstrate segmental demyelination (Malik, 2005). Axon loss and axon thinning are associated with reduced nerve conduction velocity, which is frequently reported on nerve conduction studies of patients with DPN. Altered heat perception and decreased sensation as a whole is due to c-fibre dysfunction. Impaired axon regeneration prevents fibre re-growth and, hence, an overall loss of nerve fibre density (Kennedy & Zochodne, 2005). Nerve cells undergo a variety of transformations as a result of hyperglycaemia, direct tissue damage secondary to glucotoxicity, exposure to noxious metabolic by-products, and altered gene expression at the mitochondrial level. This culminates in progressive and irreparable damage to peripheral nerves accompanied by clinical symptoms of DPN.

1.3.1 Prevalence of Diabetic Peripheral Neuropathy

Three major studies have investigated the prevalence of peripheral neuropathy in the diabetes population. Young et al. (1993) recruited 6487 patients from 118 hospital based out-patient diabetes clinics across the UK. Of these, 2414 (37.0%) were diagnosed with type 1 diabetes, and 3949 (61.0%) had type 2 diabetes, whilst 124 (2.0%) were of unknown aetiology. The overall prevalence of DPN in the study population of patients with diabetes attending a hospital-based clinic was 28.5% (95% confidence interval 27.9%-29.6%). Prevalence of DPN was significantly higher in type 2 diabetes (32.1%) than in type 1 diabetes (22.7%) ($p<0.001$). The sample size of 6487 patients should imply a reasonable reflection of the diabetes population as a whole. However, the distribution of type 1 and type 2 diabetes within the sample does not concur with current knowledge of approximately 5% for the former and 95% for the latter. The difference has arisen due to the authors' diagnostic criteria for type 1 and type 2 diabetes. The methods state that *type 2 diabetes mellitus*, previously also known as Non-Insulin Dependent Diabetes Mellitus (NIDDM), was used to describe patients either not on insulin treatment or those that did not start insulin within 2 years of diagnosis (Young et al.1993). In 1993, when the study was published, these criteria were widely used, but, in 1999, WHO recognised they were no longer appropriate, as classification was based on patients' treatment regime rather than pathogenesis and was, thus, open to misinterpretation. WHO determined that *type 1 diabetes* should describe patients with autoimmune beta-cell

destruction and *type 2 diabetes* should be used for defects in insulin secretion, always with major insulin resistance. Young et al. (1993) classified subjects taking insulin treatment as type 1 diabetes. However, insulin can be required for type 2 patients unable to achieve satisfactory glycaemic control through dietary and lifestyle changes. Significantly, this would lead to an over-diagnosis of type 1 diabetes, which is likely to explain why 37% of the study population were classed as type 1 diabetes, and 61% as type 2, in contrast to the 95% type 2 and 5% type 1 division observed globally when pathogenesis is used (WHO, 2013). As a result of this design limitation, some of the data has to be disregarded, including the reported correlation between disease duration and DPN. Nevertheless, the study population is likely to be a reasonable representation of the UK diabetes population overall.

The European Diabetes Study (EURODIAB), by Tesfaye et al. (1996), recruited 3250 type 1 diabetes patients randomly selected from diabetes clinic attendees in 16 European countries. In contrast to the study of Young et al. (1993), diagnosis was based on an HbA1c of 6.7%+/-1.9%. Patients were assessed for a variety of microvascular complications associated with diabetes, including DPN. Of the 3250 patients assessed, 28% of these tested positive for DPN, which concurs with results from Young et al. (1993).

The Diabetes Control and Complications Study (DCCT) (1993) was a controlled clinical trial conducted between 1989 and 1993. The study investigated the effect of

strict glycaemic control, through intensive treatment, on the development of complications associated with type 1 diabetes. Subjects were randomised to receive either intensive or conventional therapy. Intensive intervention consisted of insulin delivered by an external pump, or three or more insulin injections per day. Frequent glucose monitoring was used to guide treatment regimes. Conventional therapy involved 1-2 insulin injections per day. The prevalence of DPN at 5 years was 16.1% for those receiving intensive insulin therapy and 23% for subjects in the conventional treatment group. The results are similar to those reported by Tesfaye et al. (1996) and Young et al. (1993). The DCCT spawned a second observational study, Epidemiology of Diabetes Interventions and Complications (EDIC) (EDIC research group, 1999), which began in 1994 and followed the surviving 95% of members of the original cohort. Data collection has continued since 1994 to the present with 93-96% participant retention and this remains ongoing.

The three studies above are the largest studies of diabetes-related complications to date and have yielded a vast amount of data. However, the focus on type 1 diabetes makes it difficult to draw conclusions regarding the type 2 diabetes population. The prevalence of DPN in type 2 diabetes is unlikely to be as high as in type 1 diabetes due to essential differences in the underlying disease processes. As an auto-immune disorder, in the majority of cases, type 1 diabetes is diagnosed in early childhood, making it a lifelong disease and subsequently associated with more severe complications. People with type 1 diabetes tend to be motivated to attend

appointments regularly, possibly due to the early exposure to medical management of their diabetes in the context of having a life-threatening disease. As regular clinic attendees, adults with type 1 diabetes are likely to feature heavily in studies of diabetes that do not specify type of diabetes for inclusion. Although the DCCT recruited subjects from age 13 to 39 years old, each group contained only 9% to 19% of adolescents aged between 13 and 18 years old, constituting a small proportion of the study as a whole. It is highly unlikely the teenage cohort were non-attendees to clinic appointments due to legal parental responsibility for their care. DPN prevalence may have also been influenced by recruitment sites chosen for the studies, as all were hospital-based clinics, and, therefore, more likely to include a higher proportion of patients at the severe end of the disease spectrum. Other patients would be treated by their General Practitioner.

There have been no attempts to replicate these studies, possibly due to the extensive size and cost, but also because the data is widely acknowledged and accepted as reliable by clinicians and physicians, whilst international and national guidelines continue to include them to support clinical practice. Young and the DCCT study group's (Young et al.,1993) results underpin NICE clinical guideline 10, Prevention and management of foot problems (2004), which has not been updated as of 2014, but is anticipated to be released into the public domain by July 2015. The EURODIAB study features heavily in the International Working Group on the Diabetic Foot (IWGDF) guidelines: Practical guidelines on the management and

prevention of the diabetic foot (Bakker, Apelqvist & Schaper, 2011). New data is emerging from the rapidly expanding diabetic populations in India and Saudi Arabia, but given the significant differences in diet, lifestyle and obesity between these and Western European countries, they may not be applicable to Western European diabetes populations (International Diabetes Federation, 2013).

1.3.2. Clinical Characteristics of Diabetic Peripheral Neuropathy

Clinically, DPN describes a symmetrical alteration in sensorimotor function associated with metabolic and microvascular changes arising from chronic hyperglycaemia exposure. There is a pattern of nerve length dependence, i.e., the smallest fibres are more susceptible initially (Sumner, Sheth, Griffin, Cornblath & Polydefkis, 2003), and thus the process begins in the toes. DPN progresses proximally, thereby affecting nerve function in the foot, ankle and lower limb. The clinical symptoms of DPN vary from patient to patient, but many share similar themes in their description of symptoms, such as burning sensations, which may be hot or cold, shooting pains, and electric shock-like sensations. Other abnormal sensations reported by sufferers include skin crawling and tingling. Hyper- and hypo-sensitivity can co-exist in patients with DPN, whereby pain is evoked by non-nociceptive stimuli, or the response to nociceptive stimuli is sensitized to such a

degree that extreme pain ensues, yet other areas of the lower limb can be so desensitized that direct injury can go unnoticed (Tesfaye & Selvarajah, 2012).

The symptoms of DPN correlate with small or large fibre involvement. Abnormalities in the structure or function of thick, myelinated A-beta (Aβ) fibres may cause numbness, pins and needles, and tingling sensations. Burning, ice-cold shooting pain, and stabbing pain sensations are related to A-gamma (Aɣ) and unmyelinated c-fibre damage (Callaghan et al., 2012). When patients do complain of symptoms, this usually correlates with an advanced neuropathy.

Given the paradoxical symptoms and probable patient reluctance to report such inconsistencies, self-reporting may not be the most reliable source of diagnostic information. Assessment and diagnosis of DPN can also be problematic due to wide variability in diagnostic criteria and selection of assessment tools (Dyck, Overland, Low, Litchy, Davies & O'Brien, 2010). There have been attempts to address this issue by developing explicit guidance such as the Diagnostic Criteria and Definitions of DPN (Tesfaye, 2010), and structured, composite assessments, for example, the Neuropathy Impairment Score plus nerve conduction tests (Dyck, Davies, Litchy & O'Brien, 1997). The gold standard for assessing sensory nerve function is via nerve conduction studies which yield qualitative as well as quantitative data (Arimura et al., 2013). Needle electrodes are applied to cutaneous tissue above the target nerve and deliver electrical stimulation to generate a response in the form of an action

potential. The velocity of the action potential is measured at a further point along the nerve. Conduction velocity is indicative of the speed at which action potentials are propagated along large myelinated axons in the peripheral nerve (Kane & Oware, 2012). Nerve conduction studies have been utilised to characterise nerve function in patients with DPN and assist in diagnosis. Findings include decreased velocity, amplitude and/or latency in conduction of action potentials (Dyck et al., 2010). However, activity in c-fibres cannot be detected by this method due to the small diameter of fibres and slow conduction speed, making the action potentials almost impossible to detect. In the early stages of peripheral neuropathy, the unmyelinated c-fibres are the first group of nerves affected by diabetes and a means of determining their integrity could assist in early diagnosis of DPN. Epidermal skin biopsy, using a 3-4 mm punch and immunochemical staining, has been used to highlight c-fibres that penetrate the epidermis. Morphological analysis of stains provided data on nerve structure, including features characteristic of DPN. Lauria, DeVigili (2007) and Arimura et al. (2013) utilised skin biopsies to identify intra-epidermal nerve fibres through a fluorescent confocal scanning laser microscope. Nerve fibre density was then quantified by computerised image analysis. Changes in fibre density correlated with the degree of reduction in sensory action potentials recorded by Nerve Conduction Studies (NCS).

Both these techniques for small nerve fibre assessment could represent a means of identifying DPN before larger fibres have been affected. Anecdotal evidence from

studies carried out in Manchester identified that patients felt generally reluctant to undergo skin biopsy, with many feeling it is too invasive. Other factors that may deter biopsy usage include increased expense of materials and processing, delays in processing times for samples, and a high number of patients accessing diabetes clinics. Currently, NCS is used to assist in the diagnosis and management of DPN associated with severe pain sensations, whilst other tools, such as skin biopsy, are providing valuable data to increase the academic knowledge-base. However, within the clinical environment, assessment tools need to readily assimilate into the running of busy, multi-disciplinary diabetes clinics and, perhaps, most importantly, be acceptable to patients. Corneal, Confocal Microscopy (CCM) is a non-invasive instrumental assessment for the diagnosis of peripheral neuropathy which can detect even small fibre changes. It involves laser scanning and image capture of the cornea on the hand-dominant side which is processed by nerve analysis software to provide a measure of corneal fibre length in mm/mm^2, corneal nerve branch density (number/mm^2), and nerve fibre tortuosity measured in tortuosity units (Edwards et al., 2012). In DPN subjects, corneal fibre length and density are reduced and these changes are evident even in newly diagnosed patients (Ziegler et al., 2014). CCM also correlates with the severity of intra-epidermal fibre loss (Quattrini et al., 2007), making it a viable option for investigating early peripheral neuropathy.

National and international guidelines on management of diabetic foot complications (2012; American Diabetes Association, [ADA], 2014; Infectious Diseases Society of

America, [IDSA], 2012; International Working Group on the Diabetic Foot, [IWGDF]; CG10, [NICE] 2004;) recommend the structure and content of assessment for diabetic peripheral neuropathy to promote a consistent evidence-based approach. Assessment is similar to lower limb examination during a standard neurological medical examination and follows the anatomical and physiological pathways of the peripheral nervous system (Wills, 2012). Patients are tested at specific points along the neurological pathway, and the response elicited provides evidence to support or exclude a specific diagnosis. Assessment for DPN is focused on the lower limb and afferent pathways for sensing pain and pressure. The corresponding neuronal receptors are the small, unmyelinated c-fibres, which detect temperature difference (Schepers & Ringkamp , 2010) rather than hot versus cold. An inability to identify a change in temperature during testing is likely to indicate impaired nerve function. Patency of small fibre function can also be elicited through assessment of pinprick sensation. Detection of small fibre changes in the initial asymptomatic stages of DPN cannot be achieved clinically. However, nerve conduction studies may also fail to identify altered function. The integrity of large nerve fibres can be determined through vibration perception tests and ankle reflex testing (McGlone, 2010). Inability to determine pressure sensation in one or more sites on the foot is indicative of large fibre involvement.

To summarise the sections above: the processes involved in the destruction of sensory nerve fibres in the foot commence due to excess blood glucose. Chronic

hyperglycaemia disrupts mitochondrial function, increases reactive oxygen species, promotes the formation of advanced glycation end products, and alters gene expression, culminating in direct damage to nerve fibres and cessation of axon regeneration. This results in altered sensation or loss of protective sensation, the implication of which is an increased risk of developing an associated foot ulcer. The next section will briefly explore the management of diabetic foot ulcers and the financial cost to complete the clinical pathway from diabetic peripheral neuropathy.

1.3.3. Diabetic Peripheral Neuropathy and Lower Limb Complications

DPN increases the risk of foot ulceration through the loss of protective sensation, in the absence of which patients become vulnerable to trauma (Reiber et al., 1999). Soft tissue trauma is a major causative factor in the development of diabetic foot ulceration in patients with DPN (Boulton et al., 1998). Falls are associated with soft tissue trauma and, unlike their healthy counterparts, people with DPN are less likely to notice cuts, grazes, puncture wounds etc. in the lower extremities due to the loss of protective sensation. If DPN increases the risk of falls which often result in soft tissue trauma, an increased risk of foot ulceration is highly likely.

In the UK, the annual incidence and prevalence of foot ulceration in patients with diabetes was calculated at 2.2% and 1.7% respectively in 2002 (Abbott et al., 2002). According to Kerr (2012), data on foot ulcer incidence is not collected in the UK and

so more recent data is not available. Scotland does extract data from GP databases and identified that 2.5% of the diagnosed diabetes population had an active foot ulcer at the beginning of December 2010 (Leese et al., 2011). Diabetic foot disease is associated with a risk 23 times that of a person without diabetes (Holman, Young & Jeffcoate, 2012). A study by theEuropean Study Group on Diabetes and the Lower Extremity (Eurodiale) (Prompers et al. 2008)followed 1232 diabetes patients with a foot ulcer, and found that 5% of these went on to require major amputation (above or below knee) during the 12 month follow-up period (Prompers et al., 2008), Krishnan, Nash, Baker, Fowler & Raymen (2008) reported an amputation rate of 16.5 per 10,000 people with diabetes in the UK.

Estimates of costs of treating Diabetic Foot Ulcers (DFUs) have demonstrated inconsistencies in calculations between countries, and within different regions of the same country. Prompers (2008) used data from the Eurodiale study to calculate an average cost of €10,000 for treating a non-infected ulcer. An infected ulcer with concurrent peripheral arterial disease was calculated to cost €17,000 to treat. All centres involved (14 in 10 countries) followed the same assessment and management protocols as detailed in clinical guidelines from the International Working Group on the Diabetic Foot. Despite this, there were wide variations in treatments provided between countries and centres. For example, use of casting varied from 0% to 68% despite clinical guidelines recommending it as the most efficacious treatment for plantar ulcers. The authors reported similar variation in imaging techniques employed for ulcers with additional ischaemia. Resource

allocation by Clinical Commissioning Groups (CCGs) and health care trusts can have a profound effect on DFU management due to workforce numbers, staff skill mix, and accessibility of modern, effective treatments. There is an associated risk that out-dated treatments may be retained by healthcare providers due to the high costs associated with obtaining and implementing more advanced alternatives. Cavanagh et al. (2012) examined costs of treating a hypothetical DFU with severe infection which was unresponsive to treatment. The pre-defined outcome was below knee amputation. Estimated costs of treating such an ulcer incorporated several failed antibiotic regimens, hospital admission for intravenous antibiotics, management of sepsis, attempted limb salvage and, finally, a major limb amputation with associated aftercare. Total costs amounted to $188,645 based on USA insurance billing receipts. Similar calculations have not been forthcoming using UK data, which is likely due to differences in the nature of data collected. USA healthcare bills capture details of treatments to ensure every intervention is paid for. The focus of UK data collection for the NHS is driven by service planning and improvement - prevalence data for specific conditions is compiled in the Public Health Observatories prevalence model, for example. The Quality Outcomes Framework and reference costs provided to Clinical Commissioning Groups also provide data, but often this is somewhat generic.

There are few databases that capture diabetic foot ulceration as a distinct entity. Diabetes UK analysed data from the Public Health Observatory and National Diabetes In-patient Audit to produce "The Cost of Diabetes" report (Diabetes UK,

2014), which explored the cost of specific diabetes-related complications to the NHS. Diabetic foot conditions were grouped with amputations, and, together, they cost the NHS £300 million in 2010/2011. Amputations are expensive due to surgical and in-patient bed use, but financial models of total treatment costs for DFU management versus amputation management have demonstrated that complex DFUs are substantially more expensive than amputations (Kerr, 2012).

Treatment of the majority of uncomplicated diabetic foot ulcers consists of debridement of non-viable tissues and an appropriate dressing tailored to the requirements of the individual wound, followed by a degree of offloading (IWGDF, 2011). This is, perhaps, the key to healing diabetes-related foot ulcers, and outcomes are often positive when offloading advice is followed. Total contact casts are the gold standard for offloading, based on evidence of a 90% success rate for ulcer healing, as supported by several randomised controlled trials (Armstrong et al., 2001; Armstrong, Lavery, Kimbriel, Nixon & Boulton, 2003; Armstrong, Lavery, Wu & Boulton, 2005; Katz et al., 2005; Piagessi et al., 2007). Other offloading devices, such as a removable cast walker or adapted footwear, have not demonstrated the same degree of success. The reason for the variation in healing rates was revealed in a study by Armstrong et al. (2003) who covertly recorded the activity levels of patients whilst they wore a prescribed removable cast walker as treatment for neuropathic foot ulcers. Findings demonstrated that patients only wore the offloading device for 72% of their total daily activity. Persistence with weight bearing

on a diabetic neuropathic foot ulcer will undoubtedly prevent healing and, in most cases, promotes further deterioration. A total contact cast, on the other hand, provides the foot with an alternative means of protection in the absence of normal sensation. Total contact casting is contraindicated for use with ischaemic ulcers, and osteomyelitis, due to the risk of additional complications such as ulcer deterioration due to poor arterial inflow and the difficulty in prompt detection with a non removable cast (Walker, Helm & Pulliam, 1987).

1.3.4 Prevention of Diabetes-Related Foot Complications

The ideal intervention for diabetic lower limb complications should be prevention. One of the key messages in the National Institute for Health and Care Excellence (NICE) guidelines on Type 2 diabetes (NICE, 2008) is self-management, whereby patients are educated regarding specific aspects of their condition, thus empowering them to share in the responsibility for their health through self-monitoring. The aim is to achieve an increased awareness, facilitating improved compliance with professional advice, which should ultimately lead to a reduction in complications. Education programmes, as recommended in the National Service Framework (NSF) for Diabetes (Department of Health, 2001) and NICE (2008), have attempted to achieve patient self-management through education sessions from the diabetes multi-disciplinary team. The DESMOND programme (Diabetes Education and Self-Management for Ongoing and Newly Diagnosed) offers education sessions for

patients as part of a highly structured training programme. In 2008, the efficacy of the DESMOND programme was investigated via a cluster randomised controlled trial in England and Scotland (Davies et al., 2008). The intervention group (receiving the DESMOND programme) consisted of 437 newly diagnosed type 2 diabetes subjects, and the control group consisted of 387 newly diagnosed type 2 diabetes subjects. Outcomes included a 1% improvement in HbA1c, weight and psychosocial beliefs relating to their diagnosis. Results were adjusted for a clustering effect, but failed to demonstrate a statistically significant change at the 5% level for changes in HbA1c (p=0.52). However, a significant improvement in weight (p=0.02) was identified at four-month and twelve-month follow-up, with DESMOND participants losing a mean of 2.98 kg versus the control group weight loss of 1.86 kg. Improved depression scores (p=0.03) of intervention group participants were also observed at twelve-month follow up. The positive outcomes were not maintained after study completion, and a three-year follow-up period failed to show any differences in biomedical outcomes between the control and intervention groups (Khunti et al., 2012).

To date, the only intervention proven to halt or reduce diabetes-related complications is strict glycaemic control, as reported in The Diabetes Control and Complications Trial (DCCT, 1993). No other treatment has demonstrated such a profound impact on clinical diabetic complications, and, as a result, glycaemic control remains at the forefront of diabetes management (Inzucchiet al., 2015). The DCCT recruited 1441 subjects in a multi-centre, randomised controlled trial to investigate the effects of an

intensive insulin regime and stringent blood glucose monitoring on diabetes-related complications. The intensive regime was defined as pre-prandial ranges of 3.9 – 6.7 mmol/l and post-prandial of less than 10 mmol/l, plus 3 injections per day or the use of an insulin pump, combined with regular glucose monitoring. Subjects on the intensive regime demonstrated a 76% reduction in the onset of retinopathy ($p=0.04$), a 39% reduction in nephropathy ($p=0.02$), and a 60% reduction in neuropathy over 6.5 years ($p=0.006$). Furthermore, glycaemic control over the duration of the study was significantly better in the intensive group versus the conventional cohort (8.6 ± 1.7SD (standard deviation) versus 12.8 ± 3.1SD mmol/l, $p<0.001$).

Diabetes-related complications can be prevented and even reversed, but, in practice, DPN remains a major cause of diabetic foot ulceration. Treatment of DFUs is based on a sound understanding of the physiological changes that occur in the lower limb as a result of diabetes. However, prevention is always more preferable than attempting to heal an acute or chronic ulcer. Targeting prevention through daily self-inspection of feet for signs of injury is just one example of trying to reduce risk. Falling in the home or outside, and an associated soft tissue injury could be the catalyst for foot ulceration. Ulcers can have a devastating impact on a patient's quality of life and psychological profile, not to mention the economic considerations to the healthcare provider.

To summarise, the previous sections have explored diabetes physiology and the development of DPN, followed by the clinical consequences of DPN, including DFUs. However, the peripheral nerves of the lower limb are not restricted to a purely protective function; they also play a huge role in sensory feedback during ambulation. The next sections will present the physiological evidence for the role of the peripheral nerves during gait, and the rationale for proposing DPN disturbing gait.

1.4 Normal and Ageing Gait

The lower limb provides body weight support and assists in mainlining equilibrium, but its principal role is locomotion. Peripheral neuropathy and gait are linked by shared physiology. Normal human locomotion involves a complex interplay between the peripheral and central nervous systems to enable movement of the human body through its centre of gravity. Simultaneously, information from the external environment is collected, processed and assimilated, so that any necessary adaptations can be initiated as quickly and efficiently as possible. The foot and ankle possess an array of sensory receptors that contribute to the processes involved in maintaining safe, effective locomotion. Cutaneous receptors are involved in the detection and transmission of information received from the external environment. Meisseners corpuscles are located in the dermis of the foot and consist of encapsulated nerve endings. These receptors generate rapidly adapting

action potentials to convey information about the "dynamic" low frequency vibration (levels less than 100Hz) (Brodal, 2004).

Pacinian corpuscles are another type of encapsulated afferent receptor, and are located at the dermis-subcutaneous border. They are rapidly adapting in the generation of action potentials similar to Meisseners corpuscles, but, in contrast, have a lower response threshold, thus detecting high frequency vibration (above 100Hz) (McGlone, 2010). In the epithelial tissues of the foot, Merkels discs convey touch sensation, specifically that of form and surface judgement. Ruffini corpuscles are present in the dermis, parallel to the skin surface, but can also be found in ligament and tendon. They may detect position sense. Temperature sensation is conveyed by receptors specifically designated for cold or hot stimuli using A-delta (δ) fibres and c-fibres (Schepers & Ringkamp, 2010).

Beyond the foot, moving to the ankle joint and lower limb, peripheral receptors are embedded in the joint capsules and connective tissues receiving information via small afferents from group III and group IV fibres. Group III are very thinly myelinated and Group IV fibres are unmyelinated (Gilman & Cooper, 2002). The receptors within the joint capsule and connective tissue are essentially free nerve endings interspersed with encapsulated endings which are similar in structure and function to the Pacinian and Ruffini endings of the dermis. Spindles are housed within a capsule containing intrafusal fibres and sensory dendrites from the muscle

spindle afferent. The capsules are interspersed throughout the body of the muscle so that alterations in muscle length are accompanied by a corresponding spindle stretch (Kumar & Clarke, 2002). This information is communicated to the spinal cord via grade Ia and grade II afferent fibres. Type Ia fibres are heavily myelinated, and, as such, exhibit rapid conduction velocities necessary to relay information about muscle stretch (Proske, 2005). Group II fibres are myelinated, but not to the same degree as Ia fibres, and their slower conduction velocity means they are suited to conveying information on static muscle position.

Receptors in the Golgi tendon organs are responsible for monitoring and signalling forces, whilst receptors within the muscle spindles relay and receive signals regarding alteration in muscle length and velocity (De Carlos & Borrell, 2007).

During limb loading, a number of receptors are activated, including the pressure receptors in the foot, Golgi tendon organs within the ankle, and spindles within stretched muscles. Further information is transmitted from the vestibular system. Force is sensed by the Golgi tendon organs, and this in turn modulates muscle activity in the leg (Wakeling, von Tscharner, Nigg & Stergiou, 2001). Position of the body and limbs, and subsequent movement is sensed by the muscle spindles. Sensory integration of the information occurs in the thalamus. Neurological control of locomotion is complex, and, in order to function effectively, the components need to be intact. It follows that a disturbance in the core parts of the system is likely to

result in a degree of malfunction. Peripheral neuropathy increases the vulnerability of the lower limb to trauma and ulceration. It is logical to assume that peripheral neuropathy also increases the possibility of gait disturbance.

1.4.1 The Gait Cycle in Level Walking

The normal gait cycle broadly consists of two phases, stance and swing, which are sub-divided to capture the specific constituents of each phase. The stance phase consists of initial contact, a loading response, mid-stance, and terminal stance, plus the first half of pre-swing. During level walking, heel strike represents initial contact at which point the toes of the contralateral limb are still in contact with the ground pending swing. This creates a position of double limb support, which provides maximum stability and shock absorption into the loading response. At the same time, knee flexion is achieved, controlled by the quadriceps, and hip extension begins as the trunk moves forward, regulated by eccentric contraction by gluteus maximus and the hamstrings (Anderson & Pandy, 2003). Plantar-flexion of the ankle occurs with eccentric contraction of anterior tibialis, and the lesser dorsiflexors produce a smooth, controlled descent of the foot. Mid-stance is marked by the plantar surface of the foot having achieved full contact with the ground.   The heel will be approximately three degrees inverted in relation to the supporting surface in order to lock the sub-talar and mid-tarsal joints (Root et al., 1977). Once the medial and lateral columns of the foot make contact with the ground, plantar-flexion allows the

mid and anterior foot to follow, having become compressed and fixed to provide maximum stability (Lafortune, Cavangh, Sommer & Kalenak, 1994). Muscles active during this phase include gluteus medius, hamstrings, quadriceps, and pretibial muscles. Lengthening of the quadriceps during knee flexion provides shock absorption for the foot, whilst triceps surae, tibialis anterior and the plantar fascial band promote a smooth, controlled foot descent.

During mid-stance, body weight is supported by a single limb, causing the longitudinal arch of the foot to flatten in order to increase stability. Additional support from the plantar fascial band and full plantar contact with the ground provide maximum stabilisation. Forefoot loading and supination of the sub-talar joint move the sub-talar joint into a neutral position, whilst the mid-tarsal joint locks. At the point of maximum forefoot loading, the "windlass mechanism" (Hicks, 1954) assists with "toe off", and subsequent limb propulsion. The tightening of the plantar fascial band was likened to a windlass by Hicks, mimicking a rope-and-pulley system to pull the calcaneous forwards, simultaneously raising the medial longitudinal arch. This promotes elevation of the heel and compression of the foot joints. Heel elevation signifies the start of terminal stance, during which body weight moves forward over the supporting foot and becomes concentrated at the metatarsal heads. The metatarsal and phalanges spread to give additional support. Throughout mid and terminal stance, stability is maintained by the soleus and gastrocnemius (Leardini et al., 2007).

The swing phase consists of a portion of pre-swing, initial swing, mid swing and terminal swing. Pre-swing begins when the foot on the contralateral limb enters initial contact to create a second period of double support. Body weight is transferred to the other limb, whilst the pre-swing limb flexes at the knee and hip to support the trunk and limb. During initial swing, "toe off" occurs as described above. Ankle dorsiflexion and contraction of the lower limb muscles assist in achieving ground clearance for the foot. As advancement of the limb continues, the tibia assumes a vertical position, and ankle dorsiflexion prevents the forefoot from dragging on the surface below (Mills & Barrett, 2001). The knee is extended in preparation for heel strike, and the foot assumes a neutral position. The point at which the same limb achieves heel strike for the second time constitutes the end of one gait cycle.

1.4.2 The Gait Cycle During Stair Negotiation

The gait cycle for stair ascent and descent differs substantially from level walking (McFadyn & Winter, 1988). Some of the differences reported include greater maximum angles for hip and knee flexion and ankle plantar/dorsiflexion during the swing phase (Lark, Buckley, Jones, & Sargeant, 2004). Mean maximum angles for ascent show a greater amount of knee and hip flexion in comparison to descent (Andriacchi et al., 1980). Ankle joint ascent requires less dorsiflexion and plantar flexion than during descent (Protopapadaki et al., 2007). Reiner, Rabuffetti and

Frigo (2002) found stair negotiation required approximately 12-20° more flexion at the knee, and 15-20° more hip flexion than level walking. Temporo-spatial gait parameters also differ for stairs versus level walking, with gait during stair negotiation being associated with lower cadence, shorter stance, and longer cycle duration in healthy adults (Nadeau, McFadyen & Malouin, 2003).

In addition to the different characteristics of gait for stair negotiation versus level walking, the structure of the gait cycle is altered. The first stage is weight acceptance, proceeding into the pull-up phase, followed by forward continuance, foot clearance and foot placement (McFadyn & Winter, 1988). During weight acceptance, initial foot contact with the ground is made by the forefoot whilst the hips and knees move into flexion with the ankle on the leading limb slightly dorsiflexed. Double support provides assistance with stability and weight bearing at this point.

The pull-up phase of stair ascent requires significant power generation from the ankle, knee and hip, primarily in the extensor muscle group, to lift the swing limb from one step to the next. The greatest muscle activity is generated by the knee during this phase, but the ankle assists with vertical lift. During weight acceptance, the knee and hip provide support for full body weight in single support, whilst also moving vertically. This is achieved by the extensor muscles of the knee and ankle. The hip flexors play a dominant role during swing for the limb to progress anteriorally before the extensors open the knee, and dorsiflexors lift the toe in preparation for

foot clearance, with hip extensors assisting in final foot placement (Graci, Elliott &

Buckley, 2009).

The phases of stair descent begin with weight acceptance by limb loading in the

direction of gravity, and thus requiring greater control from the muscles. During

weight acceptance, the lateral border of the foot makes contact with the step below,

and ankle stability is maintained by the plantar flexors as body weight shifts forwards

and down. By the time "toe-off" occurs in the contralateral limb, the body will have

dropped to the level of the stair below, which requires significant dorsiflexion at the

ankle. The travelling leg is pulled through by the hip flexors with only slight flexion

needed at the knee. Between leg pull-through and final foot placement, the hip and

knee move into extension, and the ankle joint is plantar flexed in preparation for

contacting the step below. The process of descending from one step to the next

(step over step) is described by McFadyn and Williams (1988) as being a process of

"controlled lowering", whereby eccentric muscle activity dominates to maintain

posture and stability.

1.4.3 Alterations in Gait

Changes in the gait cycle are visibly apparent in neurological disease states, for

example, the shuffling gait associated with Parkinson's disease (Plotnik, Giladi &

Hausdorff, 2007), the asymmetrical hemiparetic limb of cerebrovascular accident

(Patterson et al., 2008), and the dyskinetic, ataxic gait of Huntington's disease (Hausdorf, Cudcowicz, Firtion, Wei & Goldberger, 1998). Gait alterations also occur in healthy, elderly individuals as a result of the normal ageing process, but the changes are not instantly visible to the naked eye as they are with neurological disorders. Specific characteristics associated with elderly gait have been established via gait analysis, and comparisons have been made with the gait of younger people. Ferrandez, Pailhous and Durup (1990) studied gait in 67 adults aged between 60-92 years, labelled in the study as the elderly group, plus 9 males with a mean age of 25 years as controls. Data were collected for temporo-spatial gait parameters whilst subjects walked the width of a six-metre room. Subjects from the elderly group walked at a lower velocity and used a shorter stride length than the younger group (p<0.001) in the walking task. This could not have been an intentional modification, as the overall cycle duration did not change and these findings have been reflected in later studies (Grabiner, Biswas & Grabiner, 2001).

Maki (1997), like Ferrandez (1990), reported reduced gait speed in a study of 72 healthy adults (mean age 82 years) during level walking. A follow-up interview twelve months later was used to determine if patients had experienced falls in that time. Results indicated that parameters such as gait speed and time spent in double support were predictive of fear of falling, but not actual falling. The best independent predictor of falling was stride-to-stride variability in speed, which Maki proposed could be useful in predicting falls.

Other age-related alterations to gait have been observed when the stability of walking is challenged by an unexpected physical disruption during walking. Studies have utilised a variety of methods to achieve this effect, including pulling at the ankle, and pop-up pieces of metal in the floor. These techniques are termed, in the field of gait analysis, gait perturbations. Eng, Winter and Patia (1994) established that healthy, young (19-29 year old) subjects responded to perturbations presented early in the swing phase by either elevating or lowering the perturbed leg to maintain stability. A combination of both strategies was demonstrated by Cordero, Koopman and van der Helm (2003), whereby elevation of the perturbed leg is attempted but abandoned, and the leg is lowered at a shorter step length (Cordero et al., 2003). Krasovsky et al. (2012) reported a different response to unexpected perturbations in older subjects (mean age 68 years) characterised by a lowering strategy, i.e., the perturbed leg was lowered to the ground in combination with a reduction in step length and step time. Utilising this gait strategy results in a prolonged Centre of Mass (COM) displacement, thereby producing a period of destabilisation (Krasovsky, 2012). The reasons why older subjects utilise a gait strategy that is likely to increase the risk of falling is unclear. Older people take longer to respond to perturbations and require more time to recover central stability in comparison to younger people (Krasovsky, Lamontagne, Feldman & Levin, 2014).

Responses to perturbations in older people demonstrate increased vulnerability to destabilisation due to prolonged recovery time after perturbation and prolonged COM displacement. The method of sabotaging a subject's stability on a treadmill is the closest investigators can get to assessing changes in gait when stability is challenged. The aim is to work towards understanding the underlying gait changes that increase the risk of falls in older adults. However, applying these findings to the elderly population as a whole is difficult due to perturbations presented at different points in the gait cycle across different studies which could influence the gait response. Furthermore, there is the possibility of a priming effect if subjects are exposed to multiple perturbations: if gait disturbances are anticipated, then the results are not representative of a normal gait response. However, Hernandez, Slider and Herderscheit (2009) addressed some of these issues by demonstrating that healthy, elderly subjects (mean age 72 years) controlled COM differently during level walking than young subjects, and also displayed reduced medio-lateral COM acceleration, thereby increasing lateral instability.

Walking is influenced by many health-related factors such as orthopaedic health, vascular health, cardiac health, Body Mass Index (BMI), muscle strength, joint range of motion and joint strength, cognition, motivation, mood, and fear (Maki, 1997). It is difficult to separate these components and determine which has the greatest influence on gait. Nevertheless, clarification of whether diabetes changes gait would be beneficial in the battle to reduce DFUs.

1.4.4 Gait Changes Associated with Falls

The literature demonstrates that gait patterns alter with ageing, but the nature of the relationship with falls is less clear, largely due to practical difficulties associated with obtaining data about an event that is not predictable and, therefore, cannot be observed. As a result, data regarding fall frequency either has to be collected retrospectively using medical records or through questionnaires. This relies heavily on memory, recall and the honesty of the individual to report if and how a fall occurred. The admission of a fall carries many negative connotations for elderly people, and it is possible that people avoid reporting a fall when it occurs. The attitudes and belief systems elderly people hold about falls was investigated in a qualitative study by Yardley, Donavan-Hall, Francis & Todd (2006). Data were generated in focus groups consisting of 3-6 people with a facilitator to assist in promoting discussion. Follow-up one-to-one sessions also took place at participants' houses in case of information being withheld due to confidentiality concerns. Sixty-six healthy, independently living people aged between 61 and 94 years of age took part in the study. The results revealed some interesting attitudes, with falls being associated with loss of independence and loss of control over the environment, and falls were seen as an indicator of having become "old". It is necessary, therefore, to consider that the answers of older people, when questioned about falls history, may

be coloured by their beliefs about what a fall represents, rather than representing an accurate reflection of falls frequency.

The influence of emotional state on falls risk was reported by Maki et al. (1997), who demonstrated that changes in temporo-spatial gait parameters, such as decreased stride length and speed, together with prolonged double support time, were independently associated with fear of falling rather than falling *per se.* In calculating falls frequencies from information obtained via questions and answers, the influences of individuals' belief systems needs to be considered as a possible confounder. An alternative to obtaining temporo-spatial data is the assessment of gait variability. Gabell et al. (1984) proposed that the gait characteristics of healthy adults were subject to small fluctuations between strides, and the magnitude of the fluctuations could be used to determine the degree of falls risk. Support for this came from Maki (1997), who reported increased stride-to-stride variability among subjects despite all other gait parameters being normal. Hausdorff et al. (2001) explored the possibility of gait variability as a predictor of falls in a prospective one-year study of 52 healthy elderly (over 70 years of age) subjects. Results indicated approximately 40% of the subjects suffered a fall in the 12-month follow-up period. Those that fell demonstrated greater stride-to-stride fluctuations than non-fallers ($p<0.05$), including increased stride time variability ($p=0.04$), and swing time variability ($p=0.02$). Greater variability in these parameters was predictive of falling (increased stride time variability, OR ((odds ratio) = 5.3, $p=0.04$), (increased swing

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time variability, OR=2.2, p=0.02)). The findings, however, need consideration in the context of the methods used for collecting data on falls frequency. Subjects were interviewed weekly, by telephone, and, as such, objective data or evidence of a fall is lacking, opening up the possibility of falls being under-reported due to embarrassment or fear of social consequences. Other possible confounders were minimised through detailed assessments of cognition using the mini-mental status examination (Folstein, Folstein & McHugh, 1975), the geriatric depression scale (Yesavage, Lum, Heersema, Adey & Rose, 1982), and functional assessment of balance (Berg & Norman, 1996), all of which disturb gait.

Although the methods employed to obtain information on falls occurrence in studies of older people is limited to the individuals' subjective report, the strength of Hausdorff's study lies with the extensive efforts to reduce confounders to a minimum. This is not seen in other studies investigating gait and falls.

Variability in temporo-spatial gait parameters, such as double support time, step length, and step time, was demonstrated by Callisaya et al. (2010). Their sample size was 412, and ages of participants ranged from 60 to 86 years old. Gait analysis demonstrated falls risk was greater in subjects with increased double support time (variability (p=0.01), and increased step length variability (p=0.02)). Furthermore, increasing age was associated with greater variability across all gait measures. This provides data that supports the findings of Hausdorff (2001), but there are two

factors that need to be addressed: firstly, a proportion of the subjects recruited had co-morbidities that would influence gait parameters, for example, 12.5% had diabetes, 7.8% had cerebrovascular accident, and 44.3% had arthritis. Secondly, subjects were contacted about previous falls after a full twelve months had elapsed, with no reference made by the authors to any interim reminders or liaison to prompt subjects' ongoing monitoring of falls. There is no evidence that the self-reported falls are accurate, but there is evidence to suggest that older people under-report falls (Mackenzie et al., 2006). However, the falls incidence in the study may be over-estimated due to the presence of co-morbidities that significantly increase the risk of falling. It is difficult, therefore, to draw accurate conclusions about the relationship between gait variability and falls from this study.

Consensus regarding specific gait variables most predictive for falls has not been achieved to date, and investigation into the value of standard temporo-spatial parameters versus gait variability is ongoing. The Hausdorff study (2001) perhaps comes closest to achieving validity due to the depth and breadth of baseline data obtained in order to reduce as much as possible the confounding variables inherent in falls research.

1.4.5 Summary

The introductory chapter has presented the anatomy and physiology underlying DPN, falls, and human gait thus illustrating the underlying links between the three. DPN and gait are connected through shared anatomy of the lower limb and also through shared neurology. DPN impairs sensory function whilst gait relies on intact sensory function for feedback to enable continual refinements and adjustments during walking. It is logical, therefore, to question whether the impairments in neurological function associated with DPN might also have a negative effect on gait and, if so, would this place people with DPN at risk for falling? Should this be the case, the implications for patients and service providers would be far-reaching. Gait disturbances inevitably increase the risk for falls, which are associated with high levels of mortality and morbidity. If DPN disturbs gait to an extent that this risk is increased, it may also be necessary to review current Podiatry practice in diabetes to determine if there is an unmet need.

In considering a possible relationship between DPN, gait and falls, a number of questions emerge: firstly is there any evidence in the current knowledge base that illustrates DPN gait characteristics that differ significantly from healthy gait? Is there general agreement between authors regarding the nature of gait alterations for patients with DPN? What, specifically, links DPN gait with falls? The answers to these questions have been generated through the literature search and accompanying search results.

1.5 Literature Review

Search Strategy

The literature search was initiated using a PICO framework (Population, Intervention,Contol, Outcome) to guide the search strategy. However, the focus of the current work was not related to an intervention but rather the effect of DPN on joint range of motion. As a result a PECO framework (Population, Exposure, Control,Outcome) was used to represent the key areas of interest (Richardson, Wilson, Nishikawa & Hayward, 1995). The study population (P) was concerned with people with DM, who were exposed (E) to DPN. Participants included controls (C) with DM but no PN and healthy, non-diabetic people. Outcomes (O) of interest were alterations in kinematic gait parameters.

MEDLINE, CINAHL, Embase, and Pubmed databases were searched for the timeframe 1990 to June 2013 using MeSH terms and text word searches. Terms used were: *diabetes mellitus*, *gait*, *gait variability*, *gait kinematics*, *gait kinetics*, and *peripheral neuropathy*. Only English articles were included. Further articles were generated through hand searches of reference sections in articles generated from the electronic databases.

416 papers were generated from the search, of which 109 were excluded by title alone as being not relevant, leaving 307 abstracts. 40 exclusions were due to a

range of lower limb amputations or deformities. A total of 146 papers either lacked any gait analysis data, or only collected kinetic data, also resulting in exclusion. 17 studies were either single case reports or reviews of collected works, thus providing no new data. Studies that did not have a DPN group of subjects amounted to 15, and a further 15 studies included peripheral neuropathy of multiple neurological causes. Examination of full texts allowed the exclusion of 53 studies due to no comparison group with the DPN/DM groups. 5 studies were excluded due to poor methodology, leaving 9 for the literature review.

An additional 7 studies were included, having been obtained as cross-references appearing in the 9 studies identified by the literature search.

1.5.1 Gait Alterations Associated with Diabetic Peripheral Neuropathy

An association between diabetic peripheral neuropathy and an increased risk for falls was initially identified by Cavanagh, Derr, Ulbrecht, Maser and Orchard (1992). In a study of type 1 diabetes patients with and without peripheral neuropathy, it was found that there was an increased tendency for falls in those with peripheral neuropathy (OR 15.0; 95%CI 1.04-216.6). The data for this study was obtained, prospectively, via questionnaires completed fortnightly over the telephone, whereby participants were asked if they had fallen since the previous telephone call. The subject groups had mean ages of 31.9 years (diabetes with Peripheral Neuropathy

[PN]) and 32.9 years (diabetes without PN), with all subjects part of a larger epidemiological study of diabetes complications, having undergone testing for DPN. This study became the foundation upon which future research in diabetes and gait abnormalities would be based, with Cavanagh et al. (1992) and, later, Mueller, Minor, Sahrmann, Schaaf and Strube (1994) cited by the majority of authors included in this current literature review. However, there are significant limitations in the study's methodology that need exploration before accepting this as a seminal piece of work. There was no face-to-face assessment of subjects engaged in locomotion, and falls data was collected via telephone interviews only and, therefore, objective confirmation of falling events through medical records or medical examination is lacking. The mean age of subjects was between approximately 32 and 33 years old, which is not an age group associated with falls, which is due to a lack of identifiable risk factors for falling. In addition, self-reporting of falls has been found to be inaccurate in older patients (over 65 years of age) in terms of both fall severity and frequency of falling (Mackenzie, Byles & D'Este, 2006). Furthermore, the phrasing of questions put to individuals can influence their responses. For example, the Centre for Disease Control (CDC) analysed data on falls via telephone surveys conducted in 2006 for the Behavioural Risk Factor Surveillance System (BRFSS) (CDC, 2008). Individuals over the age of sixty-five were asked if they had fallen and suffered a related injury in the three months prior to the telephone contact. Results found approximately 5.8 million people, over the age of sixty-five, had fallen at least once in the previous three months. A similar study was conducted by Boyd and Stevens

(2009) who identified 3.5 million older adults as having fallen in the same time frame. The disparity in results, after exclusion of other possible influences, was attributed to the content of the questions asked. The CDC had provided individuals with clear definitions of what constituted a fall and/or injury at the time of questioning, thereby establishing a shared semantic framework to assist responses. In contrast, Boyd and Stevens (2009) asked participants only if they had fallen in the last three months, leaving it to the individual to determine what constituted a fall. The relevance of this to Cavanagh et al. (1992) and other studies of falls is the fact that self-reporting may not be a reliable method of obtaining data on falls frequency and, therefore, results of studies utilising this method to investigate falls and DPN should be considered in this context.

Mueller et al. (1994) carried out gait assessments on ten people with DPN and ten healthy, age-matched controls. Kinematic and kinetic data were generated as subjects walked along a 6.8 metre walkway. Results indicated that people with DPN had a lower walking velocity (p=0.031) and shorter stride length (p=0.004) than healthy age-matched controls. Significant differences between groups were demonstrated for reduced ankle joint motion, peak ankle moment, and peak ankle power during walking. Ankle range of motion during gait was significantly reduced in DPN subjects (p=0.001), and this was also observed for plantar-flexor peak torque (p=0.001). The authors suggest that the differences in gait parameters between groups could be indicative of weakness in the plantar flexors of the DPN subjects,

which would decrease the potential for developing plantar flexor moments during terminal stance. DPN subjects also illustrated a gait pattern which favoured the use of the hip flexors to pull the leg forward during terminal stance (hip strategy) rather than making use of the weaker plantar flexors (ankle strategy) to push the leg forward and propel body weight. Reduced plantar flexion strength during terminal stance may also account for the shorter step length observed due to insufficient power generation during "toe off".

The clinical implication of these data is related to the destabilising effect of a hip strategy, which could increase the risk for falls, and some of the issues identified by Mueller have continued to be researched today. However, there are methodological issues in this study that limit the conclusions that can be made: firstly, the sample size was small with only 10 subjects in each group. Secondly, the diagnostic criteria for peripheral neuropathy were not sufficiently specific to exclude ulcers of other causes that would influence results, e.g. non-neuropathic vascular ulcers. A history of a diabetic neuropathic ulcer is not a suitable diagnostic parameter for a clinical setting, or research. Although subjects were recruited from a diabetic foot centre, it could be assumed that all DPN subjects had previously undergone appropriate assessment as part of their care, but, unfortunately, this information is not provided. Furthermore, the timeframe for a "history of a neuropathic ulcer" is unclear. A very recently healed plantar ulcer would be likely to influence pressures generated during "toe off", or any kinematic parameters. Additionally, foot ulcers are usually treated

with some degree of offloading, which, if an individual is immobilised for a protracted period, could lead to disuse atrophy in the plantar flexors. Based on the issues above, it is difficult to generalise the results to DPN patients as whole. However, the authors claim to have identified the reason for gait differences, focusing on a reduction in ankle strength and range of motion. Despite methodological shortfalls and over-generalisation of results, both studies are frequently cited in relation to diabetes and gait abnormalities, and are valuable from a historical perspective. A literature review could be construed as incomplete without Cavanagh et al. (1992) and Mueller et al. (1994) but, nevertheless, neither study provides conclusive evidence for diabetes-related gait alterations.

Significant differences in the gait characteristics of DPN subjects and healthy controls were identified by Courtemanche et al. (1996) as part of a study (total sample n= 21) investigating the influence of attention diversion on gait. The authors hypothesised that the decreased proprioception associated with DPN would increase the demands on cortical processing in an attempt to compensate for reduced sensory information. During walking tasks simultaneously accompanied by auditory distracters, DPN subjects demonstrated shorter cycle amplitude (the distance travelled between successive heel contacts of the same foot) and slower cycle speed (amplitude divided by cadence). Increased time spent in double support and longer reaction times to diversion stimuli were also recorded. Although Courtemanche et al. (1996) only had a total of 21 subjects, the results illustrate the

potential for DPN to increase risk factors for falling when cognitive load is increased. In everyday life, locomotion occurs amidst a vast range of sensory distractors. How well older individuals with DPN adapt to environmental and cognitive demands in the context of impaired proprioception could assist in identification of those most at risk of falling.

Richardson, Thies, DeMott and Ashton-Miller (2004) continued on a similar theme to Courtemanche by challenging the locomotion system of subjects with peripheral neuropathy and observing the effect on gait. Subjects with peripheral neuropathy (n=12) were compared with healthy controls (n=12) whilst walking over a variety of different surfaces. A textured and uneven walkway consisted of carpet flooring with pieces of wood protruding from underneath with the aim of exploring whether or not the reduced proprioception in the peripheral neuropathy group reduced their ability to negotiate the walkway. In order to decrease the amount of support from the visual system, the experiment was conducted under dim lighting. This is more reflective of the everyday environment than previous studies, and places a greater load on proprioceptive processing. On a flat walkway, the neuropathic subjects displayed slower speed, shorter step length and longer step time when compared to the controls. However, there were no significant differences between the two groups on the parameters of step width, step width variability or step time variability. The authors suggest that neuropathy does not destabilise subjects when mobilising on a

flat surface. The challenge of the uneven surface for the neuropathy group elicited a wider, more temporally variable gait.

The findings imply that subjects with neuropathy can maintain a relatively normal gait pattern until challenged by uneven surfaces and reduced lighting, at which point gait alterations can occur that reduce the speed and efficiency of mobilisation. It is possible that subjects with peripheral neuropathy were unable to meet the sensory demands of a more challenging environment due to a reduction in sensory receptors in the foot. However, a wide range of aetiologies for peripheral neuropathy are included such as connective tissue disease, chemotherapy-induced neuropathy, and idiopathic neuropathy, and these in addition to DPN. Whilst all of these conditions ultimately reduce lower limb sensation, other medical symptoms associated with each of these diagnoses may have also influenced the results. Other confounding variables include duration of neuropathy, type of diabetes, and duration of diabetes. . The strength of this study is the departure from standard gait analysis on a flat surface to a variety of surfaces similar to those experienced in everyday life.

Katoulis et al. (1997) used a greater number of subjects (n=80) for a study of gait characteristics in people with diabetes. Four study groups were formed as follows; 20 healthy controls, 20 non-neuropathic diabetes subjects, 20 with diabetes and peripheral neuropathy, 20 with diabetes, peripheral neuropathy plus a history of previous diabetic foot ulceration. All groups were matched for age, sex, and BMI.

Robust inclusion and exclusion criteria reduced the possibility of confounding variables to a minimum whilst also maintaining external validity.

Results illustrated that subjects with DPN and a history of foot ulceration demonstrated a significantly slower gait speed than the healthy controls or diabetic non-neuropathic group ($p < 0.02$). Smaller joint angles were observed at the knee and ankle, whilst joint moment was higher in the DPN group than the diabetes and control groups. This study provided joint angle and moment measures, which other studies did not assess. These are particularly valuable, as they equate to muscle strength, which can decrease in the presence of DPN.

Few studies have explored whether the gait patterns demonstrated by subjects with DPN are attributable to peripheral neuropathy or the condition diabetes mellitus. Petrofsky, Lee and Bweir (2005) reported the results of their study investigating gait changes in people with diabetes but no peripheral neuropathy. In comparison to healthy controls, the diabetes subjects walked more slowly ($p < 0.01$) and used more steps to complete the linear walking course. Swing width was altered in that the diabetes subjects kept their legs wider than their shoulders at the widest point during gait ($p < 0.001$). For the turns at the end of the path, the diabetes group demonstrated a lower velocity ($p < 0.01$), and required longer to execute the turn ($p < 0.05$). Petrovsky et al. (2005) reported increased gait variability in the diabetes subjects, especially at the hip and knee. Almost all of the findings above have been

reported previously by other authors and attributed to DPN rather than diabetes *per se*, but based on the data of Petrovsky et al., subsequent studies would need to match DPN, diabetes but no peripheral neuropathy, and healthy controls in order to establish which condition was producing the gait alterations.

Both Mueller et al. (1994) and Katoulis et al. (1997) report similar gait changes across kinematic and kinetic parameters. This could be a reflection of their inclusion criteria in that the more severe presentations of neuropathy were represented in both studies. Katoulis et al. (1997) included DPN subjects with a history of foot ulceration, whilst Mueller et al. (1994) used history of a neuropathic foot ulcer as the diagnostic criteria for DPN. The ideal groups would be healthy subjects, diabetes but no neuropathy, and DPN but no history of ulceration.

Given that the main features of DPN gait appear to be reduced velocity and shorter stride length, Dingwell et al. (1999) investigated the effects of removing speed as a variable to determine the nature of any gait alterations remaining. Three groups of 17 subjects were assembled and consisted of individuals with DPN, those with diabetes and minimal/absent peripheral neuropathy, and healthy controls. Data was captured during the last minute of a fifteen-minute treadmill walk at a speed of 1 m/s. The timeframe for data capture was based on a pilot study conducted by the authors that demonstrated stable state locomotion is not achieved until 15 minutes of walking has been completed (Cavanagh et al., 1993), which is optimum timing for

assessment of variability. No significant differences were identified between the groups for average stride time, minimum toe clearance, and coefficient of variation in knee angles or coefficient of variation in ankle angles. The authors suggest that gait changes identified in subjects with DPN could be the product of reduced speed rather than adaptations to reduced proprioception. However, the fact that Dingwell's subjects could have been vulnerable to a fatigue effect because of the duration of the treadmill task also needs to be considered when appraising this study.

Altered temporo-spatial gait parameters were also reported by Menz et al. (2004) specifically in relation to head and pelvis accelerations in subjects with diabetes and peripheral neuropathy in comparison to healthy, age-matched controls (total sample size=60). Accelerations at the head and pelvis were measured during a walking task on regular and irregular surfaces. In contrast to many of the studies in this clinical field, subjects completed a thorough battery of tests prior to walking. Assessments included electromyographic studies of major leg muscles, a reaction time test, and tests of sensation, balance, and visual acuity. This provided a method for diagnosis of neuropathy, exclusion of other subjects with non-neuropathic neurological or circulatory symptoms, plus sufficient baseline information to observe any confounding variables. Results showed that diabetic subjects with peripheral neuropathy demonstrated smaller accelerations at the head and pelvis in vertical anterior-posterior and medio-lateral planes during gait tasks in comparison to their

healthy counterparts. Indeed, accelerations were reduced even further for walking on an irregular surface.

These data suggest that patients with diabetes and peripheral neuropathy use small accelerations in an attempt to maintain stability during gait, as any larger acceleration would be likely to have the opposite effect. On balance, the results indicate that this patient group have a tendency towards instability during gait and the small accelerations may counteract the instability, but further investigation into these key areas is required.

1.5.2 Gait Variability in Diabetic Peripheral Neuropathy

Studies of gait variability in people with diabetes and peripheral neuropathy have identified a number of parameters susceptible to increased variability. Menz (2004) described increased step-time variability in older (age range: 51 to 91 years) diabetes patients with peripheral neuropathy in comparison to healthy controls (p=0.003). Richardson et al. (2004) also calculated gait variability in older women (mean age 67.1 years old, standard deviation 7.9 years) with peripheral neuropathy versus healthy age-matched controls, but only found a trend towards increased step-width variability and increased step-time variability. DeMott (2007) reported increased step-time variability in patients with diabetic peripheral neuropathy (of

multiple causes) when walking on a regular surface in comparison to controls. This was not statistically significant, and the total sample size was only 20 subjects.

Dingwell (1999) calculated the coefficient of variation of the knee angle and ankle angle over the whole stride during treadmill walking in subjects with diabetes and neuropathy (n=17), diabetes and no neuropathy (n=17), and healthy controls (n=17). Differences between the three groups for the above angles only approached significance for the coefficient of variation of knee angle (p=0.082), and failed to reach significance for the coefficient of variation for ankle angle. Kinematic variables measured at 10% stride intervals showed no tendency towards significant variability. However, as discussed in the previous section, this study was carried out using a treadmill, and the imposition of constant speed and incline may have reduced the amount of variability in gait.

Increased variability in gait cycle time of subjects with DPN (p=0.002) was identified by Allet et al. (2009). Gait analysis was carried out on three groups of 15 subjects categorised by DPN, diabetes but no neuropathy, and healthy controls. No differences for the coefficient of variation were found for stride length.

Measures of gait variability have proven efficacy as a predictor for falls in the elderly, as demonstrated in an earlier section of this document. Dingwell (1999) and DeMott (2007) failed to demonstrate a significant difference in gait variability for subjects with DPN, whereas Allet (2009) did. Dingwell's results may have been affected by

inclusion of people with "minimal neuropathy" whilst De Mott used subjects with a variety of different aetiologies for the peripheral neuropathy. Allet used a range of assessments to diagnose neuropathy, which was either present or absent, and excluded any foot-related history that could influence results. As a consequence, her group of subjects is most likely to reflect the population of patients with diabetic peripheral neuropathy because she has excluded everyone else..

The literature describes a variety of alterations in gait associated with diabetic neuropathy, although the nature and extent of these remains undefined due to limitations in study design. A tendency towards increased variability in gait parameters such as step-time, step-width, step-length and joint angles has been documented, in addition to an exacerbation of variability during challenging gait tasks. Step-to-step variability is reportedly associated with an increased risk for falls, which could equate to people with DPN becoming a high-risk falls group.

Many studies of gait variability, as cited above, relate to temporo-spatial aspects. The majority have assessed gait during level over-ground walking, with only a few investigating more challenging environments such as uneven surfaces (Allet et al, 2009). Given that ambulatory humans negotiate complex internal and external environments on a daily basis, the results from studies concentrating on level ground walking may not be representative of "real life" and its daily environmental challenges. The implications of this are: firstly, that research to date may have

underestimated the degree of vulnerability to falls among diabetes patients with neuropathy and, secondly, there is a need to ascertain the specific changes in gait that occur during highly challenging gait tasks. This approach may provide data that is a more accurate reflection of the challenges encountered in everyday life and may, therefore, assist in the identification of patients most at risk of falls.

The focus and novelty of the research presented for the current thesis lies with the combination of parameters for analysis. Firstly, lower limb joint range of motion will be assessed to determine whether any restricted motion is contributing to the gait changes observed in people with DPN to date. Secondly, the study will analyse whether there is evidence of variability in joint range of motion, as this could represent a risk for falling. Data for the parameters described above will be obtained during three different gait tasks that aim to increase the demands made on the sensori-motor contribution to locomotion and, thus, representing the challenges of locomotion in daily life. These tasks include level walking, stair ascent and stair descent.

1.5.3 Research Aims

1. To examine joint range of motion in the lower limb during a range of gait tasks executed by individuals with diabetes mellitus combined with peripheral neuropathy.

2. To establish the degree of gait variability, and determine the risk of falls for individuals with diabetic peripheral neuropathy.

1.5.4 Hypothesis

People with diabetic peripheral neuropathy will exhibit differences in lower limb joint range of motion and increased kinematic variability during selected gait tasks in comparison to healthy controls. The degree of variability will increase as gait tasks become more challenging.

1.5.5 Ethics Approval

The study was presented to the National Research Ethics Service North West, Greater Manchester West review panel and the University of Huddersfield, Manchester Metropolitan University, and Manchester University ethical review panels, and was assigned REC reference number 11/NW/0686 upon approval.

Central Manchester Foundation Trust, Research and Development approved the research (reference number R01772)

IRAS (Integrated Research Application System) number – CSP 85837/GM

REC (Research Ethics Council) reference number – 11/NW/0686

NRES (National Research Ethics Service, Northwest, Greater Manchester West).

REC approval was granted on 25/10/2011

CMFT R&D approval was granted on 31/10/2011

Pan Manchester approved on 01/04/2012

Chapter Two

Methods

The hypothesis of the current study is based on data that suggest people with DPN express kinematic gait parameters and variability that are different to those people without DPN. The literature review provided information that allowed the formulation of the hypothesis, which will be tested using an analytical study design. A descriptive study is not appropriate, as the current study is not investigating prevalence. A diagnostic study design is also not appropriate, as diagnostic tests are not the focus of the investigation (Mann, 2003).

The current study is a prospective, observational study. As no intervention is being tested, it cannot be classed as experimental. Rather, subjects are being observed over the duration of the study period, and parameters of interest measured. Types of observational study include cross-sectional, case series, case control, and cohort studies. A cross-sectional study would not be suitable for the current investigation, as the characteristics being observed in the current study are not limited to one point in time. Data is not generated from retrospective sources either. Case series look at

specific diseases or individual characteristics that are not part of the current study remit (Koretz, 2007).

The design selected for the current investigation is a cohort study, which is characterised by observing a group of people with defined characteristics whom are followed to determine incidence, mortality or outcome from a specific disease. Cohort studies are described in terms of exposure, or disease status, and outcome, and these are related to the independent and dependent variables (Levin, 2006). Disease status in the current study is divided into DM, DPN, and healthy (non-diseased), and these constitute the independent variables. The dependent variables, or outcomes, are ROM and variability. The dependent variables are being compared between the groups to infer an association, but not as part of an attempt to establish or define causality. This is the study type that is most suitable for comparing the three groups to be studied.

The hypothesis of the current study requires a comparison of three groups: DPN, DM and control to ensure that any differences between groups are due to different group characteristics, and not just related to the shared diagnosis of diabetes, or being sampled from the wider population. The three groups constitute three levels of an independent variable or exposure in relation to the cohort study design.

The defined population of interest consists of people attending the Manchester diabetes centre for their diabetes care. The healthy group is drawn from the same geographical population, but they are disease free. A sample size calculation is required to promote generalisability to the wider population of people with diabetes and ensure a sufficient power to detect any differences between the groups. Losses are anticipated, and are factored into the sample calculations.

The group of people with diabetes will be subdivided at the point of initial assessment, in the current study, into those with symptoms of peripheral neuropathy and those free of neuropathy. This will assist in differentiating between outcomes associated with the disease state *per se*, and those that are specific to diabetes-induced sensory dysfunction. All assessment tools used to determine the presence or absence of neuropathy will be selected based on validity or accepted best practice, whilst also being highly reproducible (see sections below). All the non-diseased people will also be tested for neuropathy to reduce the likelihood of any undiagnosed individuals entering the study, as this would be likely to skew results for the healthy control group.

Data related to outcome will be measured using specialist gait assessment tools and associated software. The total number of people placing markers on individuals involved in the study will be restricted in order to reduce performance bias. Confounding variables will be minimised as much as possible through exclusion

criteria which also incorporate any factors with the potential to influence gait patterns, for example, reduced vision, inner ear disorders, and neurological disorders. The risk of compromising external validity (Rothwell, 2005) is acknowledged. However, the inclusion of such clinical groups in the current study has the potential to increase the risk of collecting data that is skewed by the outcome of the additional disease or exposure. Furthermore, it would be difficult to determine which exposure was associated with the differences observed between groups.

The outcomes being measured are joint range of motion, measured in degrees, and stride-to-stride variability in joint range of motion measured as standard deviation in degrees. These parameters relate to the underlying disease characteristics of interest upon which the hypothesis is based, i.e., that DPN alters sensation and alters gait. Given that the joints of the lower limb are anatomically associated with one another in their different planes of movement (Hoy, Zajac & Gordon, 1990), it is appropriate to measure ROM and variability at each joint in each plane of movement. Restricting this to one plane of movement will limit the possibility of finding any associations between the outcome and exposure.

The current study was part of a larger piece of research by S.Brown and J.Handsaaker at Manchester Metropolitan University investigating kinetic biomechanics in subjects with DPN, including joint moments and centre of mass-centre of pressure separation during stair negotiation. The methodology and data analysis for the current study examining gait kinematics and variability were

independent of the larger study, but the current author was responsible for DPN and DM recruitment to both. The kinetic data generated was utilised for two separate PhD studies, and constituted baseline data for comparison with post-intervention data after a short period of targeted rehabilitation. The kinematic data was the focus of the current study, and the kinetic data was not available to the author. The sections that follow provide details of the methods used to carry out the study.

2.1 Recruitment to the Study

Sample size was based on the assumption of a treatment effect of 20%, and 23% data variability. Given this is a cohort study investigating the effect of disease state on specific gait parameters, treatment effect is synonymous with disease effect, that is, the effect of DPN on ROM/ROM variability. Therefore a study of 17 participants per group (i.e. 51 in total for a 3-arm study) would be adequately powered to detect a significant difference between groups at standard levels of power and significance (van Belle, 2002). Hence, the current study, in which 90 participants were recruited, should be adequately powered to detect any existing effects with allowance for a certain level of attrition loss. Furthermore, all available consenting patients were recruited to the study. Hence, the study sample size is substantiated on pragmatic as well as theoretical grounds.

The size of the data set is such that the sampling distributions of the data will approach Normality regardless of the distribution of the population the sample was

taken from, according to the Central Limit Theorem. Hence, the relevant assumption is met for the ANOVA procedure, which, in any case, is robust to violations of Normality (Glass, Peckham & Sanders, 1972). The sample size for each of group in the study, *n*, is calculated using a formula based on estimated proportionate change in means (*PC*) and the coefficient of variation (*CV*) quoted by van Belle (2002):

$$n = 8 \frac{CV^2}{PC^2} [1 + (1 - PC)^2]$$

Healthy control subjects were recruited from the staff and student population at Manchester Metropolitan University via radio announcements, pamphlets, and word of mouth. The diabetes subjects were sourced from patients attending the Manchester Diabetes Centre (Central Manchester Foundation Trust) for management of type 1 or 2 diabetes mellitus, i.e., they were active patients. All staff working within the diabetes centre were educated regarding the study, and asked to notify the investigator when suitable patients arose. A laminated poster of inclusion and exclusion criteria was displayed in all clinic rooms used by physicians, nurses and allied health professionals. All patients were consented by the investigator following discussion and provision of written literature. Patients from ethnic minorities who could not speak or understand English due to the wide variation in ethnicity in central Manchester consented via an interpreter from the Trust's Interpretation and Translation Service.

2.2 Inclusion and Exclusion Criteria

Inclusion into either of the diabetes groups required a diagnosis of Type 1 or Type 2 diabetes, which was established from participants' individual medical case notes. These were actively open to the diabetes team at the diabetes centre.

Those recruited to the healthy group were questioned regarding their diabetes status, and consented to correspondence being sent to their general practitioner (GP) for clarification of whether they had any conditions listed as part of the exclusion criteria. Responses from GPs were received by letter, but in the event of no response, the investigator made a telephone call and spoke directly with the doctor. Letters were sent to the GPs of all subjects informing them of their patients' involvement in the study as a matter of courtesy.

Subjects were excluded from the study in the presence of the following conditions: unstable ischaemic heart disease, neurological impairments (apart from diabetic peripheral neuropathy), rheumatic disease, recent or past history of cerebral "injury", disorders of the vestibular system, musculoskeletal injury, recent surgery to the foot, ankle, lower limb, hip or back, lower-limb amputation, open foot ulcer, visual acuity measured on the Snellen scale <6/18 (of any aetiology), or excessive alcohol intake (>30 units per week), as the above conditions may impact on a person's ability to undertake the required set of tasks that lay ahead.

2.3 Assessment for DPN: Neurodisability Score

Assessment for DPN was conducted according to methods recommended by Boulton et al. (2005) for clinical trials and epidemiological studies. There is a distinction between the aims of assessing DPN as part of clinical practise versus assessing for research. In the former, it is important that assessment is pragmatic, rapid, practicable, and as accurate as possible within the clinical environment. NICE guidelines (CG10, 2004) recommend foot sensation is tested with a 10 g monofilament, or a test of vibration perception such as a biothesiometer or calibrated tuning fork. According to the guidelines, patients will be tested for pressure perception or vibration perception, but not both. This is sufficient within the context of screening for loss of protective sensation in the foot to identify risk factors for foot ulceration. For the purposes of research, a more detailed, highly objective assessment, such as nerve conduction studies or intra-epidermal nerve fibre density, is required, but these are invasive and therefore inappropriate for research purposes. The Neuro-Disability Score (NDS), (Boulton et al., 2005) is a multiple modality assessment tool for the purpose of testing a range of nerve functions, and is validated for use specifically in research of the diabetic foot.

2.3.1 Vibration Perception

The neuro-disability score incorporates multi-modality testing, the results of which are amalgamated to obtain a single score, with a score of ≥6 indicative of DPN (Boulton, 2005). Patients were seated on a hard medical couch with legs out-stretched so that the whole lower limb and heels were supported. The neurothesiometer (Diaped®, distributed by Algeos, Algeo Ltd) is an electrical device that produces vibration which terminates in a probe that is easily applied to the apex of the hallux. Commencing at zero volts, the amplitude is increased by adjusting the dial until the vibration is perceived by the patient. This is repeated three times to produce a mean reading, which constitutes the vibration perception threshold (VPT). A threshold of ≥ 25Hz is required for a diagnosis of DPN (Boulton, 2005). The assessment and marking is summarised in Table 1.

2.3.2 Pin-prick Sensation

This was assessed using the Neurotip (Owen Munford™), which consists of a disposable pin. The sharp point was placed proximal to the toenail on the dorsal hallux, and sufficient pressure applied to indent but not break the skin (Paisley,

Abbot, van Schie, & Boulton, 2002). Failure to identify the sharp sensation scores a one, while a normal response scores zero.

2.3.3 Temperature Perception

A Tip-therm$^{®}$ device (Bailey Instruments Ltd) was used to determine sensitivity to changes in temperature. The device has two pointers of different temperatures which are applied to the tip of hallux in succession. The patient is required to identify which is the warmer of the two (Viswanathan et al., 2002). Failure to identify the temperature difference scores a one, and normal would score zero.

2.3.4 Achilles Reflex

Patients were instructed to lie in a supine position with ankles and heels hanging loosely over the edge of the examining table. The foot was placed in neutral position 90 degrees to the leg, thus placing a stretch on the Achilles tendon. The tendon body was then tapped with a tendon hammer to elicit a response. A normal response is rapid plantar-flexion of the foot.

Neuropathy Disability Score			
	Scoring	**Right foot score**	**Left foot score**
Vibration Perception Threshold Normal = can distinguish between vibration/no vibration	Normal = 0		
Temperature Perception Normal = differentiates between warm/cold			
Pin-Prick Sensation Normal = differentiates between sharp/not sharp	Abnormal = 1		
Achilles Reflex Normal = reflex response	Present = 0 Present with reinforcement = 1 Absent = 2		
		Total = /10	Total = /10

Table 1. Score sheet for the neurodisability score.

Intact sensation should have a total score of zero. The higher the score, the greater the degree of pathology.

2.4 Gait Assessment

Data were generated from three gait tasks completed by all participants. The tasks consisted of level walking, stair ascent, and stair descent.

2.4.1 Level Walking

A 10-metre walkway was used for level walking tasks. This was constructed from concrete to represent a normal external walking surface. Two white lines marked out the start and finish. The width was set at a regular pavement width of 1 metre. Participants were fitted with retro-reflective markers and requested to stand at the beginning of the walkway with feet together, looking straight ahead. They were instructed to walk at a pace which felt comfortable to them, and to stop where the walkway terminated at 10 metres. This was repeated three times per limb to generate sufficient data to obtain a mean value for each parameter being measured, and to produce a sufficient number of strides to observe any stride-to-stride variability.

2.4.2 Stair Negotiation

Stair ascent and descent was carried out using a seven-step stair, constructed by Manchester Metropolitan University School of Healthcare Science. Seven steps were selected to capture two-and-a-half gait cycles during ascent and descent to

mimic normal stair negotiation. The stairs were designed with each step measuring 175mm high, 1050mm wide and 275mm deep, which is broadly representative of household stair measurements. The frame was metal, whilst tread and kicker plates consisted of a wood composite similar to medium density fibreboard (MDF). Smooth, metal handrails on both the right and left were included running along the full length of the stair. To obtain a starting position and posture consistent across trials, participants were instructed to focus their vision onto a target picture of three concentric circles printed onto plain white paper and positioned at eye level, placed 10 metres in front of them. The aim was to control for downward gaze being used as a strategy to aid foot placement. Once in position at the base of the stairs, participants were requested to ascend and descend the stairs as comfortably as possible using the handrails as required. Upon reaching step seven, where there was ample room to turn around, participants were instructed to descend the stairs. A minimum of three ascents and three descents were recorded for each participant to obtain mean values for each parameter. Gait speed was measured as the horizontal velocity of participants' centre of mass.

2.4.3 Marker Set and Data Capture

Data was obtained for each participant engaged in (i) level walking, (ii) stair ascent, and (iii) stair descent. Data was captured using the Vicon® three-dimensional (3D) motion capture system (Vicon Motion Systems, Oxford, UK), and Vicon Plug-in-gait kinematic model with the modified Helen Hayes marker set. Vicon MX40 (4

megapixel) cameras were used at 100Hz, and positioned around the walkway to give the best possible view of the walkway area and stairs.

Visual 3D ^{TM} (C-motion Inc, Maryland, USA) is a multiple modelling software package, compatible with a wide range of motion capture systems. It measures and quantifies movement from these systems. This is not restricted to any one gait model, allowing greater system flexibility, especially for research.

The full body marker set was used as part of an additional study collecting gait related data. The current study generated and analysed data for joint range of motion and gait speed during the three gait tasks. The descriptions for marker protocol, segment and tracking definitions, and subsequent figures are presented for full body application for completeness. To determine joint angles, the model gains information on the position and orientation of each segment (i.e., foot segment, shank segment, thigh segment), and examines each segment's position in relation to the proximal segment. This provides the joint angle in all three planes. To provide this information, each segment needs to have a minimum of 3 non-collinear markers. Modifications included the use of additional tracking markers to provide redundancy from occlusion due to the structure of the stairs, and medial ankle and knee markers to improve joint centre definition at those joints. The protocol for marker placement is given in Table 2 as per the Vicon Plug-in-gait manual. Additional information regarding placement was utilised from the work of Davis (1991), and the Helen Hayes model.

The current study's markers were placed by two Biomechanists and a Podiatrist. The current author had received training in marker application by one of the aforementioned Biomechanists.

Vicon Plug-in-gait^{TM} is an addition to the original software for the 3D motion sensor, and uses a full body set of retro-reflective markers, the placement of which is illustrated in figure 1. The body is divided up into segments containing different markers to track position and orientation of each segment. Placement of most markers relates to a particular bony landmark on the body. However, the mid-shank markers were positioned to define segment rotation in relation to joints or other markers. Joint centres were calculated from the markers. Tracking markers were used to define the position of a marker relative to a specific body segment during software model calibration, thus providing better tracking of segments during trials. Reliability and accuracy of placement was increased by ensuring that investigators had achieved competency in placement under the supervision of a senior biomechanist with extensive experience in marker application. The exact placement of markers is shown as an illustration in Figure 1.

Marker placement for Plug-in-gait: Upper Body	
Marker	**Landmark for placement**
HD_TOP	Top of head
LFHD RFHD	Headband: Left front/Right front
LBHD RBHD	Headband: Left back/Right back
C7	7th cervical vertebra
RBAK	Middle of right scapula
T10	10th thoracic vertebra
CLAV	Jugular notch, between the clavicle at meeting point with sternum
STRN	Xiphoid process
LSHO	Left Acromio-clavicular joint
LUPA	Left upper arm between elbow & shoulder markers
LELB	Left lateral epicondyle
LWRA	Styloid process of Left Ulna
LWRB	Styloid process of Left Radius
LFIN	Left hand proximal to the 2nd metacarpal head
RSHO	Right Acromio-clavicular joint
RUPA	Right upper arm between elbow & shoulder markers
RELB	Right lateral epicondyle
RWRA	Styloid process of Right Ulna
RWRB	Styloid process of Right Radius
RFIN	Left hand proximal to the 2nd metacarpal head

Table2. Protocol for marker placement.

Marker placement for Plug-in-gait: Lower Body	
Marker	**Landmark for placement**
LASI	Left anterior superior spine –placed directly over pelvis
RASI	Right anterior superior iliac spine – placed directly over pelvis
LPSI	Left posterior superior iliac spine – placed on the bony prominences below the sacro iliac joints at the point where the spine joins the pelvis
RPSI	Right posterior iliac spine – see above
SACR_INF	Sacral marker – placed midway between LPSI & RPSI markers & slightly inferior
L_PEL	Left side of pelvis level with & between LPSI & LASI markers
R_PEL	Right side of pelvis level with & in between RPSI & RASI markers
LTHI	Lateral thigh approx ½ way between hip centre & knee centre. Align anteroposteriorally with the knee & hip extension/flexion axes
LKNE	Left lateral femoral epicondyle – lateral side of knee flexion/extension axis: flex & estend knee & use most constant axial point
LKNE_MED	Left medial femoral epicondyle – medial mirror of LKNE marker so that the line connecting the two approximates the flexion/extension joint axis
LTIB_SUP	Left leg, top $1/3^{rd}$ of shank, medial to tibia
LTIB	Left leg, lateral edge of shank, same plane as the knee & ankle flexion/extension axes
LTIB_INF	Left leg, bottom $1/3^{rd}$ of shank just lateral to the sagittal plane
LANK	Left leg, medial malleolus
LANK_MED	Left leg, lateral malleolus
LHEE	On the calcaneous, at same height as LTOE marker (left foot)
LFT_MED	On foot band, medial side of left foot - position so that band is approx midway between toe markers and ankle, ensure ankle motion wont disturb band.
LFT_LAT	On foot band, lateral side of left foot - position so that band is approx midway between toe markers and ankle, ensure ankle motion wont disturb band.
LTOE	2nd metatarsal head, left foot
LMT5	5th metatarsal head, left foot

Table 3. Description of Plug-in Gait marker placement for the lower body.

Marker placement for Plug-in-gait: Lower Body (continued)	
Marker	**Landmark for placement**
RTHI	Lateral side of right thigh approx ½ way between hip centre & knee centre. Align anteroposteriorally with the knee & hip extension/flexion axes
RKNE	lateral femoral epicondyle of right leg – lateral side of knee flexion/extension axis: flex & extend knee & use most constant axial point
RKNE_MED	
RPSI	Right posterior iliac spine – see above
SACR_INF	Sacral marker – placed midway between LPSI & RPSI markers & slightly inferior
L_PEL	Left side of pelvis level with & between LPSI & LASI markers
R_PEL	Right side of pelvis level with & in between RPSI & RASI markers
RTHI	Medial femoral epicondyle right leg – medial mirror of RKNE marker so that the line connecting the two approximates the flexion/extension joint axis
RTIB_SUP	Top 1/3rd of shank, medial to tibia of right leg
RTIB	Lateral edge of shank, same plane as knee & ankle flexion/extension axes of right leg
RTIB_INF	Bottom 1/3rd of shank just lateral to the sagittal plane, right leg
RANK	Medial malleolus, right leg
RANK_MED	Lateral malleolus, right leg
RHEE	On the calcaneous (right leg), at same height as LTOE marker
RFT_MED	On foot band, medial side of right foot - position so that band is approx midway between toe markers and ankle, ensure ankle motion wont disturb band.
RFT_LAT	On foot band, lateral side of right foot - position so that band is approx midway between toe markers and ankle, ensure ankle motion wont disturb band.
RTOE	2nd metatarsal head, right foot
RMT5	5th metatarsal head, right foot
R2ND	Tip of 2nd toe, right leg

Table 3 (continued) Description of Plug-in Gait marker placement for the lower body
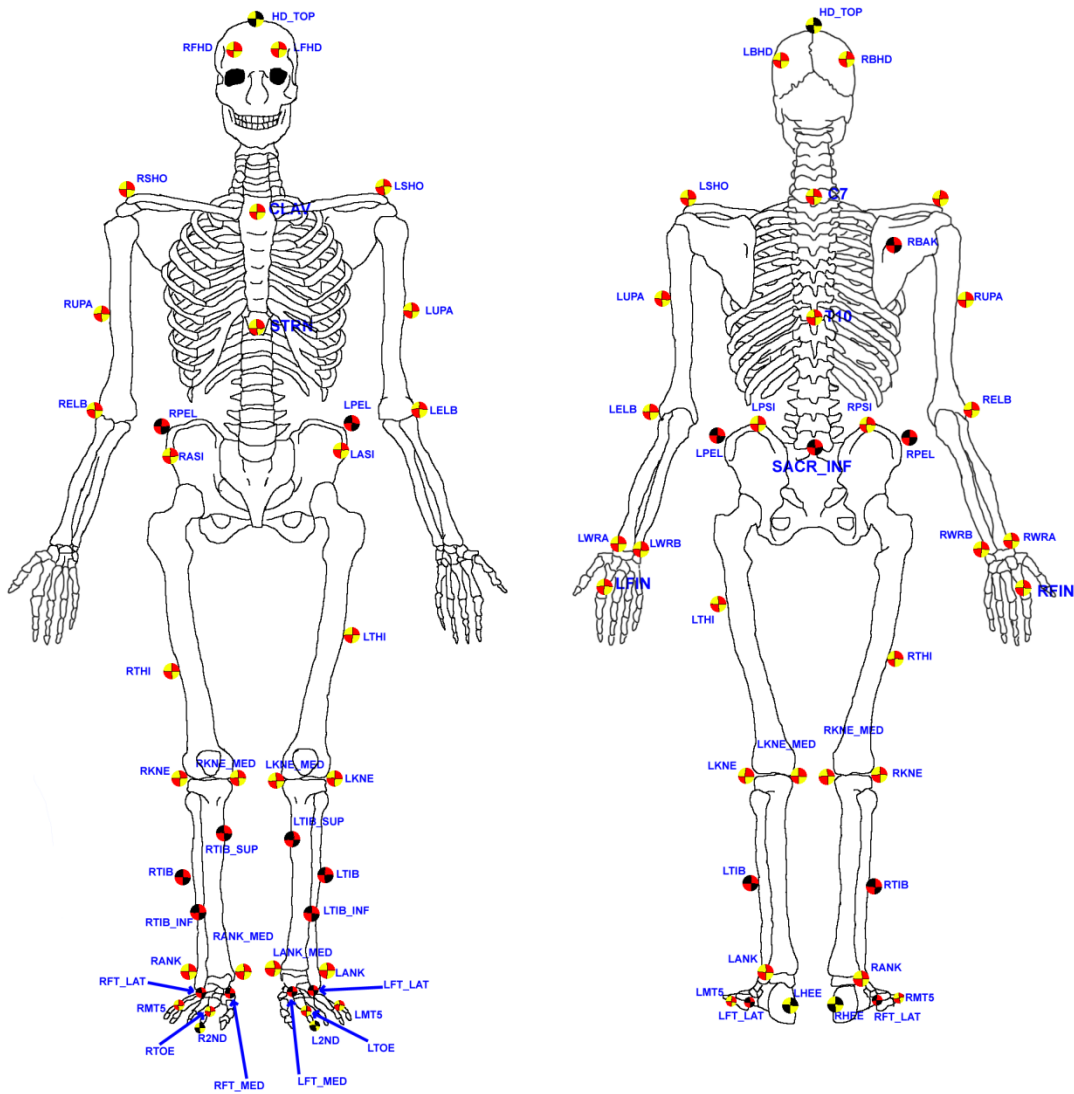
Figure 1. Positions for Plug-in-gait anatomical markers

Key: red - tracking marker, yellow – calibration marker, red and yellow – tracking and calibration marker.

Segment		Definition	Tracking
Head		HD-TOP + LFHD + RFHD + LBHD + RBHD	LFHD + RFHD + LBHD + RBHD
Thorax		RSHO + LSHO + Pelvis	LSHO + RSHO + C7 + T10 + CLAV + STRN + RBAK
Pelvis		LASI + SACR + RASI	LASI + RASI + L_PEL + R_PEL + LPSI + RPSI + SACR_INF
Upper arms	Left	LSHO + LELB + LUPA	LSHO + LUPA + LELB
	Right	RSHO + RELB + RUPA	RSHO + RUPA + RELB
Fore-arms	Left	LELB + LWRA + LWRB	LELB + LWRA + LWRB
	Right	RELB + RWRA + RWRB	RELB + RWRA + RWRB
Hands	Left	LWRA + LWRB + LFIN	LWRA + LWRB + LFIN
	Right	RWRA + RWRB + RFIN	RWRA + RWRB + RFIN
Thighs	Left	HH_LEFT_HIP + LKNE + LKNE_MED	HH_LEFT_HIP + LTHI + LKNE + LKNE_MED
	Right	HH_RIGHT_HIP + RKNE + RKNE_MED	HH_RIGHT_HIP + RTHI + RKNE + RKNE_MED
Shanks	Left	LKNE + LKNE_MED + LANK + LANK_MED	LANK + LANK_MED + LKNE + LKNE_MED + LTIB + LTIB_SUP + LTIB_INF
	Right	RKNE + RKNE_MED + RANK + RANK_MED	RANK + RANK_MED + RKNE + RKNE_MED + RTIB + RTIB_SUP + RTIB_INF
Feet	Left	LANK + LANK_MED + LMT5 + LTOE	LANK + LANK_MED + LFT_MED + LFT_LAT + LTOE + LMT5
	Right	RANK + RANK_MED + RMT5 + RTOE	RANK + RANK_MED + RFT_MED + RFT_LAT + RTOE + RMT5

Table 4. Segment and tracking definitions.

Table 4 describes the markers used to define each segment, and which markers are

then used in order to track the segment. Markers were kept in place with a low tack

tape (3M^{TM}) to prevent skin abrasions. The double-sided tape was attached to the flat surface of the retro reflective marker for fixing onto patient skin or clothing, depending upon their attire. The used tape was hygienically disposed of and fresh tape applied for every subject. On completion of data capture the markers were removed and used tape hygienically disposed of. Each subject had markers applied with fresh tape thus, the markers were never in direct skin contact so that the risk of contamination with colonised or infecting bacteria could be reduced.

2.4.4 Clothing and Footwear

Participants were instructed to wear tight-fitting clothing such as leggings, cycling shorts and non-baggy T-shirts to improve the accuracy of marker placement. To counteract the possibility of variability arising due to differences in footwear, all participants were fitted for a pair of Darco MedSurg^{TM} shoes, which are used in post-operative care. The upper is fabricated from a lightweight breathable mesh, and the sole from an ultra-high density composite rubber. Heel grips reduce slippage, and Velcro straps hold the foot firmly in place. The MedSurg^{TM} shoe is available in sizes small, medium, large, and extra-large for men. Retro-reflective markers were placed on the shoe itself as instructed in the plug-in-gait marker set. Stair ascent and descent included use of a body harness to ensure safety of the patient in the event of a fall. The gait laboratory was equipped with a Petzl full body harness made from high strength, flexible polyester webbing accompanied by the appropriate safety certification (CE, EN 12 277 type A, UIAA 105). Fully adjustable shoulder straps and

leg loops ensured suitability for a full range of subject heights and weights whilst also

being easy to put on.

Figure 2. Marker placements in lateral and anterior views. The current study utilised

the lower limb only.
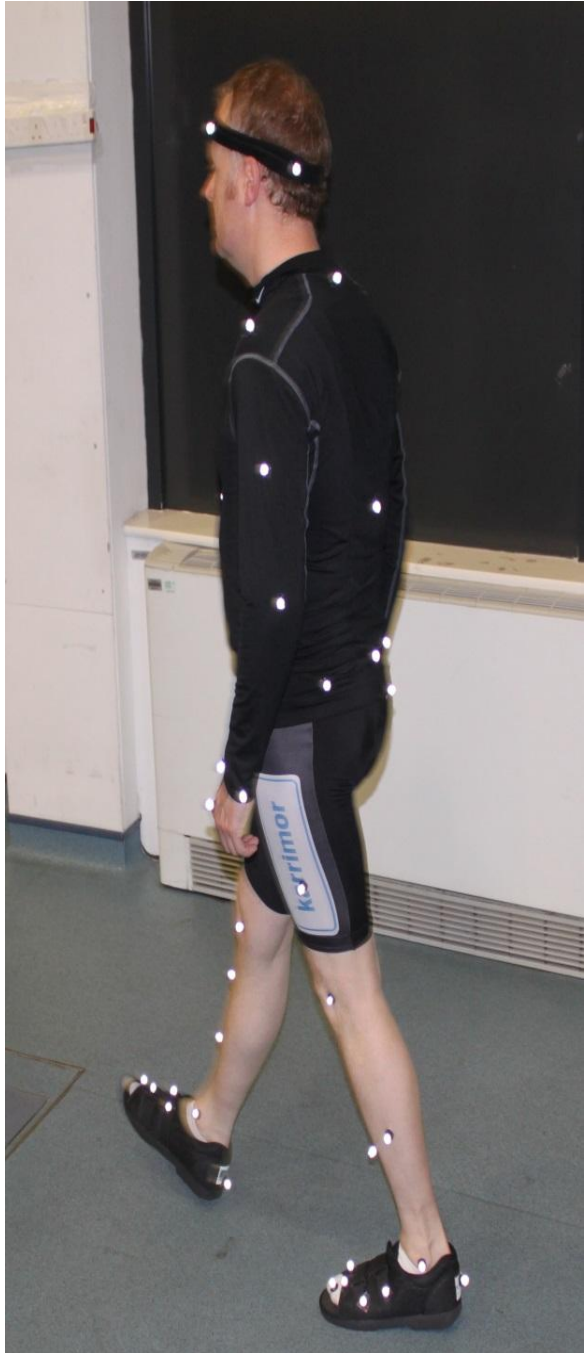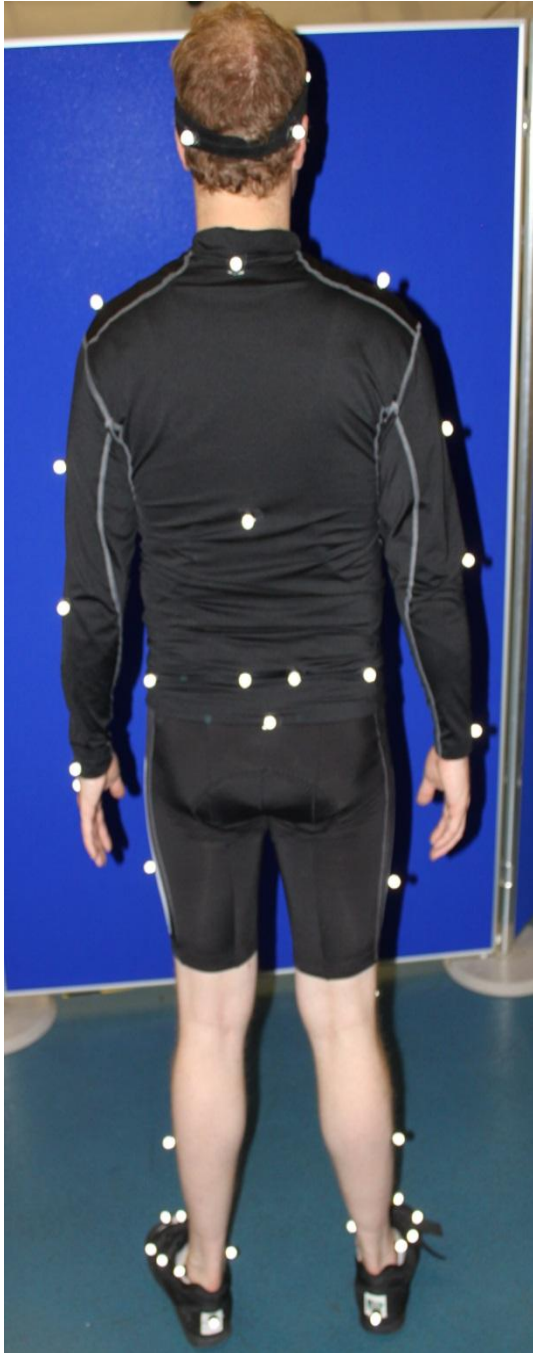
Figure 3. Marker positions from a posterior view and during level walking (lower limb only).

Figure 4 . Stair ascent and descent with harness and markers attached.

Figure 5. Over-head harness

2.5 Data Analysis

Kinematics were generated and processed using visual 3D (C-motion, Inc., MD, USA). All signals were filtered using a Butterworth filter (6Hz low-pass).

The sample was summarised descriptively by group.

Variability was measured using the standard deviation of the joint ROMs obtained from the right and left limb, over two full gait cycles, under each walking condition (level, stair ascent and stair descent), for each joint in each plane (sagittal, frontal and transverse), which allowed the calculation of the mean standard deviation per group.

Analyses of Variance (ANOVAs) were conducted on the data to identify significant differences in range of motion and gait variability between the control, DM and DPN groups (following verification of key assumptions of homogeneity of variance (using Levene's test) and independence of data). Normality of the sampling distribution could be assumed due to the sample size. Where statistical significance was indicated, *post hoc* testing was conducted using the Newman-Keuls multiple comparison procedure. Effect sizes were reported in all cases identified as showing statistical significance.

The number of outcome measures was considered in the inferences of statistical significance or otherwise. To avoid over-conservatism arising from likely correlations between different outcome measures, an amendment to the usual Bonferroni correction was applied such that the method adopted was to consider any p-value arising from a post-hoc test to be significant if it was substantially under the usual threshold of 5%, for example under 0.01. Statistical analyses were carried out using Graphpad Prism 6 © 2013 (Graphpad Software, Inc.).

Chapter Three

Results

A total of 90 subjects were recruited: 30 in the control group, 30 in the diabetes group, and 30 in the DPN group. Between the start and completion of the study, losses occurred in both the DM and DPN groups as follows: two from the DM group due to diabetic foot sepsis and drop out, 11 from the DPN group, comprising of two drop-outs, one incomplete data set due to technical failure, one fall, four due to additional hospital appointments, one parking issue, and two unable-to-contact.

3.1 Demographic and Baseline Observations

Groups were approximately evenly matched in terms of age. The mean BMI across the groups placed all three groups in the overweight category. Group means for the Neuropathy Disability Score (NDS) and Vibration Perception Threshold (VPT) demonstrated parity with clinical and study inclusion criteria for the diagnosis of diabetic peripheral neuropathy. The divisions between the groups, based on clinical assessments, are also evident in the increasing VPT from controls to DMs, with the DPNs having the highest threshold.

CHARACTERISTICS	Control			Diabetes mellitus			Diabetes mellitus & peripheral neuropathy		
Gender	Male	16		Male	14		Male	13	
	Female	14		Female	14		Female	6	
Descriptive statistics	**Mean**	**SD**	**Range**	**Mean**	**SD**	**Range**	**Mean**	**SD**	**Range**
Age (years)	51.1	16.1	26-84	58.1	11.7	27-78	57.6	9.1	41-68
Weight (kg)	74.6	13.0	50-105	79.5	12.0	55-99	86.6	19.5	61-140
Height (cm)	170	9.0	147-186	170	10.0	162-197	170	90	157-190
BMI (kg/m^2)	25.6	3.7	21-37	28.0	3.3	21-34	29.1	5.1	22-39.9
NDS *	0.8	1.0	0-4.0	1.6	1.7	0-6.0	7.1	3.0	1.0-10.0
VPT **	6.9	4.9	2.0-15.4	10.3	5.6	3.7-23.2	30.8	9.6	13.0-46.6

Table 5. Demographics for groups.

Table 5 shows the mean values for baseline characteristics of the subjects by group, including standard deviation and range values.

The healthy controls had the youngest mean age, whilst the DM and DPNs were relatively close to each other in mean age. The DPN group had the smallest range in ages (27 years) in comparison to the other groups; DM age range 51 years and control age range 58 years. In most cases the upper and lower limits of the data presented above are equally far away from the mean values suggesting similar distributions without outliers. The ranges are fairly similar to each other as a proportion of the corresponding mean to which it is attached.

There is no definitive age at which gait becomes characteristic of being elderly, but the majority of the DPNs lie between 48.5 and 66.7 years of age, which is insufficient

to impose the changes associated with being elderly on the results. According to the SD, the healthy group age majority lies between 35 and 67.2, and the DMs lie between 46.4 and 69.8. There are studies where subjects younger than 65 were included in elderly groups, but there is no evidence to suggest that subjects at this age demonstrate abnormal gait due to aging alone.

In terms of gait speed during the walking and stair tasks, the DPNs were consistently slower than the DM and control groups. For level walking, the control group were fastest with a mean speed of 1.36 metres per second (m/s) (range 0.83-1.71 m/s), followed by DMs at 1.26 m/s (range 0.98-1.61), then the DPNs at 1.18 m/s (range 0.71-1.88). Similarly, during stair ascent, the controls were fastest with a mean speed of 0.56 (range 0.39-0.82), DMs at 0.51 (range 0.33-0.77), and DPNs' mean speed was 0.44 (range 0.24-0.61). For stair descent, again, the controls were fastest at 0.6 m/s (range 0.44-0.93), followed by DMs 0.52 m/s (range 0.31-0.81), and DPNs at 0.47 (range 0.22-0.76).

The DM & DPN groups' average BMI was 28.0 kg/m^2 and 29.0 kg/m^2 respectively, neither of which equates to obesity. The healthy subjects in the current study had an average BMI of 25.6 kg/m^2, placing them in the overweight category. This is in keeping with the national trend of rising levels of overweight people in the UK population (HSCIC, 2012 health survey).

3.2 Results for Joint Range of Motion

One-way analyses of variance (ANOVAs) identified statistically significant differences between the group means during stair ascent for range of motion at the ankle joint in the frontal and sagittal planes, the knee in the frontal and sagittal planes, and the hip in the sagittal and transverse planes. A statistically significant difference in means was also identified during stair descent affecting ankle range of motion in the sagittal plane, the knee in the frontal plane and the hip in the frontal and transverse planes. In level walking, a difference between group means was only identified for ankle range of motion in the sagittal plane.

Table 6 illustrates the results from the one-way ANOVAs of the three groups for

range of motion during all three gait tasks. Significant relationships are highlighted

by bold typeface. *df* – degrees of freedom. *F* – *F* statistic.

Joint & plane	*df*	*F*	p value
Stair ascent			
Ankle frontal	2,77	2.57	0.08
Ankle sagittal	2,77	5.47	0.006
Ankle transverse	2,77	0.30	0.74
Knee frontal	2,77	8.48	**<0.001**
Knee sagittal	2,77	3.91	0.02
Knee transverse	2,77	0.71	0.49
Hip frontal	2,77	0.85	0.43
Hip sagittal	2,77	5.59	0.005
Hip transverse	2,77	3.07	0.05
Stair descent			
Ankle frontal	2,73	5.63	0.006
Ankle sagittal	2,73	10.3	**<0.001**
Ankle transverse	2,73	0.71	0.49
Knee frontal	2,73	8.11	**<0.001**
Knee sagittal	2,73	3.04	0.05
Knee transverse	2,73	3.02	0.05
Hip frontal	2,73	9.21	**<0.001**
Hip sagittal	2,73	2.52	0.08
Hip transverse	2,73	11.5	**<0.001**
Level walking			
Ankle frontal	2,77	0.33	0.72
Ankle sagittal	2,77	6.28	0.003
Ankle transverse	2,77	0.44	0.65
Knee frontal	2,77	0.15	0.85
Knee sagittal	2,77	1.13	0.32
Knee transverse	2,77	2.10	0.13
Hip frontal	2,77	0.58	0.56
Hip sagittal	2,77	0.89	0.41
Hip transverse	2,77	0.79	0.45

Table 6. Results of ANOVA, for joint range of motion during three gait tasks.

The Newman-Keuls post-hoc procedure identified statistically significant differences between groups for parameters. Twenty-seven "test triplets" were conducted on each outcome, i.e., DPN versus control, DPN versus DM, and DM versus control.

	Group mean **Ankle ROM** (degrees)			**Newman-Keuls MCT**		
	Plane of motion	**Ctl**	**DM**	**DPN**	**Group comparison**	**Q value**	**p value**
A S C E N T	Frontal	8.9	10.4	10.6			
	Sagittal	37.1	37.0	32.5	DPN v DM DPN v Ctl	4.24 4.08	p<0.05* p<0.01*
	Transverse	9.4	9.0	9.1			
D E S C E N T	Frontal	8.9	10.4	10.6	DPN v Ctl, Ctl v DM	3.95 3.94	p<0.05* p<0.01*
	Sagittal	58.8	58.0	51.0	**DPN v Ctl** **DPN v DM**	6.09 5.40	**p<0.001** **p<0.001**
	Transverse	8.6	8.9	9.4			
L E V E L	Frontal	8.1	8.1	8.6			
	Sagittal	27.8	26.5	24.3	DPN v Ctl DPN v DM	4.98 3.21	p<0.01* p<0.05*
	Transverse	11.4	10.9	10.7			

Table 7. Ankle joint ROM during stair ascent, stair descent, and level walking. Significant Newman-Keuls multiple comparisons test (MCT) results are also shown.

Table 7 illustrates that subjects in the DPN group had significantly reduced mean range of motion at the ankle during stair descent in the sagittal plane when

compared with the Ctl and DM groups. (*) denotes statistical significance not directly

inferred due to correction for multiple comparative testing.

	Group mean **Knee ROM** (degrees)			**Newman-Keuls MCT**		
	Plane of motion	**Ctl**	**DM**	**DPN**	**Group comparison**	**Q value**	**p value**
A S C E N T	Frontal	11.5	14.6	16.9	**DPN v Ctl** Ctl v DM	5.72 3.69	**p<0.001** p<0.05*
	Sagittal	85.3	90.5	87.8	Ctl v DM	3.95	p<0.05*
	Transverse	13.2	12.7	13.6			
D E S C E N T	Frontal	9.2	12.3	12.6	DPN v Ctl **Ctl v DM**	4.77 4.93	p<0.01 **p<0.001**
	Sagittal	84.5	87.8	85.5			
	Transverse	11.2	12.0	13.2			
L E V E L	Frontal	8.1	8.5	8.6			
	Sagittal	69.4	67.4	67.5			
	Transverse	12.1	11.16	13.46			

Table 8. Knee joint ROM during stair ascent, stair descent, and level walking.

After adjustments for multiple comparisons, the DPN subjects showed increased mean knee joint range of motion in the frontal plane, during stair descent, in comparison to the Ctl group. The DM group showed significantly greater range of motion during stair descent in the frontal plane, when compared with the other two groups. (*) denotes statistical significance not directly inferred due to correction for multiple comparative testing.

	Group mean **Hip ROM** (degrees)			**Newman-Keuls MCT**		
	Plane of motion	**Ctl**	**DM**	**Group comparison**	**Q value**	**p value**
A S C E N T	Frontal	14.6	15.1	15.7			
	Sagittal	55.37	59.19	58.33	DPN v Ctl Ctl v DM	3.21 4.58	p<0.05* p<0.01*
	Transverse	11.57	12.64	14.28			
D E S C E N T	Frontal	11.2	13.3	15.2	**DPN v Ctl** DPN v DM	5.97 2.86	**p<0.001** p<0.05*
	Sagittal	28.0	30.0	29.4			
	Transverse	14.4	16.0	20.2	**DPN v Ctl** **DPN v DM**	6.7 4.9	**p<0.001** **p<0.001**
L E V E L	Frontal	12.3	11.4	12.2			
	Sagittal	46.8	46.7	44.9			
	Transverse	12.7	12.4	11.4			

Table 9. Hip joint ROM during stair ascent, stair descent, and level walking.

Significant differences were identified for mean hip range of motion during stair descent; ROM in the frontal plane was greater in the DPN group than the controls, and in the transverse plane, DPN ROM was greater than the control and DM groups. (*) denotes statistical significance not directly inferred due to correction for multiple comparative testing.

3.3 Results for Gait Variability

Standard deviation was chosen as the measure of variability in keeping with previous studies by Brach (2008, 2010), and Paterson (2009). The coefficient of variation has also been used in studies to measure variability, which results in a final figure expressed as a percentage. However, as this lacks any unit of measurement, it bears little resemblance the original clinical data. The standard deviation retains this information, which is clinically more meaningful to healthcare professionals involved with this patient group. For the purpose of this study, range of motion was measured in degrees.

Table 10 illustrates results from the one-way ANOVAs of the three groups for gait variability during all three gait tasks. Significant relationships are highlighted by bold typeface. *df* – degrees of freedom. *F* – *F* statistic.

Joint & plane	*df*	*F*	p value
Stair ascent			
Ankle sagittal	2,77	2.41	0.09
Ankle frontal	2,77	2.659	0.07
Ankle transverse	2,77	0.56	0.56
Knee frontal	2,77	0.06	0.94
Knee sagittal	2,77	2.70	0.07
Knee transverse	2,77	0.36	0.69
Hip frontal	2,77	1.77	0.17
Hip sagittal	2,77	1.30	0.27
Hip transverse	2,77	0.24	0.78
Stair descent			
Ankle frontal	2,73	1.99	0.14
Ankle sagittal	2,73	2.15	0.12
Ankle transverse	2,73	0.77	0.46
Knee frontal	2,73	1.45	0.24
Knee sagittal	2,73	0.70	0.49
Knee transverse	2,73	3.25	**0.04**
Hip frontal	2,73	0.88	0.42
Hip sagittal	2,73	0.34	1.25
Hip transverse	2,73	3.85	**0.02**
Level walking			
Ankle frontal	2,77	0.23	0.79
Ankle sagittal	2,77	1.66	0.19
Ankle transverse	2,77	1.84	0.16
Knee frontal	2,77	0.73	0.48
Knee sagittal	2,77	2.67	0.07
Knee transverse	2,77	2.07	0.13
Hip frontal	2,77	2.7	0.07
Hip sagittal	2,77	0.9	0.4
Hip transverse	2,77	1.02	0.36

Table 10. ANOVA results for gait variability in joint range of motion during three gait tasks

	Gait variability standard deviation (degrees)			Newman-Keuls MCT		
	Plane of motion	Ctl	DM	DPN	Group comparison	Q value	p value
D E S C E N T	Knee transverse	2.2	2.6	3.2	DPN v Ctl	3.6	p<0.05*
	Hip transverse	30	32	43	DPN v Ctl	3.8	p<0.05*
					DM v DPN	3.2	p<0.05*

Table 11. Mean variability by group and multiple comparisons results.Comparisons initially appeared significant, but after adjustments for multiple comparisons this was no longer the case.

ANOVA identified only two parameters where a statistically significant difference between the groups occurred for gait variability: at the knee joint in the transverse plane during stair descent, and at the hip joint during stair descent in the transverse plane. Newman-Keuls multiple comparisons testing established that the DPN group demonstrated greater variability in knee joint motion versus the control group, but after corrections for multiple comparative testing, this was no longer significant. The significance of between-group differences in hip variability was not maintained after correction for multiple comparative testing.

To summarise, the ANOVAs illustrated a significant difference in means between the three groups studied for specific gait parameters. This implies the null hypothesis, that all means are equal as they originate from the same population, can be rejected.

The post-hoc Newman-Keuls test identified which groups and parameters specifically were associated with the statistically significant differences. For the most part, this arose from comparisons between the DPN and control groups, although a small number of significant differences emerged between the DM and controls, and DM versus DPN.

The dot plots illustrate intra-group distribution of results, in relation to the group mean, for the three subject groups where Newman-Keuls identified significant differences between the groups. The dot plots in figure 6 illustrate the DPN groups' significantly reduced ROM at the ankle (sagittal plane) during stair descent. The pattern of distribution around the mean is fairly symmetrical for each group.

Figure 7 is a dot plot for knee ROM (frontal plane) during stair ascent in which the DPN group showed a significantly increased ROM compared to controls, but not to DM subjects. Figure 8 illustrates knee ROM in the frontal plane during stair descent. DPN ROM was significantly greater than the control or DM groups. In figure 9, the DPN group demonstrated significantly increased ROM at the hip (frontal plane) during stair descent compared with the other groups. The majority of the DPN subjects had hip ROM above the mean, and the subjects with hip ROM below the mean appear comparable with the lower ranges of the corresponding DM group. In figure 10, hip ROM in the transverse plane illustrates the increased ROM at the hip in the DPN group, which was significantly different to both results for the DM and Ctl

groups. The DM and Ctl groups have a wide spread in their group data with some

values at the extreme ranges for the group.
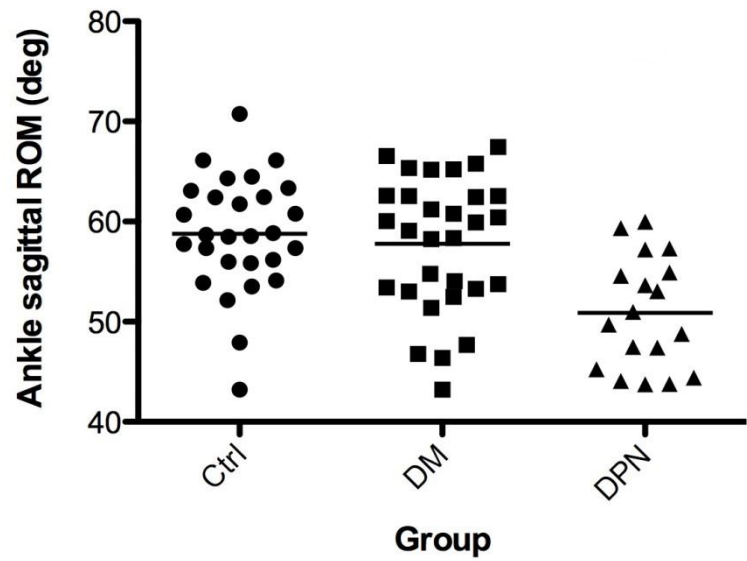
Figure 6. Ctl, DM and DPN results for ankle ROM (sagittal) during stair ascent.
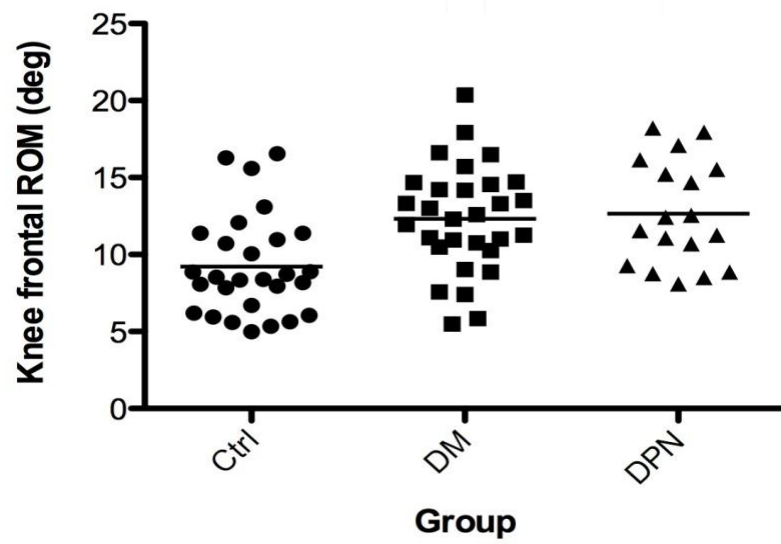
Figure 7. Knee ROM (frontal) for stair ascent.
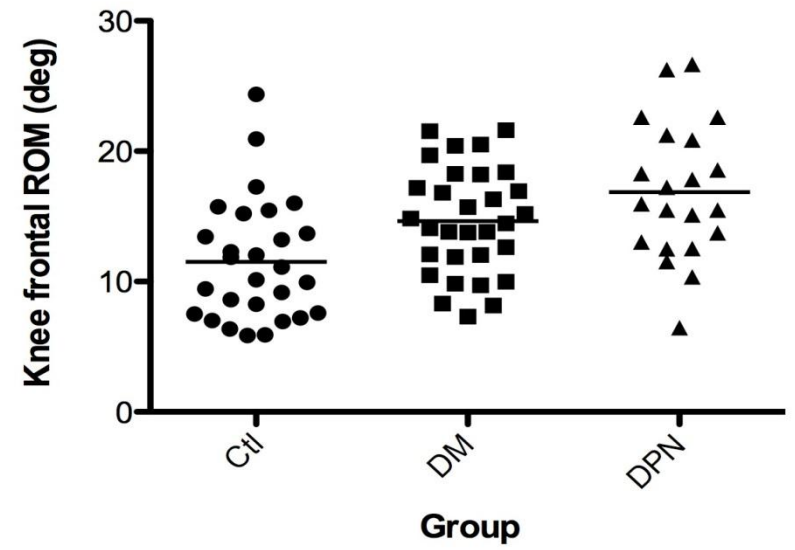
Figure 8. Knee ROM (frontal) stair descent.

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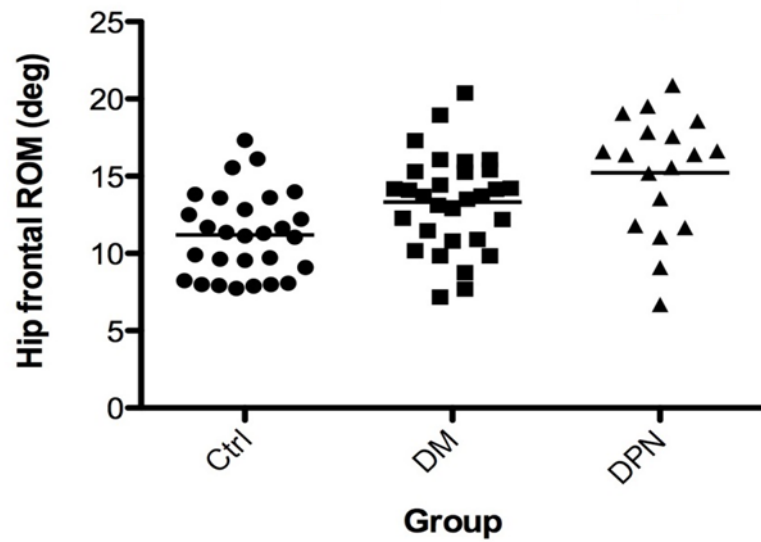
Figure 9. Hip ROM (frontal) for stair descent.
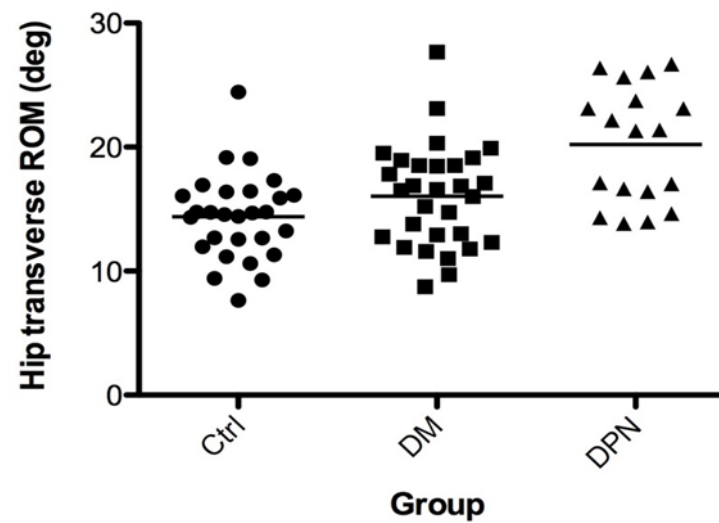
Figure 10. Hip ROM (transverse) for stair descent.

Chapter Four

Discussion

The purpose of the current study was to determine whether people with DPN demonstrate gait kinematics that are significantly different to people with DM and healthy controls. To recapitulate, joint range of motion in the lower limb and stride-to-stride fluctuations in joint range of motion were observed under three different walking conditions: level walking, stair ascent, and stair descent. Significant differences between groups were identified in gait kinematics, but to a lesser degree for measurement of stride-to-stride variability. The implications of the results will be discussed relative to each gait task.

Demographic data confirmed that the three groups were similar in terms of baseline characteristics in all but the disease-dependent parameters such as the neurodisability score, and vibration perception threshold. For a study of this size, imbalances in some of the measured variables at baseline are to be expected. There is no evidence that the measured imbalances will have any bearing on the measured outcomes. For example, it is highly unlikely that the gait characteristics of the DM and DPN groupsin the current study were due to obesity given the small magnitude of differences between their mean BMI. According to the National Clinical Guidelines for the assessment of obesity (NICE CG189, 2014), a BMI between 30 and 34.9 kg/m^2 is classed as obese. The DM & DPN groups' average BMI was 28.0

kg/m^2 and 29.0 kg/m^2 respectively, neither of which equates to obesity." Overweight "corresponds to a BMI between 25-29.9 kg/m^2, and the healthy subjects in the current study had an average BMI of 25.6 kg/m^2, also placing them in this category.The fact that all groups have a mean weight in the overweight range is in keeping with the national trend of rising levels of overweight individuals in the UK population (HSCIC, 2012 health survey). Within the DPN group itself, 32% of subjects had a BMI concurrent with obesity. In the DM group, 37% were obese, and in the healthy control group 14.3% were obese although all the groups had a large range of BMI values.

Studies of gait in obese subjects often include subjects with BMI values in excess of 30 kg/m^2. For example, in Lai (2007), mean BMI was 33.6 for 14 individuals, whilst in DeVita and Hortobagyi (2003), mean BMI for the obese group was 42.3 kg/m^2. This is reflective of the heterogeneity in data for gait and obesity, and, in a systematic review by Runhaar, Koes, Clockderts and Bierma-Zenstra (2011), lack of agreement between studies featured heavily. Nevertheless, the main characteristics of gait in healthy, obese people include slower velocity, shorter and wider steps, longer stance duration, and greater toe-out angle than non-obese individuals. It is also proposed that spending longer time in double support and assuming a wider base of support was part of a strategy aimed at increasing balance and stability. A simpler explanation was put forward by Browning (2012), who proposed gait changes to be the result of physical changes arising from obesity such as increased thigh diameter.

There is also the possibility that some gait changes are the manifestation of underlying poor cardiovascular function.

Katoulis et al (1997) recorded the following mean BMI values for their study groups; controls 25.5 kg/m^2, non-neuropathic diabetes25.1, kg/m^2 ,diabetic peripheral neuropathy 27.0 kg/m^2 and diabetic peripheral neuropathy with a history of foot ulceration 27.0. kg/m^2 . These are similar to the results for the current study. Participants for the Katoulis et al. study were taken from the same geographical catchment area as the current study, which suggests the current study's data may be reflective of the local population.

Age is unlikely to have influenced the results of this study due to the mean ages of the three groups: control 51.1, DMs 58.1, and 57.6 for DPNs, none of which concurs with other studies of "elderly" or "ageing" gait, which often make age 63 the starting age for inclusion. There is no definitive age at which gait becomes characteristic of being elderly, but the age ranges for each of our study groups are comparable with others such as Ferrandez (1990), Gomes et al. (2011), Katoulis et al. (1997) and Mueller (1994). Changes in gait kinematics associated with ageing include decreased gait speed, and impaired responses to perturbations. Age can affect velocity and normal gait velocity for over 65s is between 1.00 m/s (Ferrandez, (1990) and 0.89 m/s (Himann, 1988).

Gait speed for level walking in the current study for the healthy subjects was 1.36 metres per second (m/s), which concurs with other studies of healthy level-walking data. DPNs walked at 1.18 m/s, and DMs at 1.26 m/s. It is difficult to make comparisons with other studies, as most compare young versus old, and the age ranges in the current study fall into neither category. Lusardi, Pellecchia and Schulman (2003) divided their results according to age, and found subjects between the ages of 50 and 59 whowere healthy had a gait velocity over level ground of 1.43 m/s. The non-DMs assessed by Mueller (1999) were a similar age to the current study groups at 56.8 years old, and had a velocity over level ground of 1.26 m/s. In terms of DM and DPN, Mueller recorded 1.06 m/s for DMs. Katoulis et al. (1997) found DMs walked at 1.1 m/s, and those with a previous ulcer history at 1.07 m/s. Sawacha (2009) identified DMs at 1.10 m/s, DPNs at 1.2 m/s, and controls at 1.27 m/s. These are fairly similar results to those obtained in the current study.

The exact nature of the relationship between gait speed and gait variability has been difficult to establish, and there are many inconsistencies in the evidence base. Menz (2004) is one of few that identified increased variability in DPNs versus healthy controls, whereas other authors have failed to find any significant differences between DPN and healthy controls in terms of temporo-spatial gait variability in DPNs (DeMott et al. 2007; Dingwell 1999; Richardson 2004). Allet (2009) reported increased variability, but only when patients walked on an irregular surface. Perhaps increased gait variability only becomes apparent when the locomotor system is challenged.

4.1 Level Walking

During level walking, subjects with DPN displayed a reduction in ankle range of motion (24.3°) in the sagittal plane, compared to DM subjects (26.5°), and healthy counterparts (27.8°), although this was not statistically significant. There were no significant differences between the groups for gait variability during level walking. The findings are in keeping with previous studies that have examined joint range of motion in DPN subjects. Similar changes in ankle joint range of motion in subjects with DPN have been described by Mueller (1994), Sawacha et al. (2009), and Sacco et al. (2009).

The clinical significance of reduced ankle range of motion is related to the functional role of the ankle during the gait cycle. The sagittal plane is the plane of flexion and extension, which is controlled by the ankle plantar flexors and dorsiflexors. It is also the plane of forward progression, and the ankle makes significant contributions to many aspects of the gait cycle, including forward propulsion, body weight support (Keppel et al., 1997), vertical acceleration of COM (Wilken, Sinistski & Bagg, 2011), and maintenance of knee stability (Jonkers, Stewart & Spaepen, 2003). Thus, reduced dorsiflexion and plantarflexion during level walking has the potential to disrupt the normal gait cycle from the onset of heel strike through to heel strike of the contralateral limb. Initial foot contact requires the ankle to be dorsiflexed with the plantar surface of the foot just above the ground. The foot should be lowered

smoothly and steadily through eccentric contractions of the dorsiflexors, but if this is impaired, foot slapping can result when contact is made. This type of gait is associated with pathologies such as peroneal nerve injury, lumbar spine (L4/L5) disc herniations, and unilateral hemiparesis arising from CVA rather than DPN. However, it is likely that DPN produces a slow, progressive reduction in dorsiflexion. Although this gait pattern was not assessed as part of the current study, it is unlikely to have been overlooked during the locomotion tasks, given that it is highly audible and visually obvious. Nevertheless, reduced plantarflexion-dorsiflexion has the potential to cause gait changes with the potential for negative functional consequences.

Reduced plantarflexion is likely to result in excess sagittal plane tibial rotation as the eccentric contraction of plantar flexors required to control forward rotation of the tibia may be decreased. The outcome could be that the centre of mass overshoots the base of support leading to a moment of instability when the subject becomes at risk of loss of balance (Sutherland, Cooper & Daniel, 1980). Reduced dorsiflexion, at the point of weight transfer, mid-stance, would reduce the capacity of the supporting limb to bear body weight during swing, and could result in premature "toe off", which will create a further vulnerability to instability. This can be related to Winter's (1995) inverted pendulum hypothesis, whereby the body is envisaged as a pivot on the ankle joint and, in the absence of the pivot, balance can be lost. A reduction in sagittal plane range of motion at the ankle could increase vulnerability to balance disturbances and unsteadiness during level walking. This is also in keeping with

studies that have reported that people with DPN spend increased time in double support to assist in maintaining balance (Mueller, 2000; D'Ambroghi et al., 2005).

4.2 Stair Ascent

As discussed in the introduction of this document, few studies have examined kinematics in stair negotiation. Those that have investigated joint angles have focused almost exclusively on the sagittal plane. Furthermore, there is no consistency in approach regarding specific measurements utilised to determine joint angle motion in terms of mean peak angle, total range of motion, and angular displacement angle. The current study shares similarities and differences in methodology with others. The current study used a seven-step staircase to obtain two-and-a-half full gait cycles, whereas others use only four steps. Due to the wide range of methodologies available, the number of variables under investigation, and methods of measuring gait kinematics, it is not possible to ascertain from the literature what the "normal" range of motion for the hip, knee and ankle joints is during SA or SD in healthy, age-matched individuals.

As observed in the level-walking task, ankle joint range of motion during stair ascent was reduced in the DPN subjects (32.5°) compared with DMs (37.0°) and controls (37.1°) in the current study. Although not statistically significant, the results are

similar to the findings of Onodera, Gomes, Pripas, Mezzarane & Sacco (2011), who reported a decrease in maximum ankle dorsiflexion during stair ascent towards the end of forward continuance. Additionally, Onodera et al (2011) found theDPN subjects showed a decrease in maximum plantarflexion at the end of forward continuance compared to controls

The task of stair ascent is biomechanically demanding due to the increased range of motion required in the joints of the lower limb, and the increased strength necessary to bear body weight whilst also allowing vertical displacement of body mass (McFadyn & Winter, 1988). As illustrated in the discussion of level walking above, there are specific points during stair ascent when reduced ankle range of motion could increase the risk of tripping or falling. As weight acceptance begins, the hips and knees move into flexion and the ankle on the leading limb is dorsiflexed, the angle of which increases when single support is initiated, and the supporting limb bears full body weight whilst also being raised vertically through the ankle. Reduced dorsiflexion will impact on available knee flexion and restrict forward progression of the tibia, resulting in a posterior shift in the centre of mass, which will compromise balance and stability (Zietz, Johannson & Holland, 2011).

Decreased ankle range of motion, as identified in the DPN group of the current study, may also disrupt the pull-up phase of stair gait. This phase requires considerable power generation from the ankle, knee and hip to lift the swing limb from one step to the next. Although the greatest magnitude of muscle activity is

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generated by the knee during this phase, the ankle also assists with vertical lift. There is the potential for reduced ankle joint motion to compromise vertical lift and prevent the foot from clearing the next step (Hamel, Okita, Higginson & Cavanagh, 2005). A collision between the swing limb and stair beneath is even more likely in the presence of decreased dorsiflexion as well. It is reasonable to speculate that reduced range of motion at the ankle during stair ascent has the potential to increase the risk for falls in people with DPN by undermining balance and stability.

A significant increase in knee ROM in the frontal plane was demonstrated by the DPN group during stair ascent (16.9°) in comparison to DM (14.6°) and control (11.5°) groups. Knee abduction-adduction is associated with the frontal plane of motion, but does not usually feature in normal gait due to anatomical restrictions imposed by the hip and ankle. However, the current study also illustrated increased flexion-extension at the hip during stair ascent, which could assist the knee in achieving this abduction-adduction position. The changes at the knee and hip could also compensate for the reduced ankle range of motion, as greater hip flexion-extension would assist with foot clearance and foot placement during stair ascent (Graci, Elliott & Buckley, 2009). There would be a beneficial effect on stability as a greater degree of flexion-extension at the hip could increase the base of support, thus increasing stability. (The combination of increased knee abduction-adduction with increased hip flexion-extension appears to represent a gait adaptation to compensate for reduced plantarflexion-dorsiflexion at the ankle.)

Increased range of motion in the sagittal plane at the hip was observed, with the DPN subjects achieving a mean range of motion of 58.3°, the DM group 59.2°, and controls 55.4°. Although the DM group appears to have a range of motion that is greater than the DPN group, multiple comparison testing did not identify a significant difference between the means of the DM and DPN groups. The dot plots show the distribution as similar between the groups, so hip range of motion appears to be similar whether there is peripheral neuropathy or not. This suggests that the increased hip ROM occurs as a result of the diabetes rather than the PN, or, it may be indicative of alterations in sensation which are occurring before clinical PN emerges, and subsequent compensatory strategies are initiated.

This is in keeping with Mueller (1997) who also found increased range of motion at the hip and assumed it to be a compensatory strategy for reduced ankle range of motion. However, it would be necessary to confirm such a supposition with more data, i.e., a larger study.

4.3 Stair Descent

Stair descent is more demanding than ascent due to the requirements of greater joint angles, and control of body weight against gravity (Protopapadaki et al., 2007), which could result in more exaggerated gait disturbances. The DPN group in the current study achieved a mean ankle range of motion in the sagittal plane of 51.1°, the DM group achieved 58.0°, and controls 58.8°. Reduced plantar flexion and dorsiflexion during stair descent has been reported in one other study of stair negotiation, and the authors found this to be most evident in the weight acceptance phase (Odonera et al., 2011).

Limited ankle range of motion is likely to have significant repercussions on the safety of stair descent, as large dorsiflexion angles are required to complete the task. During forward continuance, balance relies heavily on ankle stability to bear the weight of the contralateral limb and, thus, reduced range of motion could disturb stability and compromise balance. The controlled lowering phase requires significant ankle dorsiflexion in the stance limb and plantar flexion in the swing limb in preparation for foot placement. Reduced ankle range of motion at this point in the stair descent process could result in loss of balance during controlled lowering, or

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insufficient lowering for the foot to contact the step below. As the swing leg is pulled through, foot clearance may be compromised by reduced plantar flexion. The phases of the stair gait cycle described above represent the points at which falls risk will be increased due to altered balance and/or stability. Insufficient range of motion to move the lower limb and body weight from one step to the next will also limit stair descent.

The current study demonstrated increased frontal plane ankle range of motion during stair descent in the DPN group (10.6°) versus DM (10.4°) and controls (8.9°). Additionally, the DPN group showed increased frontal plane movement at the hip (DPN 15.2°, DM 13.5°, controls 11.2°) and knee (DPN 12.6°, DM 12.3°, control 9.2°) when compared with the DM and control groups. Transverse plane hip range of motion was also significantly increased in the DPN subjects (20.2°) in comparison to DMs (16.0°) and controls (14.4°).

The data demonstrate a statistically significant difference in joint ROM between the DPN and control groups obtained during stair descent. Specifically, there is a reduction in ankle ROM in the sagittal plane accompanied by increased hip ROM in the frontal and transverse planes. The features observed at the hip are equivalent to abduction-adduction and external-internal rotation, both of which would also facilitate a more abducted position at the knee. The alterations in DPN joint ROM may represent a gait strategy to compensate for the limitations imposed by reduced plantarflexion-dorsiflexion at the ankle. Furthermore, increased abduction-adduction

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of the hips accompanied by additional rotation will reduce the overall angle of descent for the swing limb during forward continuance to the step below. Utilising the lateral thigh muscles and knee flexors should aid foot clearance, providing further compensation for reduced ankle joint ROM. Increased hip rotation and frontal plane movement during stance may also assist the ankle in supporting body weight during single stance.

Stair descent requires the absorption of kinetic energy through eccentric muscle contraction at the ankle, knee and hip (McFadyn & Winter, 1988). The beginning and end of single support are high demand periods for the ankle and knee specifically. Peak energy absorption at the knee occurs during weight acceptance and controlled lowering in stair descent.   The increase in knee range of motion in the frontal plane observed during the current study may be part of load redistribution to compensate for impairment at the ankle. This has also been reported in a study by Reeves, Spanjaard, Mohaghegi, Baltzopoulos and Magnaris (2008), whereby older people compensated for reduced ankle and knee ROM by increasing activity from the hip extensors. The redistribution of joint moments allowed subjects to operate at their moment reserve rather than at their moment limits in order to keep energy costs within safe parameters. It is possible that the DPN group in the current study is utilising a similar strategy of compensatory load redistribution. In conclusion, the current study of stair negotiation in subjects with DPN has demonstrated that DPNs have reduced range of motion at the ankle joint, which is compensated for by alterations in joint angles in other planes of motion, suggestive of a compensatory

gait strategy . To the best of this author's knowledge, a compensatory stair gait strategy in people with DPN has not been reported in the literature before.

4.4 Gait Variability

The hypothesis was based on investigating any significant differences between the groups in relation to variability in joint ROM from one gait cycle/stair cycle to the next. No significant differences were identified between the three groups of the current study for gait variability (stride-to-stride fluctuations in range of motion) during level walking or stair ascent. However, a trend towards increased variability in the DPN group was observed during stair descent in comparison with the DM and control groups. This occurred at the knee and the hip in the transverse plane of motion.

The greater challenge of stair descent may demand less variation in gait patterns given the need to work against gravity to maintain an upright position, whereby gait patterns need to be precise. In this sense, it would follow that there are no significant variations between the groups.

The absence of a significant difference between the three groups for variability in joint range of motion could be attributed to a number of factors. Firstly, there are

methodological issues related to parameters selected for measurement and sample size, and, secondly, there are physiological/theoretical, and statistical issues. Hausdorff (2001) identified gait variability as a marker for falls in a study of community-dwelling elderly people. The conclusions were based on a large body of data generated from extensive gait testing of up to 6 minutes' continuous walking to obtain kinematic data for several hundreds of strides per subject. These were analysed by taking the time series for stride time and calculating the standard deviation of the time series for comparison against each subject's mean stride time.

Dingwell (2001) measured variability in sagittal plane motion at the hip, knee, and ankle. Subjects walked 200 metres at a "natural pace". Gait variability was calculated from the "average stride times and standard deviations of stride times obtained from the individual stride times extracted from the continuous time series data"(Dingwell, 2001,p.4) Although the current study has used the standard deviation as a measure of variability, it has not been calculated within each time series variable, which may contribute to the lack of variability observed in the groups.

Hausdorff (1996) reported that fluctuations in the time elapsed from one heel strike of one limb to the next heel strike of the same limb (the stride interval) demonstrate marked similarities with the fluctuations. If gait variability measures are to encompass long-range correlations in physiological time series, then calculation of time intervals or their demarcation should be an integral part of data management.

The calculation of a single value (CV or SD) to indicate variability in the sense that Hausdorff intended may be an oversimplification.

There are obvious limitations in generating data for stair negotiation mainly related to fatigue, especially in subjects with medical conditions and co-morbidities. The reality of investigating disease state or disease effects is that methodologies used on healthy individuals may not transfer seamlessly to those suffering with a chronic disease, and the suitability of gait variability measurement may need exploring further. Lord, Howe, Green, Simpson and Rochester (2011) conducted a literature review of the clinical value of measures of gait variability paying specific attention to reliability and validity. The authors' conclusion is there is a lack of consistency in the application and calculation of gait variability.

The current study has not calculated gait variability in the form described by Hausdorff (2001), as the physical limitations imposed by diabetes and the use of stairs restricted the volume of gait data generation.

The lack of significant variability between the groups could also be related to the parameters being measured. Hausdorff et al. (2001) advocated calculating gait variability for parameters such as step-length, step-width, and stride-time, which were later correlated with falls risk through a prospective one year study of older adults living in the community (Hausdorff et al., 2001). In contrast, there are no data to support the reliability or significance of calculating stride-to-stride fluctuations in

joint range of motion, and it is possible, therefore, that this measure cannot be applied to joint range of motion. Alternatively, given the large number of tests conducted, and the fact that the transverse planes in the hip and knee had not been identified *a priori* as planes of specific interest where a significant result was expected, the p-values obtained, despite being below 0.05, should not all be interpreted as being indicative of a statistically significant difference of gait variability in these particular planes.

The present study found that people with DPN have reduced range of motion at the ankle during level walking, in comparison to DM and healthy controls, which may compromise balance and stability during gait. The DPN group also showed limited ankle range of motion during stair ascent, but increased knee adduction-abduction, together with increased hip flexion-extension as a possible compensatory mechanism. Given that stair descent is more demanding than the previous gait tasks, it was not surprising that gait adjustments were more pronounced, resulting in subjects utilising a side-stepping strategy to move down the stairs.

The alterations in knee and hip range of motion observed in the DPN group suggest a co-ordinated response to compensate for restricted ankle range of motion.

4.5 Clinical and Research Implications

The presence of a gait strategy, as illustrated in this study, would appear to enable the subjects with DPN to complete the task of stair negotiation. However, this does not necessarily concur with efficiency and safety, which may be compromised due to the new strategy. Further data is required to determine the true nature of any gait deficit that is prompting the change in underlying gait patterns during stair descent. Some authors have suggested that people with DPN generate their muscle moments more slowly than healthy counterparts whilst also working almost to their maximum capacity (Reeves et al., 2008). This could possibly respond to resistance and strength training of muscle groups.

Fear of falling is inextricably linked to a higher risk of falls, as noted by Maki (1997). It is possible that the gait strategy observed in the DPN group is related to fear of falling. Herman, Giladi, Gurevich and Hausdorff (2005) reported study results that suggested a cautious gait could be a manifestation of such a fear, arising from underlying unsteadiness.

The present study has observed a reduction in ankle range of motion during gait among people with DPN, which is unsurprising given the large number of studies that have demonstrated this previously. DPN symptoms begin distally and ascend proximally as a result of which, it is highly likely that dennervation also follows this pattern. The low threshold afferents of the sural nerve have demonstrated inhibition over tibialis anterior, whilst the afferents of the tibial nerve increased tibialis activity (Aniss, Gandevia & Burke, 1992). The results suggest mechanoreceptors in the

plantar surface of the foot have multi-synaptic connections with the motor neuron pools innervating the muscles at the ankle. Iles (1996) found that excitation of low threshold receptors on skin in humans in the dorsal foot depressed presynaptic inhibition of soleus Ia afferents, especially during ankle extension. Similarly, Nielsen and Sinkjaer (2002) performed a series of tested subject responses to unloading or stretching the plantar flexors during stance. Unloading the plantar flexors resulted in a drop in soleus activity at a latency of 60 milliseconds, which equates to tendon afferent (group II) activity. Latencies are shortest when the stimulus is closest to the efferent, and when fibres are myelinated. In addition, unloading the plantar flexors stretches the dorsiflexors, which probably contributes to inhibition of motor neurones. The findings reported by Nielsen and Sinkjaer (2002) demonstrate the interconnectivity of neurones involved in gait, and imply that group II afferents contribute to the motor neurone drive of the plantar flexors. In essence, alterations in afferent fibres, as in peripheral neuropathy, could reduce motor activity of the ankle plantar flexors and dorsiflexors via combined synaptic inputs to interneuron pools.

Another study supporting the results above is that of Fallon et al. (2005) which identified 53 afferents in the cutaneous surface of the foot innervating low threshold mechanoreceptors. 47% cent of these were rapidly adapting types of afferents (respond quickly to stimulus and return to pre-stimulus level of activation quickly), and the remaining 53% were slow adapting. Rapidly adapting type 1 afferents were found to be coupled with spinal motor neurones, and stimulation of these afferents

modulated EMG activity in tibialis anterior, gastrocnemius and soleus. The role of the small nerve fibres of the foot and ankle can be overlooked in studies of gait, but as technology advances, the influence of the peripheral nerves is becoming more apparent. Stimulation of the plantar nerve during mobilisation attempts by spinal cord injured patients resulted in modification of abnormal gait reflexes to produce a more functional gait pattern (Knikou, 2010).The aim of citing the papers above is to emphasise that the peripheral nerves in the foot and ankle have a significant influence on lower limb muscle function and gait. Diabetic peripheral neuropathy, therefore, can disturb the function of these neurones and, as such, significantly alter muscle function in the lower limb. Plantar, cutaneous afferents and mechanoreceptors have a greater role in muscle activity than previously thought, which should be incorporated into future investigations of gait function in people with DPN.

The current study has demonstrated several points during stair ascent and descent where the risk of falling may be increased due to reduced ankle range of motion. Whilst subjects employ an apparent gait strategy to compensate for this, there is no evidence that these strategies are successful in reducing the risk of falls. This would require further prospective study of a larger sample of DPN subjects, and gait analysis during stair negotiation to determine the nature and frequency of strategies used. Subjects could then be monitored in terms of "time to falling" and compared with matched controls. It would also be useful to investigate inter-subject variability

in terms of adaptive gait strategies to determine whether alterations are consistent, and whether they are suggestive of an innate adaptive process.

4.6 Study Limitations

The current study attempted to minimise confounding factors as much as possible and, given the robust inclusion and exclusion criteria, it is likely at least some of the findings can be attributed to diabetes with peripheral neuropathy. The sample size appears small from a statistical perspective, with only 19 subjects in the DPN group after losses. This is perhaps reflective of difficulties recruiting and maintaining subjects that already carry a heavy appointments burden due to their underlying disease. Furthermore, the sample size in the current study is comparable with other studies in this clinical area, for example Dingwell and Cavanagh (2001) had 10 DPN subjects and 10 matched controls, and Sawacha et al. (2009) recruited 20 controls, 26 DPN subjects and 21 DM subjects, but they do not report numbers lost to follow up. Rao (2006) recruited 10 DM subjects and 10 DPN subjects, while Sacco (2009) used 31 patients divided into two groups to form DPN and control groups, but fails to explain which group was the bigger. Finally, Carter (2009) assessed 39 subjects with DPN. Overall, the group sizes are in keeping with this study and are probably reflective of the difficulties in recruiting and retaining people with a medical condition that is associated with multi-professional care and, therefore, multiple appointments. Patients can have a full day of review, out-patient appointments, and fatigue, face

transport costs, and experience fluctuations in motivation. All of these can impact on whether or not patients arrive for research projects.

The depth and quality of neurological testing carried out is not observed in many other studies. Mueller (1994) did not perform any baseline testing of neuropathy, as the inclusion criterion was a history of foot ulceration. Carter (2009) included subjects based on their symptom descriptions plus additional assessment for an absent or decreased Achilles reflex, Michigan neuropathy score, and electro-diagnostic testing of the peroneal or sural nerve. This represents a good balance of neurological tests as they relate to human anatomy and physiology. Rao (2006) used only the monofilament, which, to diagnose neuropathy, is inadequate. Sacco (2009) used the Michigan neuropathy instrument to diagnoses diabetes, and this includes an inspection of the foot, ankle tendon reflex test, and monofilament. This is a basic screening tool and, to ensure an accurate diagnosis, it should really be carried out alongside other instrumental testing modalities.

The NDS utilised in the current study has an advantage, as it includes instrumental vibration perception testing with the Biothesiometer, used in harmony with the other tests. Sacco (2009) tested every aspect of sensation and structure in the foot, going on to test the cardiovascular system for signs of autonomic dysfunction and pelvic tilt. Dingwell (2001) utilised VPT with two devices - one custom made, with the other being the biothesiometer.

The Vicon three-dimensional analysis of gait also has the potential to be a source of error, as demonstrated in a study by Gorton, Herbert and Gaunotti (2008). The nature of variability in 3D gait analysis was investigated across 12 different laboratory sites utilising 24 different assessors measuring one subject. They reported that less than 2% of overall variance was due to system inaccuracy. The conclusion was that inaccuracies arose from variations in marker placement. However, 5 of the 12 of the laboratories used in the study did not undergo testing of system accuracy prior to assessment due to processing problems and different marker configurations. In the absence of this data, it is difficult to conclude, as the authors do, that more than 75% of the variation arising in 3D gait analysis originates with examiners and their marker placement. Moreover, the examiners came from a wide range of professional backgrounds including Orthopaedic surgery, Physiotherapy, Podiatry and Orthotics. The average maximum difference between examiners for parameters measured was 14.8 degrees and, for joint angles specifically, the difference ranged from 1.2 degrees to 7.3 degrees. In the absence of the calibration data for the other sites, it is possible that this is not a true reflection of between-examiner differences.

Summary

To summarise, it is essential for diagnostic criteria to be robust when a study aims to compare one group against another, as the disease type forms the basis of all future

investigation and analysis. In the absence of assessments with established reliability and validity, it is difficult to extract meaningful information from data. There is a wide variety of equipment available for collecting kinetic and kinematic data for gait analysis. The current study used Vicon motion capture with plug-in-gait, but other gait analysis tools reported in the literature include the DataLogger back pack and goniometers, as used by Dingwell (2001), the Optotrak 60Hz marker system (Rao, 2006), and the Pedar-X (Sacco, 2009). It is difficult to determine how comparable these are with each other, however.

In terms of data analysis, a high number of comparisons were made for different parameters between the groups. Range of motion was compared in three different joints, in three different planes of motion, for three disease groups, in addition to examining variability in range of motion for all of the preceding parameters. The high number of comparisons made between the groups increases the risk of a type 1 error, which Newman-Keuls post-hoc testing can normally correct for, but this is unlikely to be effective with such high numbers and, therefore, results should be interpreted with caution. The number of comparisons could have been reduced by selecting only one stair direction to compare with level walking. The use of three groups was important to monitor for a "diabetes effect" versus a "DPN effect". It may have been more appropriate to use a total range of motion at each joint rather than range of motion from sagittal, frontal and transverse planes. Despite the fact that 27 "test triplets" were conducted on each outcome, it is reasonable to assume that

these triplets are related to some degree, and, hence, applying a Bonferroni correction would result in over-conservatism. The method adopted was thus to conduct post-hoc tests within each triplet, and to consider the resulting p-value significant if it was substantially under the usual threshold of 5%.

The absence of gait variability across the different tasks could possibly be attributed to an insufficient number of steps captured. Gabell and Nayak (1984), Guimares and Issacs (1980), and, later, Hausdorff (1997) have been the main advocates of gait variability research and its application to falls risk. Whilst a multitude of studies have identified increased variability in selected parameters between specific healthy versus ageing-or-diseased groups, the link with falls is mainly based on inference from, albeit large, longitudinal and cross-sectional studies. There is a lack of data concerning the predictive value, validity and reliability of gait variability in predicting falls versus other validated assessments. Available data regarding gait variability and falls comes from a vast array of studies that differ significantly in terms of age and type of subject groups, measurement tools, processing technology, and type of gait task being assessed. Furthermore, there is no agreement as to whether gait variability reflects an abnormal or normal locomotor system (Hausdorrf, 2007). Bearing this in mind, it is possible that joint range of motion during stair negotiation and level walking is not an appropriate indicator of variability. This is compounded by the lack of agreement in the literature regarding the minimum number of steps to use when measuring variability. Hartmann et al. (2009) advised 20 metres, or 25

steps, for assessment of step duration or step length, whilst Dingwell and Cavanagh (2001) advocated 10 minutes' continuous walking. Paterson, Lythgo and Hill (2009) reported that short bursts of interrupted walking do not give sufficient time to accurately measure spatiotemporal parameters, as subjects do not achieve steady state walking until after 20 to 25 stride cycles. However, the first 20 to 25 stride cycles could also be where the falls risk occurs. The current study used two-and-a half gait cycles, which may be inadequate, but, by the same token, even healthy individuals would struggle to perform a high number of stair ascents and descents.

Future investigation of gait in subjects with DPN and the possible relationship to falling necessitates a prospective study, whereby baseline data is obtained for gait function, and subjects are followed up for a period of 12 months for falls occurrence. Given that fallers are not reliable sources regarding their own falls status, utilising GP records, diabetes clinic reviews, and Accident and Emergency attendance would assist in producing more reliable data.

4.7 Consideration for Future Work

Variability is inherent in many aspects of human movement, whether the motion is voluntary as with walking, or involuntary like the rhythm of the heart. The underlying function of variability in human motor systems is not fully understood, and it is

unclear whether variability is related to errors made during the execution of a movement, in which case practise should reduce variability (Summers & Anson, 2009). Other hypotheses suggests that variability arises due to interference from redundant motor systems (Domkin et al., 2002), and there is the suggestion that variability is a reflection of a biological system attempting to find a stable solution for movement in a given environment (Kamm, Thelan & Jensen, 1990).

Measures of variability have been accepted and highly utilised for gait analysis in the form of the co-efficient of variation and standard deviation. However, some authors report that motor programming and the execution of movement cannot be evaluated by linear measures of centrality, as this assumes that any variations in movements are random and unrelated to previous or future variations. Hausdorff (2009) and Dingwell (2007) have illustrated that the variations that occur during gait are not random "noise", and have fractal properties. Non-linear measures of variation in motor function may need to be considered as part of future gait research, as illustrated in studies by Cavanagh et al. (2010), Meyers et al. (2010), and Stergiou and Decker (2011). The application of variability to gait analysis of people with DPN may benefit from the involvement of professions not traditionally associated with clinical research such as biophysics and mathematics.

Researchers that utilise variability as part of gait analysis, such as Hausdorff, have expressed the need for agreed protocols on the methods to be used when gathering and analysing data on gait variability, as practise differs vastly around the world.

One of the significant findings from the current study was the lack of variability in range of motion parameters in any of the subjects studied. This may well be reflective of an inappropriate application of variability measurement to this particular gait parameter. It would be interesting to explore, using a larger sample size, whether non-linear analysis of joint range of motion would illustrate altered patterns of variation between the study groups.

There is insufficient data in the literature to conclude that DPN causes gait abnormalities which increase the risk for falls. However, given the shared anatomy, physiology and neurology, it is difficult to dispute that a relationship exists in some form. Data from a large, prospective, well-designed, and objectively measured study is required in order to establish the kinematic characteristics of DPN gait, after which subjects are monitored for actual falls.

4.8 Conclusion

This study has demonstrated that there are significant differences in joint range of motion in the lower limb between people with DPN, in comparison to DM individuals and healthy controls. This is characterised by reduced range of motion at the ankle, which appears to be offset by a simultaneous increase in knee and hip range of motion, and this may represent a strategy to compensate for limitations at the ankle.

The differences between the groups were most apparent during stair negotiation due to increased biomechanical demands, and, as such, future investigations of DPN gait could benefit from assessment of subjects ascending and descending stairs. Assessment of gait variability failed to identify consistent differences between the groups, but this may have been an inappropriate measure to use with range of motion.

Results from the current study reflect those from previous studies, but it is difficult to relate this to an increased risk of falls, as there is no evidence demonstrating a direct correlation between reduced ankle range of motion and falling. Research can sometimes be based on assumption and inference rather than evidence. Therefore, a strong, reliable evidence base is required to underpin the link between DPN and falling. Promoting real improvements in management of DPN necessitates the development of studies with increased sample sizes to provide robust methods and generation of clinically relevant, reliable data that answer the question of whether or not DPN increases the likelihood of falling.

Rehabilitation programmes to maintain muscle strength, balance and co-ordination may be beneficial at reducing the inferred risk of falling, but positive effects could be short-lived given the progressive nature of DPN. Managing falls risk in the DPN population would require considerable financial resources for surveillance, education of patients, risk assessment, risk management, and adaptations within the home where necessary. The basis for increased funding in the NHS today is robust

evidence, and demonstrating a direct link between DPN and falling should continue to be a goal in clinical research.

Chapter Five

Personal Impact Statement for Frank L. Bowling

The current research originates from patients attending the diabetes clinic in Manchester. During Podiatry assessment and treatment sessions, several patients complained about difficulties encountered during walking.

"I feel like I'm going to trip up on my own feet", "I don't know what my feet are doing when I'm out, I have to actually look at them", "I have to concentrate on my feet and keep my balance when I'm coming down the stairs".

My responses to their complaints were initially constrained by my own lack of knowledge in this area and, therefore, little significance was attached to their descriptions. Over time, it became apparent that more patients were describing similar experiences, which prompted me to question myself; perhaps I had overlooked this aspect of lower limb complications associated with diabetes. A brief literature search and discussion with colleagues allayed my fears, having discovered

there were only a handful of studies linking gait changes with diabetes, and nothing at all in associated clinical guidelines. Nevertheless, the combination of patient descriptions of walking issues and the identification of a few relevant publications was sufficient to motivate me to investigate further.

Having worked in diabetes for the last 13 years, I have devoted my employed life to the pursuit of preventing and managing diabetic lower limb complications. The possibility of a gait or balance disorder affecting this client group alarmed me due to the potential for increasing falls and soft tissue injuries with a subsequent increased risk of foot ulceration. I set out to clarify and characterise the gait patterns of people with Diabetic Peripheral Neuropathy (DPN) with a view to determining if there was an unidentified need within this patient group. The journey towards this goal has been difficult, not least due to working full time, but it has yielded new insights into the world of research across higher education institutions, NHS Trusts, and the NHS as an organisation.

The current work has illustrated that people with DPN use what appears to be a gait strategy during stair descent tasks, and this is probably the result of reduced range of motion at the ankle joint. We can infer that this may increase the risk for falling, which has huge implications for DPN patients and service providers. Further research is necessary in order to establish how many of these patients go on to fall, and a prospective study would be beneficial.

Evidence, in the form of research, provides the basis for reallocation of resources, re-organisation of clinics, and new strategies to facilitate prevention and management of a newly identified risk. In considering the impact of the current thesis on people, there is insufficient evidence here or in the studies cited in the literature to inform a change in practise. Research cannot promote change for change's sake. Change in practise should be based on the principles of evidence-based medicine which incorporate structured and critical appraisal of the evidence, clinical knowledge, and experience. Soper and Hanney (2007) conclude that implementing research is hugely complex, and has been underestimated.

My vision for this work is that it promotes and inspires further investigation of gait alterations in people with DPN, and a prospective study of falls risk in this patient group. The findings have been published in a peer reviewed journal, and presented at two European conferences attended by experts in diabetes and lower limb complications. It is anticipated that the wider dissemination of the study's findings will sow the seeds of further research questions related to gait changes and falls risk in DPN so as to achieve a collective, relevant research base upon which new practise guidelines can be built.

One of the major difficulties encountered during the study became a significant learning opportunity for me. The study was conducted between two universities and a hospital trust in order to secure appropriate equipment and patient recruitment.

The collaboration was not without difficulties, which, on reflection, arose due to frustrations based on misconceptions. A lack of exposure to people with chronic diseases led to collaborators from a non-clinical background becoming frustrated by the constraints associated with this. Moreover, training in the use of equipment technology for the study was more time-consuming than first envisaged, increasing time pressures on all involved. The net result was a slightly charged atmosphere.

This situation has illustrated to me, on a personal level, that I need to be more descriptive and transparent regarding my own gaps in knowledge. This would have probably resulted in training issues being given a higher priority, and reduced frustrations on all sides. I also now appreciate that shared knowledge cannot be assumed between professionals, and should be clarified. Advanced communication skills are vital if this is to be achieved. With the benefit of hindsight, this can also be relevant when investigators from a non-clinical background are involved in patient-based study. Observation of patients undergoing a relevant assessment or treatment provides an opportunity to familiarise researchers with targeted patient groups, for example, spending half a day attending a clinic to observe and build a picture of health needs, physical and psychological demeanour, and social issues that may influence patients' attendance/non-attendance. This could also foster an understanding of the different roles involved in the research process.

The lessons learned above are also directly applicable to multi-disciplinary or inter-disciplinary projects within the NHS Trust. Assumptions breed misunderstandings, which can ultimately lead to conflict. One solution is to share the knowledge,

experience and perspective of others involved in projects from the outset, which can promote mutually agreeable outcomes. This solution can also be utilised to increase the understanding of the perspectives of researchers, clinicians, managers, and commissioners.

In conducting this research I have encountered literature regarding the wider role of the researcher, and the benefits associated with research within the NHS. This has broadened my understanding and enabled me to see the possibility of using my skills to actively promote research within my own profession, and in the NHS Trust. I envisage my contribution to the next generation of future researchers in DPN and gait through inspiring and promoting research originating at the patient/service interface. The initial steps towards this require assisting clinical staff to understand and interpret the available knowledge. Allied Health Professionals often avoid reading studies due to difficulty understanding the statistics (Metcalfe, Lewin, Wisher, Perry, & Bannigan, 2001), which can be addressed easily. Journal clubs can increase familiarity with data analysis techniques through a group forum, whilst Continuing Professional Development (CPD) workshops focused on areas of identified learning needs within departments could also be beneficial. More novel ideas include a "research surgery" where professionals can drop in and ask for advice. Undertaking taught research modules can provide staff with the confidence to consider higher-level study. It is unfortunate that many healthcare professionals feel they possess inadequate knowledge and skills to interpret or undertake research (Shakeshaft, 2008), but increasing the feeling of confidence among staff is possible.

Establishing the nature of the research culture within my own professional department can also assist with the dissemination of research by illuminating barriers. Obtaining information regarding perceptions of research and roles from management level downwards can highlight where specific problems lie, and assist in targeting where education and joint working is needed (Perry, Grange, Heyman & Noble, 2008).

I intend to disseminate my experiences of research within the Podiatry department - partly to demonstrate the potential impact of successful projects, and partly to dispel myths associated with experienced researchers. The aim is to increase familiarity with the processes involved in research, address misconceptions, and reduce the trepidation with which research is approached by many clinicians.

At an organisational level, inter-professional research strategy groups can be an effective means of increasing professional inclusion and of influencing joint research strategy. Such meetings can be intimidating for new or potential researchers, but attendance with a mentor may help.

Engaging patients more by increasing their awareness of good quality care and guidelines defining this can also generate research from patients themselves. Patients have a different set of experiences, perceptions and motivations related to the NHS, and their views can be very different to the professionals' assumption of need (Powell, 2003). After all, the experiences and comments of diabetes patients motivated the current work.

Research can generate more research, and raising professional profiles can assist with obtaining funding (Sopper & Hanney, 2007). Publications stimulate further research nationally and internationally whilst also raising the NHS Trust profile. My employer, Central Manchester University Hospitals NHS Foundation Trust (CMFT), in particular, aims to become a research leader, and individuals possessing a wide range of relevant skills can make a significant contribution to this process through the flow of information from strategic level to staff/patient level, and vice versa.

Research implementation is just as much about changing attitudes as it is about the facts obtained from the study. Whilst the study findings are insufficient to promote changes in practise at present, the research journey and the emphasis on critical reflection has revealed to me a means of promoting a new understanding of the clinical guidelines that underpin practise through empowering others to develop critical thinking and experience the formulation of research ideas.

Completing the professional doctorate has altered my views on research in relation to the overall contribution of findings. In reviewing NHS England's research and development strategy (2013), I was struck by the long-term vision for the future of increasing healthcare research through empowering health care staff and, yet, research priorities would be set by commissioners and NHS England. Emphasis is placed on improving outcomes for patients without considering that many areas of research depend on the accumulation and assimilation of multiple works before translation to patient outcomes is possible. My work, when considered in a short term context, is insufficient to promote a change in practise at present. The longer

term impact will be based on the contribution made to the pool of knowledge developing on DPN and gait abnormalities. It is important that, in promoting research, the value of a piece of work is not restricted to whether it initiates a change in practise or not. The true value of a study may not become apparent until related works have been completed over time, in which case, the outcome may not become apparent for many years and studies later.

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Appendices
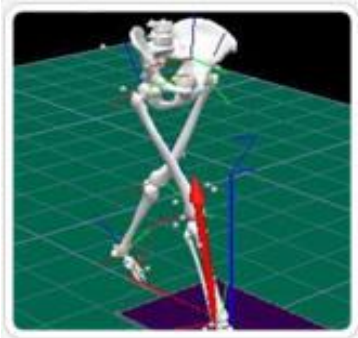
Protocol Version Two

"Gait Variability and Kinematic Alterations in People with Diabetes Mellitus and Peripheral Neuropathy"

Investigator: Professional Doctorate Student

Frank. L. Bowling

Research Supervisors:

Karen Ousey, Ph.D. University of Huddersfield.

John Stephenson, Ph.D. University of Huddersfield.

Wesley Vernon, Ph.D. University of Huddersfield.

Introduction

People with diabetes and neuropathy display gait instability and are, in fact, up to 20 times more likely to fall compared to aged-matched controls. One of the factors thought to contribute to an increased risk for falling is an increase in the variability of many parameters of gait such as stride length and stride time (e.g., Richardson et al., 2008) Increased variability in key temporal gait parameters may also become more evident between at risk groups when the environment negotiated becomes more challenging (e.g., Menz et al., 2004). We will investigate a range of everyday gait tasks that vary in the complexity of the environment to be negotiated. Tasks investigated will include level walking, stair ascent, stair descent, and stepping over an obstacle on level ground. Differences in gait variability will be investigated between three separate groups: people with diabetes and no/only mild neuropathy, people with diabetes and severe neuropathy, and a matched control group without diabetes.

Research Aims

1. To examine selected kinematic gait parameters in individuals with diabetes mellitus and peripheral neuropathy.

2. To establish the degree of gait variability and thereby determine the risk of falls for individuals with diabetic peripheral neuropathy.

Hypothesis

People with diabetic peripheral neuropathy will exhibit significant differences in lower limb joint range of motion and increased kinematic variability during selected gait tasks in comparison to healthy controls. The degree of variability will increase as gait tasks become more challenging.

Methods

The study population will be (1) patients with diabetes but no/only mild neuropathy, (2) patients with diabetes and severe peripheral neuropathy, and (3) age and body mass index-matched controls without diabetes.

Inclusion Criteria

1) Consenting patients with Type 1 or 2 diabetes (for the diabetes patient groups).
2) Male or female, aged 20-80 years.
3) Presence of significant neuropathy (for the neuropathy group only) as defined below.
4) Absence of diabetes (for the matched control group only).

Exclusion Criteria

1) Unstable ischaemic heart, neurological (other than diabetic aetiology), or rheumatic disease.
2) Cerebral injury.
3) Disorders of the vestibular system.
4) Musculoskeletal injury/recent surgery affecting gait.
5) Amputation.
6) Open foot ulcer.
7) Use of centrally acting medications.
8) Excessive alcohol intake (>30 units per week).
9) Unable to speak and comprehend English.
10) Unreliable, unwilling or unable to comprehend informed consent.

Screening

1) A detailed medical history will be taken, including questions about typical weekly alcohol intake and relevant medications used.

2) A visual acuity test will be performed.

3) Tests to assess the presence/extent of peripheral sensory neuropathy will be performed. These tests will assess participants' ability to detect very small applications of force and vibration to different areas of their feet. Neuropathy will be defined as moderate/severe according to standard assessments of a composite neuropathy disability score (normal = 0, moderate/severe neuropathy ≥6) and quantitative sensory testing of the vibration perception threshold. All patients allocated into the neuropathy group for this study will have a neuropathy disability score ≥6, and vibration perception threshold ≥25.

Procedures

Participants will be assessed in the gait laboratory within the Institute for Biomedical Research into Human Movement and Health at the Manchester Metropolitan University. The work for this doctoral thesis will link into a larger study on gait and diabetes already underway at the Manchester Metropolitan University. The ethical permissions and all other relevant approvals are currently in place for this study.

Participants will be provided with standardised specialist diabetic footwear as well as other clothing appropriate for gait analysis (non-restrictive, but relatively tight-fitting clothing). We will measure participants' height and weight and some other anthropometric measures, such as joint widths, using a measuring tape and callipers. Small retro-reflective markers will be placed onto specific parts of participants' bodies to define joint centres of rotation and limb segments. The movement of these markers will be accurately tracked using a motion analysis system (Vicon system) consisting of ten infra-red cameras surrounding the testing area.

Participants will also be asked to walk up and down a custom-built experimental staircase in the laboratory a number of times. The staircase is of standard

dimensions with handrails present. As an additional safety measure while walking on the stairs, participants will be secured in a harness.

During all gait tasks, participants will walk at their self-selected speed and complete a number of trials for each task. Key parameters of interest are expected to be temporal characteristics such as step width, step length, stride time, and other kinematic variables such as centre of mass. The variability of these parameters can be evaluated within individuals, between repeated trials. In addition to this, participants will also walk on level ground.

Central Manchester University Hospitals NHS
NHS Foundation Trust

PATIENT CONSENT FORM

Title of Project: Factors compromising the safety of gait in people with diabetic peripheral neuropathy and the influence of intervention

Chief Investigators: Neil D Reeves & Frank Lee Bowling. **Principal Investigator:** Andrew

J M Boulton,

Please

I confirm that I have read and understand the information sheet dated 12/07/2011 (version 1) for the above study and have had the opportunity to ask questions.

I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

I agree to take part in the above study.

I agree to my GP being informed of my participation in the study and if severe osteoarthritis is identified.

I agree to members of the research team at the Diabetes Centre looking at my medical notes.

I agree to my anonymised information being exported to members of the research team at the Manchester Metropolitan University.

I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.

_____   _____   _____

Name of Participant   Signature   Date

_____   _____   _____

Name of Person taking consent   Signature   Date

Central Manchester University Hospitals **NHS**
NHS Foundation Trust

Manchester
Metropolitan
University

IRM

bio*move*
europe

Do you have
Diabetes?

Take part in a research study and improve the way you walk and use stairs.......

Would you be willing to give some of your time to take part in a research study at the Manchester Metropolitan University?

We are conducting a study to try and understand why diabetes may cause problems with walking and other everyday tasks. We will also organise an exercise-based programme to improve the safety of these everyday tasks for people with diabetes.

For further information and to find out about taking part please contact:

<researcher's & research nurse's name>
<email>
<telephone number>

V2. 17/10/2011

How do you Walk?

Healthy volunteers needed

Interested in taking part in a research study and learning something about the way you walk?

We are conducting a study to try and understand why some people with diabetes experience problems with walking and other everyday tasks.

As part of this study we need healthy control participants without diabetes aged between 20-80 years.

This study is taking place at the Manchester Metropolitan University and would involve an assessment of how you walk in our laboratory and also some measurements of your leg strength.

For further information and to find out about taking part please contact:

<researcher's name>

<email>

<telephone number>
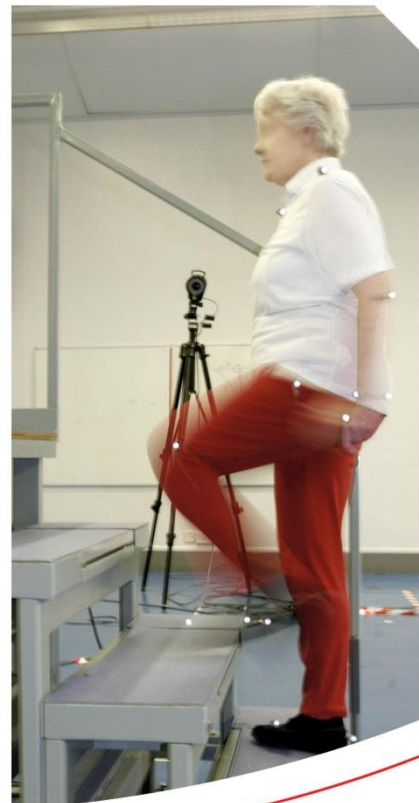
Participant Information Sheet Generic for all Studies Involved in Gait

Study title:
"Factors compromising the safety of gait in people with diabetic peripheral neuropathy and the influence of intervention"

You are being invited to take part in a research study being conducted at the Manchester Metropolitan University. Before you decide whether or not to take part it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and ask any questions you may have to the research team afterwards.

Why have you been selected?
Either: **1)** you have been diagnosed with diabetes, or **2)** you do not have diabetes and are being asked to take part as part of a comparison group without diabetes (defined as a 'control participant').

What is the purpose of the study?
Some people with diabetes may have problems when they do everyday tasks such as walking and going up and down stairs. These problems may cause some people to fall and injure themselves. A lack of sensation in the feet and also weakness of the muscles that help us to walk may be two possible reasons as to why some people with diabetes may have problems with these everyday things. We want to understand exactly why some people with diabetes may have problems with these everyday tasks. We also want to try to improve certain things that may cause problems for some people with diabetes by carrying out a training program that targets muscles and walking ability. By doing this we hope to reduce unsteadiness during walking and improve the safety of everyday tasks for some people with diabetes.

What will I have to do if I take part?
You will be asked to sign a consent form to show that you understand what is involved in taking part. If you are a control participant you will be asked to attend the laboratory at the Manchester Metropolitan University on 3 separate occasions (described below). If you are a

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participant with diabetes you will be asked attend the laboratory at the Manchester Metropolitan University on 3 separate occasions before and 3 separate occasions after the intervention programme. It may be possible to combine some of these test visits so that you can attend on fewer occasions if you prefer. The time commitment for each session is indicated below.

The intervention programme is only intended for people with diabetes and will last between 4-6 months, requiring one visit to the Manchester Metropolitan University each week. There is a chance that you may not actually receive the intervention and will instead go into a comparison group who do not receive any intervention, but are tested before and after the same period of time that the intervention lasts for. The purpose of this is so that we can see the true effect of the intervention, in comparison to a group that does not receive the intervention (i.e., the comparison group). We will randomly allocate people to one of these two groups by giving everyone a number; putting these numbers into a computer and using a computer programme to randomly pick out the number of people we need in the intervention group.

We can reimburse your travel expenses to attend the university (we will just need a public transport receipt, details of car mileage etc.).

During the first laboratory visit we will ask about your medical history, test your vision and perform some simple non-invasive tests to check for nerve damage (peripheral neuropathy) in your feet. Tests for peripheral neuropathy will involve pressing on different areas of your feet and also placing a vibrating device on your feet to see if you can detect these sensations.

We will also take a 'finger-prick' blood sample to measure blood glucose level. If you are a *control participant* and we identify that you may have peripheral neuropathy or a particularly high blood glucose level, we will not include you within the study and with your consent will notify your GP who may then suggest following an appropriate course of action with you.

Gait laboratory visit 1: [*This visit will last approximately $2^1/_2$ hours*]
We will provide you with non-restrictive, but relatively tight-fitting clothing and velcro-strap sandals for this test and simply observe and measure as you walk naturally in our testing area.

We will place small reflective markers onto different parts of your upper and lower body. The movement of these markers will be measured by a number of cameras and will allow us to assess the movement of your body as you walk. These cameras will only 'see' the reflective markers. In a few cases, we may also use a video camera to record how you walk and help us further understand the data – if we do so, you will be notified of this and we will ask for your consent.

Small sensors will be placed onto the surface of your skin over the muscles on your legs to measure the activity from your muscles.

Thin, flexible insole sensors will be inserted into your shoes to measure the pressures on the sole of your foot during walking.

We will ask you to wear a light-weight head-band containing a small camera for a short period to measure where you look as you walk.

On a few occasions we will also ask you to step over a small obstacle on the ground (approximately 10cm high). We will tell you exactly when we place this small obstacle in your path so that you are fully aware that it is there. Two members of the research team will be in close attendance to ensure your safety.

We will also ask you to walk along at your own speed, stepping onto specific irregularly positioned targets for each step.

During this test visit we will also ask you to complete two questionnaires: one about your knees and another about your hips. These questionnaires will ask how you feel about your knees and hips: whether you experience any symptoms such as pain and how they feel when performing certain activities.

Gait laboratory visit 2: [*This visit will last approximately $2^1/_2$ hours*]
We will again provide you with non-restrictive, but relatively tight-fitting clothing and velcro-strap sandals for this test and simply observe and measure as you walk naturally up and down a small staircase in our testing area. Handrails will be present to use on the stairs if needed and we will secure you in a harness for your safety.

We will place small reflective markers onto different parts of your upper and lower body. The movement of these markers will be measured by a number of cameras and will allow us to assess the movement of your body as you walk. These cameras will only 'see' the reflective markers. In a few cases, we may also use a video camera to record how you walk and help us further understand the data – if we do so, you will be notified of this and we will ask for your consent.

Small sensors will be placed onto the surface of your skin over the muscles on your legs to measure the activity from your muscles.

Thin, flexible insole sensors will be inserted into your shoes to measure the pressures on the sole of your foot during walking.

We will ask you to wear a light-weight head-band containing a small camera for a short period to measure where you look as you walk.

Muscle Strength Laboratory Visit: [*This visit will last approximately $1^1/_2$ hours*]
We will assess the strength in your legs using a specific machine. We will test each of your legs separately and assess the strength of the muscles on the front of your thigh and those on the back of your calf.

You will be seated on the chair of the testing machine and asked to exert force by extending your leg at the knee (using the front thigh muscles) and also by extending your foot (using the calf muscles).

You will be asked to exert force only for very short periods of time and will be given plenty of rest in between efforts.

This experience will be similar to a short gym session for your leg muscles and you may experience some muscle stiffness/soreness one or two days afterwards, but this is completely normal and will disappear after 3 days.

The Intervention Programme (*Participants with diabetes only*)
[*One visit per week, for 4-6 months. Each visit will last less than 1 hour*]
As mentioned above, there is a chance that you may not actually receive the intervention and will instead go into a comparison group who do not receive any intervention. We will randomly allocate people to one of these two groups by giving everyone a number; putting these numbers into a computer and using a computer programme to randomly pick out the number of people we need in the intervention group. Before and after the intervention period, you will also be asked to complete a questionnaire about any difficulties you may experience with gait tasks.
For those people who undertake the intervention programme it will mainly involve exercise for your leg muscles. The exercise will be carried out using resistance exercise machines and will be individually tailored to your capabilities. You will always be supervised closely during the exercise. As part of the intervention for some people, we may also include a walking task where we ask you to step onto specific targets that are irregularly spaced along a walkway. This intervention programme is designed to increase the strength and speed of your leg muscles and to reduce unsteadiness during walking. At the start of the intervention, you will be given a leaflet containing more detailed information about the intervention.

What are the potential risks or discomfort?
The assessment of your leg strength will involve a high level of effort but just in short bursts and we will give you plenty of rest between efforts. This experience will be similar to a short gym session for your leg muscles and you may experience some muscle stiffness/soreness one or two days afterwards, but this is completely normal (it is a sign of your muscles

adapting) and will disappear after 3 days. You may experience the same sensation in your muscles (stiffness/soreness) for up 3 days after the exercise sessions. This is the sign of your muscles adapting and getting stronger and each exercise session you complete will help to reduce this sensation. During assessment of your normal walking pattern, just as in everyday life, there is a risk of falling. However, this risk is much lower than in normal daily life because research staff will monitor you very closely and you will also be secured in a harness when walking up and down stairs.

Are there any possible benefits?

You will receive feedback on how you walk and your level of leg muscle strength. We expect that your leg muscles will become stronger as a result of the intervention programme and that unsteadiness during walking will be reduced. Ultimately, we expect that the intervention programme will make walking and other everyday tasks safer for you.

Do I have to take part?

No, taking part is **entirely voluntary.** If you would prefer not to take part you do not have to give a reason. If you do take part but later change your mind you can withdraw from the study at any time.

GP Letter.

If you are a person with diabetes and decide to take part, a letter will be sent with your consent to your GP to inform him/her of your participation in the study. If you part of the control group and we identify that you may have peripheral neuropathy or a particularly high level of blood glucose, with your consent we will notify your GP, who may then suggest following an appropriate course of action with you.

What if I have any Concerns?

If you have a concern about any aspect of this study you should ask to speak to the researchers who will do their best to answer your questions (Neil Reeves: 0161 2475429, or Joe Handsaker: 07779913791). If you remain unhappy and wish to complain formally, you can do this by contacting the Director of Research at the Manchester Metropolitan University, Prof. Valerie Edwards-Jones by calling 0161 2471025.

In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against the Manchester Metropolitan University, but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you (if appropriate).

Medical Records.

If you are a person with diabetes, existing members of the clinical care team at the Central Manchester NHS Hospitals Foundation Trust may look at relevant sections of your medical notes and data. All information will be kept confidential. Study data that is exported to the Manchester Metropolitan University will only be identified by the unique participant code and not by name.

Storage and Disposal of Study Data

All research data will be held in secure storage at the Manchester Metropolitan University. The research data may also include video recordings that will be viewed by the research team. Any video recordings will be securely stored in a digital format, on password-protected computers, within a locked office/laboratory. Disposal of this data will be done by securely deleting the files. All participant data will be anonymous and only identified by a unique number.

What do I do now?

Thank you very much for considering taking part in our research. Please discuss this information with your family, friends or GP if you wish.

If you would like to obtain any further information about this research project please contact a member of the research team or the research nurse by e-mail or telephone.

They will then answer any questions you might have and if you are interested will arrange a convenient appointment for you to attend for your initial visit.

<*Researcher's Name*, at the Manchester Metropolitan University>
<*Researcher's* email address>
<*Researcher's* telephone number>

<*Researcher Nurse's Name*, at the Manchester Diabetes Centre>
< *Researcher Nurse's* email address>
< *Researcher Nurse's* telephone number>
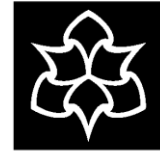
FACULTY OF SCIENCE AND ENGINEERING

M E M O R A N D U M

TO   Neil Reeves & Frank Bowling

FROM   Will Smith

DATE   25 July 2015

SUBJECT   Faculty Ethics Committee Application – **SE111201**

_____

Your recent application to the Ethics Committee (**SE111201)** entitled ""Factors compromising the safety of gait in people with diabetic peripheral neuropathy and the influence of intervention" has been considered.

The application received a favourable opinion from the committee and was approved by Chairs Action.

The application was also held as an excellent example of a detailed Ethics Application.

The Committee requires that you report any Adverse Event during this study immediately to the Chair and Committee Secretary. Adverse Events are adverse reactions to any modality, drug or dietary supplement administered to subjects or any trauma resulting from procedures in the protocol of a study.

An Adverse Event may also be accidental loss of data or loss of sample, particularly human tissue. Loss of human tissue or cells must also be reported to the designated individual for the Human Tissue Authority licence (currently Prof Bill Gilmore).

Regards

Will Smith

Student Information Point

All Saints North (John Dalton Building)

http://www.mmu.ac.uk/sas

Central Manchester University Hospitals **NHS**

NHS Foundation Trust

Central Manchester University Hospitals

NHS Foundation Trust

Research & Development

1st Floor Post Graduate Centre

Manchester Royal Infirmary

Oxford Road

Manchester Ml3 9WL

Tel: 0161-276-3340

Fax: 0161-276-5766

Lorraine.BrpadfootjgJcrnft.njis.uk

Professor Andrew Boulton, Dr Frank Bowling

Professor of Medicine / Consultant Physician

Central Manchester University Hospitals NHS Foundation Trust

Department of Medicine

Manchester Royal Infirmary

Oxford Road

Manchester

MI 3 9WL

Ref: R01772-Ltr2-Boulton

Dear Professor Boulton, Dr Frank Bowling

PIN: R01772 (Please quote this number in all future correspondence)

CSP Reference: 85837/GM

Research Study: Factors compromising the safety of gait in people with diabetic peripheral neuropathy and the influence of intervention.

Thank you for submitting the above study for approval.

We acknowledge that the Manchester Metropolitan University has accepted the role of Research Governance Sponsor for this study.

We understand that this study has been adopted by the NIHR Portfolio.

I am pleased to confirm that the Research Office has now received all necessary documentation, and the Trust Director of Research &. Innovation has given approval for the project to be undertaken.

This approval is in relation to the documentation supplied to us below.

Approval is given subject to the attached conditions - please ensure you and all members of the research team are familiar with these before commencing your research.

Please note: You must tell your Divisional Research Manager - Manju Luckson

• the date that you intend to start recruiting to this study AND

• the date on which the first participant is recruited/consented

The Trust aims for its research projects to recruit their first participant within 30 days of the recruitment start date. If you do not tell us your actual recruitment start date, we will use this approval date. This information is important for monitoring Trust recruitment performance for internal and external assessment.

I would like to take this opportunity to wish you well with your research.

R01772-Ltr2-Boulton

Yours sincerely

Lorraine Broadfoot

Research Operations Manager

Encs SSI Form - Fully Signed

Manju Luckson, Divisional Research Manager for Medicine and Community Services Division and Specialist Medical Services Division - CMFT

National Research Ethics Service

NRES Committee North West - Greater Manchester West

Barlow House
3rd Floor
4 Minshull Street
Manchester
M1 3DZ

Telephone: 0161 625 7815

25 October 2011

Dr. Neil Reeves
Senior Research Fellow
Institute for Biomedical Research into Human Movement & Health
School of Healthcare Science
Manchester Metropolitan University
John Dalton Building
Oxford Road
Manchester
M1 5GD

Dear Dr. Reeves

Study title:	**Factors compromising the safety of gait in people with diabetic peripheral neuropathy and the influence of intervention.**
REC reference:	**11/NW/0686**

Thank you for your letter of 21 October 2011, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

<u>Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.</u>

This Research Ethics Committee is an advisory committee to the North West Strategic Health Authority
*The National Research Ethics Service (NRES) represents the NRES Directorate within
the National Patient Safety Agency and Research Ethics Committees in England*

Appendix

Literature Search Results

Search History

1. EMBASE; "diabetes mellitus".ti,ab; 175106 results.

2. EMBASE; "diabetes type 1".ti,ab; 923 results.

3. EMBASE; "diabetes type 2".ti,ab; 1427 results.

4. EMBASE; exp DIABETIC NEUROPATHY/; 18269 results.

5. EMBASE; exp DIABETES MELLITUS/; 631693 results.

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17. EMBASE; fall*.ti,ab; 182577 results.

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20. EMBASE; exp WALKING/; 68096 results.

21. EMBASE; WALKING AID/; 3799 results.

22. EMBASE; WALKING HARNESS/; 19 results.

23. EMBASE; exp WALKING PATTERN/; 30750 results.

24. EMBASE; WALKING SPEED/; 6648 results.

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26. EMBASE; exp GAIT/; 30750 results.

27. EMBASE; exp GAIT DEVIATIONS/ OR exp GAIT/; 44369 results.

28. EMBASE; exp FALLING/; 26835 results.

29. EMBASE; FALL RISK/ OR exp FALLING/; 28155 results.

30. EMBASE; BIOMECHANICS/; 79265 results.

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32. EMBASE; 4 OR 6; 76259 results.

33. EMBASE; 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR

24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 40 OR 41; 943464 results.

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years or Aged 65+ years)]; 669 results.

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56. Medline; "gait variab*".ti,ab; 571 results.

57. Medline; fall*.ti,ab; 166327 results.

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60. Medline; WALKING/; 20669 results.

61. Medline; LOCOMOTION/; 19240 results.

62. Medline; exp GAIT/; 18597 results.

63. Medline; exp ACCIDENTAL FALLS/; 16058 results.

64. Medline; biomechanics.ti,ab; 10698 results.

65. Medline; 38 OR 39 OR 40 OR 41 OR 42 OR 43; 284340 results.

66. Medline; 44 OR 46; 13861 results.

67. Medline; 47 OR 48 OR 49 OR 50 OR 51 OR 52 OR 53 OR 54 OR 55 OR 56 OR 57 OR 59 OR 60 OR 61 OR 62

OR 63 OR 64; 750338 results.

68. Medline; 65 AND 66 AND 67; 648 results.

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71. CINAHL; "diabetes type 2".ti,ab; 100 results.

72. CINAHL; exp DIABETES MELLITUS,TYPE 2/ OR exp DIABETES MELLITUS,TYPE 1/ OR exp DIABETES

MELLITUS/; 71694 results.

73. CINAHL; "diabetic neuropathy".ti,ab; 762 results.

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87. CINAHL; exp GAIT ANALYSIS/; 4037 results.

88. CINAHL; exp GAIT/; 4034 results.

89. CINAHL; BIOMECHANICS/; 11238 results.

90. CINAHL; GAIT DISORDERS, NEUROLOGIC/; 430 results.

91. CINAHL; LOCOMOTION/; 625 results.

92. CINAHL; exp ACCIDENTAL FALLS/; 11184 results.

93. CINAHL; 69 OR 70 OR 71 OR 72; 75475 results.

94. CINAHL; 73 OR 74; 7047 results.

95. CINAHL; 75 OR 76 OR 77 OR 78 OR 79 OR 80 OR 81 OR 82 OR 83 OR 84 OR 85 OR 86 OR 87 OR 88 OR 89

OR 90 OR 91 OR 92; 97268 results.

96. CINAHL; 93 AND 94 AND 95; 481 results.

97. CINAHL; 96 [Limit to: (Language English) and (Age Groups All Adult)]; 239 results.

98. Medline; adult*.ti,ab; 842952 results.

99. Medline; aged.ti,ab; 378224 results.

100. Medline; elder*.ti,ab; 186971 results.

101. Medline; ageing.ti,ab; 26060 results.

102. Medline; geriatric.ti,ab; 28925 results.

103. Medline; old.ti,ab; 755301 results.

104. Medline; ADULT/; 4002371 results.

105. Medline; GERIATRICS/; 26880 results.

106. Medline; 98 OR 99 OR 100 OR 101 OR 102 OR 103 OR 104 OR 105; 5359325 results.

107. Medline; 68 AND 106; 316 results.

110. Medline; 107 [Limit to: Publication Year 2005-2015]; 127 results.

111. CINAHL; 97 [Limit to: Publication Year 2005-2015 and (Language English) and (Age Groups All Adult)]; 148

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91. CINAHL; LOCOMOTION/; 625 results.

92. CINAHL; exp ACCIDENTAL FALLS/; 11184 results.

93. CINAHL; 69 OR 70 OR 71 OR 72; 75475 results.

94. CINAHL; 73 OR 74; 7047 results.

95. CINAHL; 75 OR 76 OR 77 OR 78 OR 79 OR 80 OR 81 OR 82 OR 83 OR 84 OR 85 OR 86 OR 87 OR 88 OR 89

OR 90 OR 91 OR 92; 97268 results.

96. CINAHL; 93 AND 94 AND 95; 481 results.

97. CINAHL; 96 [Limit to: (Language English) and (Age Groups All Adult)]; 239 results.

98. Medline; adult*.ti,ab; 842952 results.

99. Medline; aged.ti,ab; 378224 results.

100. Medline; elder*.ti,ab; 186971 results.

101. Medline; ageing.ti,ab; 26060 results.

102. Medline; geriatric.ti,ab; 28925 results.

103. Medline; old.ti,ab; 755301 results.

104. Medline; ADULT/; 4002371 results.

105. Medline; GERIATRICS/; 26880 results.

106. Medline; 98 OR 99 OR 100 OR 101 OR 102 OR 103 OR 104 OR 105; 5359325 results.

107. Medline; 68 AND 106; 316 results.

110. Medline; 107 [Limit to: Publication Year 2005-2015]; 127 results.

111. CINAHL; 97 [Limit to: Publication Year 2005-2015 and (Language English) and (Age Groups All Adult)]; 148

1. Plantar pressure reduction in step-to gait: a biomechanical investigation and clinical feasibility study.

Citation: Clinical Biomechanics, 01 October 2008, vol./is. 23/8(1073-1079), 02680033

Author(s): Drerup B; Szczepaniak A; Wetz HH

Source: CINAHL

Full Text: Available from *Elsevier* in *Clinical Biomechanics*

2. The relationship of reduced peripheral nerve function and diabetes with physical performance in older white and

black adults: the health, aging, and body composition (Health ABC) study.

Citation: Diabetes Care, 01 September 2008, vol./is. 31/9(1767-1772), 01495992

Author(s): Strotmeyer ES; de Rekeneire N; Schwartz AV; Faulkner KA; Resnick HE; Goodpaster

BH; Shorr RI; Vinik AI; Harris TB; Newman AB

Source: CINAHL

Full Text: Available from *EBSCOhost* in *Diabetes Care*

Available from *Highwire Press* in *Diabetes Care*

Available from *ProQuest* in *Diabetes Care*

3. Intermittent claudication in diabetes mellitus due to chronic exertional compartment syndrome of the leg: an

observational study of 17 patients.

Citation: Acta Orthopaedica, 01 August 2008, vol./is. 79/4(534-539), 17453674

Author(s): Edmundsson D; Svensson O; Toolanen G

Source: CINAHL

Full Text: Available from *EBSCOhost* in *Acta Orthopaedica*

Available from *EBSCOhost* in *Acta Orthopaedica*

Available from *EBSCOhost* in *Acta Orthopaedica*

4. Diabetic neuropathy in older adults.

Citation: Clinics in Geriatric Medicine, 01 August 2008, vol./is. 24/3(407-435), 07490690

Author(s): Vinik AI; Strotmeyer ES; Nakave AA; Patel CV

Source: CINAHL

Full Text: Available from *Elsevier* in *Clinics in Geriatric Medicine*

5. The effect of diabetic neuropathy and previous foot ulceration in EMG and ground reaction forces during gait.

Citation: Clinical Biomechanics, 01 June 2008, vol./is. 23/5(584-592), 02680033

Author(s): Akashi PMH; Sacco ICN; Watari R; Hennig E

Source: CINAHL

Full Text: Available from *Elsevier* in *Clinical Biomechanics*

6. Custom therapeutic insoles based on both foot shape and plantar pressure measurement provide enhanced

pressure relief.

Citation: Diabetes Care, 01 May 2008, vol./is. 31/5(839-844), 01495992

Author(s): Owings TM; Woerner JL; Frampton JD; Cavanagh PR; Botek G

Source: CINAHL

Full Text: Available from *EBSCOhost* in *Diabetes Care*

Available from *Highwire Press* in *Diabetes Care*

Available from *ProQuest* in *Diabetes Care*

7. Pressure gradient and subsurface shear stress on the neuropathic forefoot.

Citation: Clinical Biomechanics, 01 March 2008, vol./is. 23/3(342-348), 02680033

Author(s): Lott DJ; Zou D; Mueller MJ

Source: CINAHL

Full Text: Available from *Elsevier* in *Clinical Biomechanics*

8. Age, gangrene among predictive factors for amputation in diabetic foot patients.

Citation: Orthopedics Today, 01 February 2008, vol./is. 28/2(38-38), 02795647

Author(s): Brockenbrough G

Source: CINAHL

Full Text: Available from *ProQuest* in *Orthopedics Today*

9. Sensitivity and specificity of plantar pressure threshold in neuropathic midfoot ulcers... 2008 Combined Sections

Meeting...Nashville, Tennessee, February 6-9, 2008.

Citation: Journal of Orthopaedic & Sports Physical Therapy, 02 January 2008, vol./is. 38/1(0-0), 01906011

Author(s): Sinacore DR; Bohnert KL

Source: CINAHL

10. Pressure gradient and subsurface shear stresses contributing to skin breakdown on the neuropathic foot... 2008

Combined Sections Meeting...Nashville, Tennessee, February 6-9, 2008.

Citation: Journal of Orthopaedic & Sports Physical Therapy, 02 January 2008, vol./is. 38/1(0-0),

01906011

Author(s): Tuttle LJ; Mueller MJ; Zou D; Bohnert KL; Sinacore DR

Source: CINAHL

11. Postural instability in postmenopausal women with type 2 diabetes.

Citation: Diabetic Foot Journal, 01 December 2007, vol./is. 10/4(210-212), 14622041

Author(s): Hyer S; Plank M; Rodin A; Patel S

Source: CINAHL

12. Knowledge and practice of foot care in Iranian people with type 2 diabetes.

Citation: International Wound Journal, 01 December 2007, vol./is. 4/4(298-302), 17424801

Author(s): Khamseh ME; Vatankhah N; Baradaran HR

Source: CINAHL

Full Text: Available from *EBSCOhost* in *International Wound Journal*

Available from *Wiley* in *International Wound Journal*

13. Diabetic neuropathy is related to joint stiffness during late stance phase.

Citation: Journal of Applied Biomechanics, 01 November 2007, vol./is. 23/4(251-260), 10658483

Author(s): Williams DS 3rd; Brunt D; Tanenberg RJ

Source: CINAHL

14. Peak plantar pressure and shear locations: relevance to diabetic patients.

Citation: Diabetes Care, 01 October 2007, vol./is. 30/10(2643-2645), 01495992

Author(s): Yavuz M; Erdemir A; Botek G; Hirschman GB; Bardsley L; Davis BL

Source: CINAHL

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Full Text: Available from *EBSCOhost* in *Diabetes Care*

Available from *Highwire Press* in *Diabetes Care*

Available from *ProQuest* in *Diabetes Care*

15. Changes in pedal plantar pressure variability and contact time following massage therapy: a case study of a client

with diabetic neuropathy.

Citation: Journal of Bodywork & Movement Therapies, 01 October 2007, vol./is. 11/4(295-301),
13608592

Author(s): Finch P; Baskwill A; Marincola F; Becker P

Source: CINAHL

Full Text: Available from *Elsevier* in *Journal of Bodywork and Movement Therapies*

16. Custom-made total contact insoles and prefabricated functional diabetic insoles: a case report.

Citation: Diabetic Foot Journal, 01 September 2007, vol./is. 10/3(138-142), 14622041

Author(s): Paton J; Stenhouse E; Jones R; Bruce G

Source: CINAHL

17. Use of a retrograde nail for ankle arthrodesis in charcot neuroarthropathy: a limb salvage procedure.

Citation: Foot & Ankle International, 01 September 2007, vol./is. 28/9(967-970), 10711007

Author(s): Paola LD; Volpe A; Varotto D; Postorino A; Brocco E; Senesi A; Merico M; De Vido D; Da Ros R; Assaloni R

Source: CINAHL

Full Text: Available from *Highwire Press* in *Foot and Ankle International*

18. Daily-life activities and in-shoe forefoot plantar pressure in patients with diabetes.

Citation: Diabetes Research & Clinical Practice, 01 August 2007, vol./is. 77/2(203-209), 01688227

Author(s): Guldemond NA; Leffers P; Sanders AP; Schaper NC; Nieman F; Walenkamp GHI

Source: CINAHL

Full Text: Available from *Elsevier* in *Diabetes Research and Clinical Practice*

19. Does Tai Chi improve plantar sensory ability? A pilot study.

Citation: Diabetes Technology & Therapeutics, 01 June 2007, vol./is. 9/3(276-286), 15209156

Author(s): Richerson S; Rosendale K

Source: CINAHL

20. Segmental foot mobility in individuals with and without diabetes and neuropathy.

Citation: Clinical Biomechanics, 01 May 2007, vol./is. 22/4(464-471), 02680033

Author(s): Rao S; Saltzman C; Yack HJ

Source: CINAHL

Full Text: Available from *Elsevier* in *Clinical Biomechanics*

21. Painful diabetic neuropathy: impact of an alternative approach.

Citation: Diabetes Care, 01 April 2007, vol./is. 30/4(999-1001), 01495992

Author(s): Gillespie EA; Gillespie BW; Stevens MJ

Source: CINAHL

Full Text: Available from *EBSCOhost* in *Diabetes Care*

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Available from *Highwire Press* in *Diabetes Care*

Available from *ProQuest* in *Diabetes Care*

22. Muscle tone in diabetic polyneuropathy evaluated by the quantitative pendulum test.

Citation: Archives of Physical Medicine & Rehabilitation, 01 March 2007, vol./is. 88/3(368-373), 00039993

Author(s): Lin CC; Ju MS; Huang HW

Source: CINAHL

Full Text: Available from *Elsevier* in *Archives of Physical Medicine and Rehabilitation*

23. An off-the-shelf instant contact casting device for the management of diabetic foot ulcers: a randomized

prospective trial versus traditional fiberglass cast.

Citation: Diabetes Care, 01 March 2007, vol./is. 30/3(586-590), 01495992

Author(s): Piaggesi A; Macchiarini S; Rizzo L; Palumbo F; Tedeschi A; Nobili LA; Leporati E;

Scire V; Teobaldi I; Del Prato S

Source: CINAHL

Full Text: Available from *EBSCOhost* in *Diabetes Care*

Available from *Highwire Press* in *Diabetes Care*

Available from *ProQuest* in *Diabetes Care*

24. Off-loading neuropathic plantar heel ulcers with a metal stirrup brace: case report.

Citation: Foot & Ankle International, 01 March 2007, vol./is. 28/3(385-387), 10711007

Author(s): Tamir E; Daniels TR

Source: CINAHL

Full Text: Available from *Highwire Press* in *Foot and Ankle International*

25. Learning to "live with" chronic pain: lessons from Mrs. Tandy.

Citation: Topics in Advanced Practice Nursing, 01 March 2007, vol./is. 7/1(0-7), 15352250

Author(s): Arnstein P

Source: CINAHL

26. Diabetes, hand and/or foot ulcers: a cross-sectional hospital-based study in Port Harcourt, Nigeria.

Citation: Diabetes Research & Clinical Practice, 01 February 2007, vol./is. 75/2(148-152),

01688227

Author(s): Unachukwu C; Babatunde S; Ihekwaba AE

Source: CINAHL

Full Text: Available from *Elsevier* in *Diabetes Research and Clinical Practice*

27. The "flap-shaft" prosthesis for insensate feet with chopart or lisfranc amputations.

Citation: Foot & Ankle International, 01 February 2007, vol./is. 28/2(255-262), 10711007

Author(s): Krause FG; Aebi H; Lehmann O; Weber M

Source: CINAHL

Full Text: Available from *Highwire Press* in *Foot and Ankle International*

28. The effects of insole configurations on forefoot plantar pressure and walking convenience in

diabetic patients with

neuropathic feet.

Citation: Clinical Biomechanics, 01 January 2007, vol./is. 22/1(81-87), 02680033

Author(s): Guldemond NA; Leffers P; Schaper NC; Sanders AP; Nieman F; Willems P; Walenkamp GHI

Source: CINAHL

Full Text: Available from *Elsevier* in *Clinical Biomechanics*

29. The impact of diabetes and peripheral neuropathy on fall risk and function in adults.

Citation: [Dissertation] 01 January 2007, (163 pages)

Author(s): Shaffer SW

Source: CINAHL

30. Reduction of digital plantar pressure by debridement and silicone orthosis.

Citation: Diabetes Research & Clinical Practice, 01 December 2006, vol./is. 74/3(263-266), 01688227

Author(s): Slater RA; Hershkowitz I; Ramot Y; Buchs A; Rapoport MJ

Source: CINAHL

31. A simplified protocol to screen for distal polyneuropathy in type 2 diabetic patients.

Citation: Diabetes Research & Clinical Practice, 01 September 2006, vol./is. 73/3(292-297), 01688227

Author(s): Costa LA; Maraschin JF; Xavier de Castro JH; Gross JL; Friedman R

Source: CINAHL

32. Location of plantar ulcerations in diabetic patients referred to a Department of Veterans Affairs podiatry clinic.

Citation: Journal of Rehabilitation Research & Development, 01 July 2006, vol./is. 43/4(421-426), 07487711

Author(s): Perell KL; Merrill V; Nouvong A

Source: CINAHL

Full Text: Available from *EBSCOhost* in *Journal of Rehabilitation Research & Development*

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Available from *ProQuest* in *Journal of Rehabilitation Research and Development*

33. An alternative method of offloading the neuropathic foot ulcer... including commentary by Varnado MF.

Citation: Journal of Wound, Ostomy & Continence Nursing, 01 July 2006, vol./is. 33/4(408-415), 10715754

Author(s): Wood-Belford K

Source: CINAHL

Full Text: Available from *Ovid* in *Journal of Wound, Ostomy and Continence Nursing*

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34. Meeting reporter.

Citation: Patient Care, 01 July 2006, vol./is. 40/7(10-10), 0031305X

Author(s): Asch-Goodkin J; Kaplan D

Source: CINAHL

Full Text: Available from *EBSCOhost* in *Patient Care*

35. Prediction of diabetic foot ulcer occurrence using commonly available clinical information: the Seattle Diabetic

Foot Study.

Citation: Diabetes Care, 01 June 2006, vol./is. 29/6(1202-1207), 01495992

Author(s): Boyko EJ; Ahroni JH; Cohen V; Nelson KM; Heagerty PJ

Source: CINAHL

Full Text: Available from *EBSCOhost* in *Diabetes Care*

Available from *Highwire Press* in *Diabetes Care*

Available from *ProQuest* in *Diabetes Care*

36. Measurement of the walking duration with therapeutic shoes in neuropathic diabetic patients by a novel device

(show-me).

Citation: Diabetes Care, 01 June 2006, vol./is. 29/6(1456-1456), 01495992

Author(s): Kastenbauer T; Wassermann J; Krippl E; Prager R; Irsigler K

Source: CINAHL

Full Text: Available from *EBSCOhost* in *Diabetes Care*

Available from *Highwire Press* in *Diabetes Care*

Available from *ProQuest* in *Diabetes Care*

37. Gait deviations of patients with diabetes mellitus: looking beyond peripheral neuropathy.

Citation: Europa Medicophysica, 01 June 2006, vol./is. 42/2(127-133), 00142573

Author(s): Yavuzer G; Yetkin I; Toruner FB; Koca N; Bolukbas N

Source: CINAHL

38. All that is gas is not gas gangrene: mechanical spread of gas in the soft tissues: a case report.

Citation: Journal of Bone & Joint Surgery, American Volume, 01 June 2006, vol./is. 88A/6(1345-1348), 00219355

Author(s): Panchbhavi VK; Hecox SE

Source: CINAHL

Full Text: Available from *Ovid* in *Journal of Bone and Joint Surgery - American Volume*

Available from *EBSCOhost* in *Journal of Bone & Joint Surgery, American Volume*

39. Efficacy and mechanism of orthotic devices to unload metatarsal heads in people with diabetes and a history of

plantar ulcers.

Citation: Physical Therapy, 01 June 2006, vol./is. 86/6(833-842), 00319023

Author(s): Mueller MJ; Lott DJ; Hastings MK; Commean PK; Smith KE; Pilgram TK

Source: CINAHL

Full Text: Available from *EBSCOhost* in *Physical Therapy*

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Available from *EBSCOhost* in *Physical Therapy*

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Available from *ProQuest* in *Physical Therapy*

40. A new wound-based severity score for diabetic foot ulcers: a prospective analysis of 1,000 patients.

Citation: Diabetes Care, 01 May 2006, vol./is. 29/5(988-992), 01495992

Author(s): Beckert S; Witte M; Wicke C; Königsrainer A; Coerper S

Source: CINAHL

Full Text: Available from *EBSCOhost* in *Diabetes Care*

Available from *Highwire Press* in *Diabetes Care*

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41. Biomechanical risk factors associated with neuropathic ulceration of the hallux in people with diabetes mellitus.

Citation: Journal of the American Podiatric Medical Association, 01 May 2006, vol./is. 96/3(189-197), 87507315

Author(s): Nubé VL; Molyneaux L; Yue DK

Source: CINAHL

42. Pain assessment and management for a dialysis patient with diabetic peripheral neuropathy.

Citation: CANNT Journal, 01 April 2006, vol./is. 16/2(12-19), 14985136

Author(s): Innis J

Source: CINAHL

Full Text: Available from *EBSCOhost* in *CANNT journal (1996)*

Available from *ProQuest* in *CANNT Journal*

43. The prevalence and occurrence of diabetic foot ulcer pain and its impact on health-related quality of life.

Citation: Journal of Pain, 01 April 2006, vol./is. 7/4(290-299), 15265900

Author(s): Ribu L; Rustøen T; Birkeland K; Hanestad BR; Paul SM; Miaskowski C

Source: CINAHL

44. Risk of plantar ulceration in diabetic patients with single-leg amputation.

Citation: Clinical Biomechanics, 01 March 2006, vol./is. 21/3(306-313), 02680033

Author(s): Kanade RV; van Deursen RWM; Price P; Harding K

Source: CINAHL

45. Mortality and morbidity after transmetatarsal amputation: retrospective review of 101 cases.

Citation: Journal of Foot & Ankle Surgery, 01 March 2006, vol./is. 45/2(91-97), 10672516

Author(s): Pollard J; Hamilton GA; Rush SM; Ford LA

Source: CINAHL

46. A 1-year study of gait characteristics in diabetes: the impact of rosiglitazone... including commentary by de

Camargo Neves Sacco I.

Citation: International Journal of Therapy & Rehabilitation, 01 February 2006, vol./is. 13/2(74-81), 17411645

Author(s): Petrofsky J; Lee S; Cuneo M; Dial R; Sanchez M; Kwan S; Lohman E

Source: CINAHL

Full Text: Available from *EBSCOhost* in *International Journal of Therapy & Rehabilitation*

47. Reversal of diabetic peripheral neuropathy with phototherapy (MIRE) decreases falls and the fear of falling and

improves activities of daily living in seniors.

Citation: Age & Ageing, 01 January 2006, vol./is. 35/1(11-16), 00020729

Author(s): Powell MW; Carnegie DH; Burke TJ

Source: CINAHL

Full Text: Available from *EBSCOhost* in *Age & Ageing*

Available from *Oxford University Press* in *Age and Ageing*

Available from *Highwire Press* in *Age and Ageing*

Available from *AGE AND AGEING* in *CMFT Library Services*

48. Noise-enhanced balance control in patients with diabetes and patients with stroke.

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Citation: Annals of Neurology, 01 January 2006, vol./is. 59/1(4-12), 03645134

Author(s): Priplata AA; Patritti BL; Niemi JB; Hughes R; Gravelle DC; Lipsitz LA; Veves A; Stein J; Bonato P; Collins JJ

Source: CINAHL

Full Text: Available from *Wiley* in *Annals of Neurology*

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49. Late diabetes complications and non-dipping phenomenon in patients with type 1 diabetes.

Citation: Diabetes Research & Clinical Practice, 01 January 2006, vol./is. 71/1(14-20), 01688227

Author(s): Stella P; Tabak AG; Zgibor JC; Orchard TJ

Source: CINAHL

50. "Pressure gradient" as an indicator of plantar skin injury.

Citation: Diabetes Care, 01 December 2005, vol./is. 28/12(2908-2912), 01495992

Author(s): Mueller MJ; Zou D; Lott DJ

Source: CINAHL

Full Text: Available from *EBSCOhost* in *Diabetes Care*

Available from *Highwire Press* in *Diabetes Care*

Available from *ProQuest* in *Diabetes Care*

51. A comparison of the 1-step, 2-step, and 3-step protocols for obtaining barefoot plantar pressure data in the

diabetic neuropathic foot.

Citation: Clinical Biomechanics, 01 November 2005, vol./is. 20/9(892-899), 02680033

Author(s): Bus SA; de Lange A

Source: CINAHL

52. Plantar pressure in off-loading devices used in diabetic ulcer treatment.

Citation: Wound Repair & Regeneration, 01 November 2005, vol./is. 13/6(537-542), 10671927

Author(s): Beuker BJ; Van Deursen RW; Price P; Manning EA; Van Baal JG; Harding KG

Source: CINAHL

Full Text: Available from *EBSCOhost* in *Wound Repair & Regeneration*

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Available from *Wiley* in *Wound Repair and Regeneration*

53. Pain severity in diabetic peripheral neuropathy is associated with patient functioning, symptom levels of anxiety

and depression, and sleep.

Citation: Journal of Pain & Symptom Management, 01 October 2005, vol./is. 30/4(374-385),
08853924

Author(s): Gore M; Brandenburg NA; Dukes E; Hoffman DL; Tai K; Stacey B

Source: CINAHL

54. Reduction of plantar pressure using a prototype pressure-relieving dressing.

Citation: Diabetes Care, 01 September 2005, vol./is. 28/9(2236-2237), 01495992

Author(s): van Schie CH; Rawat F; Boulton AJM

Source: CINAHL

Full Text: Available from *EBSCOhost* in *Diabetes Car*

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55. Disability and quality of life in Canadian Aboriginal and non-Aboriginal diabetic lower-extremity amputees.

Citation: Archives of Physical Medicine & Rehabilitation, 01 August 2005, vol./is.
86/8(1594-1602), 00039993

Author(s): Meatherall BL; Garrett MR; Kaufert J; Martin BD; Fricke MW; Arneja AS; Duerksen F;
Koulack J; Fong HM; Simonsen JN; Nicolle LE; Trepman E; Embil JM

Source: CINAHL

56. Wear and biomechanical characteristics of a novel shear-reducing insole with implications for high-risk persons

with diabetes.

Citation: Diabetes Technology & Therapeutics, 01 August 2005, vol./is. 7/4(638-646), 15209156

Author(s): Lavery LA; Lanctot DR; Constantinides G; Zamorano RG; Athanasiou KA; Agrawal CM

Source: CINAHL

57. At-home foot temperature monitoring reduced foot complications in high risk patients with diabetes.

Citation: Evidence Based Nursing, 01 July 2005, vol./is. 8/3(80-80), 13676539

Author(s): Chyun D

Source: CINAHL

Full Text: Available from *Highwire Press* in *Evidence-Based Nursing*

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58. Relationship between changes in activity and plantar ulcer recurrence in a patient with diabetes mellitus.

Citation: Physical Therapy, 01 June 2005, vol./is. 85/6(579-588), 00319023

Author(s): Lott DJ; Maluf KS; Sinacore DR; Mueller MJ

Source: CINAHL

Full Text: Available from *EBSCOhost* in *Physical Therapy*

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59. A randomized trial of two irremovable off-loading devices in the management of plantar neuropathic diabetic foot

ulcers.

Citation: Diabetes Care, 01 March 2005, vol./is. 28/3(555-559), 01495992

Author(s): Katz IR; Harlan A; Miranda-Palma B; Prieto-Sanchez L; Armstrong DG; Bowker JH; Mizel MS; Boulton AJM

Source: CINAHL

Full Text: Available from *EBSCOhost* in *Diabetes Care*

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60. Cooling the foot to prevent diabetic foot wounds: a proof-of-concept trial.

Citation: Journal of the American Podiatric Medical Association, 01 March 2005, vol./is. 95/2(103-107), 87507315

Author(s): Armstrong DG; Sangalang MB; Jolley D; Maben F; Kimbriel HR; Nixon BP; Cohen IK

Source: CINAHL

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61. The impact of neuropathic pain and other comorbidities on the quality of life in patients with diabetes

Citation: Health and Quality of Life Outcomes, December 2014, vol./is. 12/1, 1477-7525 (December 03, 2014)

Author(s): Dermanovic Dobrota V.; Hrabac P.; Skegro D.; Smiljanic R.; Dobrota S.; Prkacin I.; Brkljacic N.; Peros K.; Tomic M.; Lukinovic-Skudar V.; Basic Kes V.

Source: EMBASE

Full Text: Available from *EBSCOhost* in *Health & Quality of Life Outcomes*

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62. Early risk stratification in paediatric type 1 diabetes

Citation: Acta Ophthalmologica, March 2015, vol./is. 93/A102(1-19), 1755-375X;1755-3768 (01 Mar 2015)

Author(s): Broe R.

Source: EMBASE

Full Text: Available from *Wiley* in *Acta Ophthalmologica*

63. Abnormalities of plantar pressure distribution in early, intermediate, and late stages of diabetic neuropathy

Citation: Gait and Posture, 2014, vol./is. 40/4(570-574), 0966-6362;1879-2219 (2014)

Author(s): Sacco I.C.N.; Hamamoto A.N.; Tonicelli L.M.G.; Watari R.; Ortega N.R.S.; Sartor C.D.

Source: EMBASE

Full Text: Available from *Elsevier* in *Gait and Posture*

64. Adipose tissue content, muscle performance and physical function in obese adults with type 2 diabetes mellitus

and peripheral neuropathy

Citation: Journal of Diabetes and its Complications, March 2015, vol./is. 29/2(250-257),

1056-8727;1873-460X (01 Mar 2015)

Author(s): Bittel D.C.; Bittel A.J.; Tuttle L.J.; Hastings M.K.; Commean P.K.; Mueller M.J.; Cade

W.T.; Sinacore D.R.

Source: EMBASE

Full Text: Available from *Elsevier* in *Journal of Diabetes and Its Complications*

65. Multimodal treatment of distal sensorimotor polyneuropathy in diabetic patients: A randomized clinical trial

Citation: Journal of Manipulative and Physiological Therapeutics, May 2014, vol./is.

37/4(242-252), 0161-4754;1532-6586 (May 2014)

Author(s): Taveggia G.; Villafane J.H.; Vavassori F.; Lecchi C.; Borboni A.; Negrini S.

Source: EMBASE

Full Text: Available from *Elsevier* in *Journal of Manipulative and Physiological Therapeutics*

66. Patient expectations in the treatment of painful diabetic polyneuropathy: Results from a non-interventional study

Citation: Pain Medicine (United States), April 2014, vol./is. 15/4(671-681), 1526-2375;1526-4637

(April 2014)

Author(s): Schneider E.; Ziegler D.; Wilhelm S.; Schacht A.; Birklein F.

Source: EMBASE

Full Text: Available from *EBSCOhost* in *Pain Medicine*

Available from *Wiley* in *Pain Medicine*

67. Effect of self-perceived motion on gait alteration in people with type two diabetes

Citation: Endocrine Reviews, 2013, vol./is. 34/3 SUPPL. 1, 0163-769X (2013)

Author(s): Huang C.-K.; Shivaswamy V.; Mack L.R.; Siu K.-C.

Source: EMBASE

68. Augmented asymmetrical visual field dependence in asymptomatic diabetics: Evidence of subclinical

asymmetrical bilateral vestibular dysfunction

Citation: Journal of Diabetes and its Complications, January 2015, vol./is. 29/1(68-72),

1056-8727;1873-460X (01 Jan 2015)

Author(s): Razzak R.A.; Bagust J.; Docherty S.; Hussein W.; Al-Otaibi A.

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Citation: Muscle and Nerve, April 2013, vol./is. 47/4(497-503), 0148-639X;1097-4598 (April

2013)

Author(s): Richardson J.K.; Allet L.; Kim H.; Ashton-Miller J.A.

Source: EMBASE

Full Text: Available from *EBSCOhost* in *Muscle & Nerve*

Available from *Wiley* in *Muscle and Nerve*

130. The association between skin collagen glucosepane and past progression of microvascular and neuropathic

complications in type 1 diabetes

Citation: Journal of Diabetes and its Complications, March 2013, vol./is. 27/2(141-149),

1056-8727;1873-460X (March-April 2013)

Author(s): Monnier V.M.; Sell D.R.; Strauch C.; Sun W.; Lachin J.M.; Cleary P.A.; Genuth S.

Source: EMBASE

Full Text: Available from *Elsevier* in *Journal of Diabetes and Its Complications*

Available from *EBSCOhost* in *Journal of Diabetes & its Complications*

Available from *ProQuest* in *Journal of Diabetes and its Complications*

131. Do the biomechanical properties of the ankle-foot complex influence postural control for people with Type 2

diabetes?

Citation: Clinical Biomechanics, January 2013, vol./is. 28/1(88-92), 0268-0033;1879-1271

(January 2013)

Author(s): Cheing G.L.Y.; Chau R.M.W.; Kwan R.L.C.; Choi C.-H.; Zheng Y.-P.

Source: EMBASE

Full Text: Available from *Elsevier* in *Clinical Biomechanics*

132. Effects of tai chi exercise on glucose control, neuropathy scores, balance, and quality of life in patients with type

2 diabetes and neuropathy

Citation: Journal of Alternative and Complementary Medicine, December 2012, vol./is. 18/12(1172-1178), 1075-5535;1557-7708 (01 Dec 2012)

Author(s): Ahn S.; Song R.

Source: EMBASE

Full Text: Available from *EBSCOhost* in *Journal of Alternative & Complementary Medicine*

Available from *EBSCOhost* in *Journal of Alternative & Complementary Medicine*

Available from *EBSCOhost* in *Journal of Alternative & Complementary Medicine*

133. Use of a new high-sensitivity assay for cardiac troponin T to stratify the risk of cardiovascular disease in

outpatients with type-2 diabetes

Citation: Diabetology International, March 2012, vol./is. 3/1(29-36), 2190-1678;2190-1686 (March 2012)

Author(s): Asano S.; Suzuki A.; Ishii J.; Sekiguchi-Ueda S.; Shibata M.; Yoshino Y.; Nakamura K.; Akiyama Y.; Kitagawa F.; Sakuishi T.; Fujita T.; Itoh M.

Source: EMBASE

134. Unusual case of recurrent falls: Myasthenia gravis in an elderly patient

Citation: Canadian Family Physician, November 2012, vol./is. 58/11(1231-1232), 0008-350X (November 2012)

Author(s): Alaama T.; Basharat P.; Nicolle M.W.

Source: EMBASE

Full Text: Available from *EBSCOhost* in *Canadian Family Physician*

Available from *Highwire Press* in *Canadian Family Physician*

Available from *National Library of Medicine* in *Canadian Family Physician*

135. Offloading effect of therapeutic footwear in patients with diabetic neuropathy at high risk for plantar foot

ulceration

Citation: Diabetic Medicine, December 2012, vol./is. 29/12(1534-1541), 0742-3071;1464-5491 (December 2012)

Author(s): Arts M.L.J.; Waaijman R.; de Haart M.; Keukenkamp R.; Nollet F.; Bus S.A.

Source: EMBASE

Full Text: Available from *EBSCOhost* in *Diabetic Medicine*

Available from *EBSCOhost* in *Diabetic Medicine*

Available from *Wiley* in *Diabetic Medicine*

136. Which lower limb frontal plane sensory and motor functions predict gait speed and efficiency on uneven surfaces

in older persons with diabetic neuropathy?

Citation: PM and R, October 2012, vol./is. 4/10(726-733), 1934-1482 (October 2012)

Author(s): Allet L.; Kim H.; Ashton-Miller J.A.; Richardson J.K.

Source: EMBASE

Full Text: Available from *Elsevier* in *PM&R*

137. Microalbuminuria is an independent risk factor for nausea caused by glucagon-like peptide-1 receptor agonists

Citation: Diabetologia, October 2012, vol./is. 55/(S300), 0012-186X (October 2012)

Author(s): Umematsu H.; Suzuki R.; Awazawa M.; Hada Y.; Izumida Y.; Shojima N.; Okazaki Y.; Fujishiro M.; Iizuka Y.; Sakoda H.; Ohsugi M.; Hara K.; Yamauchi T.; Ueki K.; Kadowaki T.

Source: EMBASE

Full Text: Available from *EBSCOhost* in *Diabetologia*

Available from *ProQuest* in *Diabetologia*

138. A gastroretentive gabapentin formulation for the treatment of painful diabetic peripheral neuropathy: Efficacy

and tolerability in a double-blind, randomized, controlled clinical trial

Citation: Diabetes Research and Clinical Practice, September 2012, vol./is. 97/3(438-445), 0168-8227;1872-8227 (September 2012)

Author(s): Sandercock D.; Cramer M.; Biton V.; Cowles V.E.

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Source: EMBASE

Full Text: Available from *Elsevier* in *Diabetes Research and Clinical Practice*

139. Muscle weakness and other late complications of diabetic polyneuropathy

Citation: Acta Clinica Croatica, 2011, vol./is. 50/3(355-355), 0353-9466 (2011)

Author(s): Bokan V.

Source: EMBASE

140. Contribution of multisegment 3D foot kinematics, kinetics and EMG data to the assessment of diabetes subjects'

lower limb impairments

Citation: Gait and Posture, June 2012, vol./is. 36/(S36-S37), 0966-6362 (June 2012)

Author(s): Sawacha Z.; Spolaor F.; Guiotto A.; Guarneri G.; Negretto M.; Munari A.; Ferrari R.; Venturin A.; Avogaro A.; Cobelli C.

Source: EMBASE

Full Text: Available from *Elsevier* in *Gait and Posture*

141. Elevated cerebrospinal fluid tau in Wernicke encephalopathy

Citation: BMJ Case Reports, 2012, 1757-790X (2012)

Author(s): Frijlink D.W.; Tilanus J.J.; Roks G.

Source: EMBASE

Full Text: Available from *EBSCOhost* in *BMJ Case Reports*

Available from *National Library of Medicine* in *BMJ Case Reports*

142. A controlled study of medial arterial calcification of legs: Implications for diabetic polyneuropathy

Citation: Archives of Neurology, October 2011, vol./is. 68/10(1290-1294), 0003-9942;1538-3687 (October 2011)

Author(s): Moon J.-S.; Clark V.M.; Beabout J.W.; Swee R.G.; Dyck P.J.

Source: EMBASE

Full Text: Available from *Silverchair Information Systems* in *Archives of Neurology*

143. Selection of an above or below-ankle orthosis for individuals with neuropathic partial foot amputation: A pilot

study

Citation: Prosthetics and Orthotics International, June 2012, vol./is. 36/2(217-224), 0309-3646;1746-1553 (June 2012)

Author(s): Spaulding S.E.; Chen T.; Chou L.-S.

Source: EMBASE

Full Text: Available from *Highwire Press* in *Prosthetics and Orthotics International*

144. Population pharmacokinetics of ABT-594 in subjects with diabetic peripheral neuropathic pain

Citation: Journal of Clinical Pharmacy and Therapeutics, August 2012, vol./is. 37/4(475-480), 0269-4727;1365-2710 (August 2012)

Author(s): Dutta S.; Awni W.

Source: EMBASE

Full Text: Available from *EBSCOhost* in *Journal of Clinical Pharmacy & Therapeutics*

Available from *EBSCOhost* in *Journal of Clinical Pharmacy & Therapeutics*

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Available from *Wiley* in *Journal of Clinical Pharmacy and Therapeutics*

145. Evaluation and optimization of therapeutic footwear for neuropathic diabetic foot patients using in-shoe plantar

pressure analysis

Citation: Diabetes Care, July 2011, vol./is. 34/7(1595-1600), 0149-5992;1935-5548 (July 2011)

Author(s): Bus S.A.; Haspels R.; Busch-Westbroek T.E.

Source: EMBASE

Full Text: Available from *EBSCOhost* in *Diabetes Care*

Available from *Highwire Press* in *Diabetes Care*

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146. Insulin resistance is independently associated with peripheral and autonomic neuropathy in Korean type 2

diabetic patients

Citation: Acta Diabetologica, April 2012, vol./is. 49/2(97-103), 0940-5429;1432-5233 (April 2012)

Author(s): Lee K.O.; Nam J.S.; Ahn C.W.; Hong J.-M.; Kim S.-M.; Sunwoo I.-N.; Moon J.-S.; Na S.-J.; Choi Y.-C.

Source: EMBASE

Full Text: Available from *EBSCOhost* in *Acta Diabetologica*

Available from *ProQuest* in *Acta Diabetologica*

147. Effects of a combined strengthening, stretching and functional training program versus usual-care on gait

biomechanics and foot function for diabetic neuropathy: A randomized controlled trial

Citation: BMC Musculoskeletal Disorders, 2012, vol./is. 13/, 1471-2474 (2012)

Author(s): Sartor C.D.; Watari R.; Passaro A.C.; Picon A.P.; Hasue R.H.; Sacco I.C.N.

Source: EMBASE

Full Text: Available from *EBSCOhost* in *BMC Musculoskeletal Disorders*

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Available from *National Library of Medicine* in *BMC Musculoskeletal Disorders*

Available from *ProQuest* in *BMC Musculoskeletal Disorders*

148. Time-course changes in nerve conduction velocity (NCV) in type 2 diabetes

Citation: Journal of Diabetes and its Complications, May 2012, vol./is. 26/3(237-240), 1056-8727;1873-460X (May-June 2012)

Author(s): Morimoto J.; Suzuki Y.; Tada A.; Akui M.; Ozawa Y.; Maruyama T.

Source: EMBASE

Full Text: Available from *Elsevier* in *Journal of Diabetes and Its Complications*

Available from *ProQuest* in *Journal of Diabetes and its Complications*

149. Limb salvage for spreading midfoot osteomyelitis following diabetic foot surgery

Citation: Journal of Tissue Viability, May 2012, vol./is. 21/2(64-70), 0965-206X;1876-4746 (May 2012)

Author(s): Aragon-Sanchez J.; Lazaro-Martinez J.L.; Cecilia-Matilla A.; Quintana-Marrero Y.; Hernandez-Herrero M.J.

Source: EMBASE

Full Text: Available from *Elsevier* in *Journal of Tissue Viability*

150. Parkinson's disease and risk of hip fracture: An 8-year follow-up study in Taiwan

Citation: Parkinsonism and Related Disorders, June 2012, vol./is. 18/5(506-509), 1353-8020;1873-5126 (June 2012)

Author(s): Chen Y.-Y.; Cheng P.-Y.; Wu S.-L.; Lai C.-H.

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Source: EMBASE

Full Text: Available from *Elsevier* in *Parkinsonism and Related Disorders*

151. Prevalence of and risk factors for abnormal ankle-brachial index in patients with type 2 diabetes

Citation: Journal of Diabetes, June 2012, vol./is. 4/2(140-146), 1753-0393;1753-0407 (June 2012)

Author(s): Li X.; Wang Y.-Z.; Yang X.-P; Xu Z.-R.

Source: EMBASE

Full Text: Available from *EBSCOhost* in *Journal of Diabetes*

Available from *Wiley* in *Journal of Diabetes*

152. Treatment Guidelines for the Pharmacological Management of Pain in Older Persons

Citation: Pain Medicine, April 2012, vol./is. 13/SUPPL. 2(S57-S66), 1526-2375;1526-4637 (April 2012)

Author(s): Fine P.G.

Source: EMBASE

Full Text: Available from *EBSCOhost* in *Pain Medicine*

Available from *Wiley* in *Pain Medicine*

153. Guidelines in practice: Treatment of painful diabetic neuropathy

Citation: CONTINUUM Lifelong Learning in Neurology, February 2012, vol./is. 18/1(192-198), 1080-2371;1538-6899 (February 2012)

Author(s): Shenoy A.M.

Source: EMBASE

154. Neuropathic pain: Mechanisms, therapeutic approach, and interpretation of clinical trials

Citation: CONTINUUM Lifelong Learning in Neurology, February 2012, vol./is. 18/1(161-175), 1080-2371;1538-6899 (February 2012)

Author(s): Attal N.

Source: EMBASE

155. The interdependency of peak pressure and pressure-time integral in pressure studies on diabetic footwear: No

need to report both parameters

Citation: Gait and Posture, January 2012, vol./is. 35/1(1-5), 0966-6362;1879-2219 (January 2012)

Author(s): Waaijman R.; Bus S.A.

Source: EMBASE

Full Text: Available from *Elsevier* in *Gait and Posture*

156. Development of insulin resistance by chronic hyperinsulinemia and subsequent reduction of Akt signaling in

dorsal root ganglion neurons

Citation: Diabetes, July 2011, vol./is. 60/(A6-A7), 0012-1797 (July 2011)

Author(s): Kim B.; Mclean L.; Feldman E.L.

Source: EMBASE

Full Text: Available from *EBSCOhost* in *Diabetes*

Available from *Highwire Press* in *Diabetes*

Available from *ProQuest* in *Diabetes*

157. Hospitalization-associated disability "She was probably able to ambulate, but i'm not sure"

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Citation: JAMA - Journal of the American Medical Association, October 2011, vol./is. 306/16(1782-1793), 0098-7484;1538-3598 (26 Oct 2011)

Author(s): Covinsky K.E.; Pierluissi E.; Johnston C.B.

Source: EMBASE

Full Text: Available from *EBSCOhost* in *JAMA: Journal of the American Medical Association*

Available from *Silverchair Information Systems* in *JAMA Journal of the American*

Medical Association

158. Cilostazol: A pilot study on safety and clinical efficacy in neuropathies of diabetes mellitus type 2 (ASCEND)

Citation: Angiology, November 2011, vol./is. 62/8(625-635), 0003-3197;1940-1574 (November 2011)

Author(s): Rosales R.L.; Delgado-Delos Santos M.M.S.; Mercado-Asis L.B.

Source: EMBASE

Full Text: Available from *EBSCOhost* in *Angiology*

Available from *Highwire Press* in *Angiology: The Journal of Vascular Diseases*

159. Selective contribution of waist circumference reduction on the improvement of sleep-disordered breathing in

patients hospitalized with type 2 diabetes mellitus

Citation: Internal Medicine, 2011, vol./is. 50/18(1895-1903), 0918-2918;1349-7235 (2011)

Author(s): Kashine S.; Kishida K.; Funahashi T.; Yasuda T.; Okita K.; Matsuzawa Y.; Shimomura I.

Source: EMBASE

160. Opioid titration and conversion in patients receiving morphine sulfate and naltrexone hydrochloride extended

release capsules

Citation: Postgraduate Medicine, September 2011, vol./is. 123/5(155-164), 0032-5481;1941-9260 (September 2011)

Author(s): Webster L.R.; Brewer R.; Morris D.; Cleveland J.M.; Setnik B.

Source: EMBASE

161. Dynamic stability training improves standing balance control in neuropathic patients with type 2 diabetes

Citation: Journal of Rehabilitation Research and Development, 2011, vol./is. 48/7(775-786), 0748-7711;1938-1352 (2011)

Author(s): Salsabili H.; Bahrpeyma F.; Forogh B.; Rajabali S.

Source: EMBASE

Full Text: Available from *EBSCOhost* in *Journal of Rehabilitation Research & Development*

Available from *EBSCOhost* in *Journal of Rehabilitation Research & Development*

Available from *ProQuest* in *Journal of Rehabilitation Research and Development*

162. Lower limb electromygraphy and kinematics of neuropathic diabetic patients during real-life activities: Stair

negotiation

Citation: Muscle and Nerve, August 2011, vol./is. 44/2(269-277), 0148-639X;1097-4598 (August 2011)

Author(s): Onodera A.N.; Gomes A.A.; Pripas D.; Mezzarane R.A.; Sacco I.C.N.

Source: EMBASE

Full Text: Available from *Wiley* in *Muscle and Nerve*

163. Electromyography and kinematic changes of gait cycle at different cadences in diabetic neuropathic individuals

Citation: Muscle and Nerve, August 2011, vol./is. 44/2(258-268), 0148-639X;1097-4598 (August 2011)

Author(s): Gomes A.A.; Onodera A.N.; Otuzi M.E.I.; Pripas D.; Mezzarane R.A.; Sacco I.C.N.

Source: EMBASE

Full Text: Available from *Wiley* in *Muscle and Nerve*

164. Post herpetic neuralgia

Citation: Journal of Palliative Medicine, June 2011, vol./is. 14/6(765-773), 1096-6218;1557-7740 (01 Jun 2011)

Author(s): Philip A.; Thakur R.

Source: EMBASE

Full Text: Available from *EBSCOhost* in *Journal of Palliative Medicine*

Available from *EBSCOhost* in *Journal of Palliative Medicine*

165. Impact of pregabalin treatment on pain, pain-related sleep interference and general well-being in patients with

neuropathic pain: A non-interventional, multicentre, post-marketing study

Citation: Clinical Drug Investigation, 2011, vol./is. 31/6(417-426), 1173-2563;1179-1918 (2011)

Author(s): Anastassiou E.; Iatrou C.A.; Vlaikidis N.; Vafiadou M.; Stamatiou G.; Plesia E.; Lyras L.; Vadalouca A.

Source: EMBASE

Full Text: Available from *ProQuest* in *Clinical Drug Investigation*

166. Changes in the thickness and stiffness of plantar soft tissues in people with diabetic peripheral neuropathy

Citation: Archives of Physical Medicine and Rehabilitation, September 2011, vol./is. 92/9(1484-1489), 0003-9993;1532-821X (September 2011)

Author(s): Sun J.-H.; Cheng B.K.; Zheng Y.-P.; Huang Y.-P.; Leung J.Y.; Cheing G.L.

Source: EMBASE

Full Text: Available from *Elsevier* in *Archives of Physical Medicine and Rehabilitation*

167. Twelve steps per foot are recommended for valid and reliable in-shoe plantar pressure data in neuropathic

diabetic patients wearing custom made footwear

Citation: Clinical Biomechanics, October 2011, vol./is. 26/8(880-884), 0268-0033;1879-1271 (October 2011)

Author(s): Arts M.L.J.; Bus S.A.

Source: EMBASE

Full Text: Available from *Elsevier* in *Clinical Biomechanics*

168. Epidermal Thickness and Biomechanical Properties of Plantar Tissues in Diabetic Foot

Citation: Ultrasound in Medicine and Biology, July 2011, vol./is. 37/7(1029-1038), 0301-5629;1879-291X (July 2011)

Author(s): Chao C.Y.L.; Zheng Y.-P.; Cheing G.L.Y.

Source: EMBASE

Full Text: Available from *Elsevier* in *Ultrasound in Medicine and Biology*

169. Auxiliary sensory cues improve automatic postural responses in individuals with diabetic neuropathy

Citation: Neurorehabilitation and Neural Repair, February 2011, vol./is. 25/2(110-117), 1545-9683;1552-6844 (February 2011)

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Author(s): Rao N.; Aruin A.S.

Source: EMBASE

Full Text: Available from *Highwire Press* in *Neurorehabilitation and Neural Repair: An International Journal of Translational Science for Researchers and Clinicians*

170. Early-onset copper deficiency following Roux-en-Y gastric bypass

Citation: Nutrition in Clinical Practice, February 2011, vol./is. 26/1(66-69), 0884-5336 (February 2011)

Author(s): O'Donnell K.B.; Simmons M.

Source: EMBASE

Full Text: Available from *Highwire Press* in *Nutrition in Clinical Practice*

171. Degree of control and delayed intensification of antihyperglycaemic treatment in type 2 diabetes mellitus patients

in primary care in Spain

Citation: Diabetes Research and Clinical Practice, January 2011, vol./is. 91/1(108-114), 0168-8227 (January 2011)

Author(s): Conthe P.; Mata M.; Orozco D.; Pajuelo F.; Barreto C.S.; Anaya S.F.; Gomis R.

Source: EMBASE

Full Text: Available from *Elsevier* in *Diabetes Research and Clinical Practice*

172. Calculation of pressure time integral, a different approach

Citation: Clinical Biomechanics, July 2011, vol./is. 26/6(677), 0268-0033 (July 2011)

Author(s): Melai T.; Jzerman H.I.; De Lange T.L.H.; Willems P.B.; Meijer K.; Schaper N.C.; Savelberg H.H.C.M.

Source: EMBASE

Full Text: Available from *Elsevier* in *Clinical Biomechanics*

173. Relationship between foot range of movement and plantar pressure distribution in diabetic neuropathic patients

Citation: Clinical Biomechanics, July 2011, vol./is. 26/6(674), 0268-0033 (July 2011)

Author(s): Sartor C.D.; Picon A.P.; Roveri M.I.; Dinato R.C.; Sacco I.C.N.

Source: EMBASE

Full Text: Available from *Elsevier* in *Clinical Biomechanics*

174. Treatment considerations for elderly and frail patients with neuropathic pain

Citation: Mayo Clinic Proceedings, March 2010, vol./is. 85/3 SUPPL.(S26-S32), 0025-6196 (March 2010)

Author(s): Schmader K.E.; Baron R.; Haanpaa M.L.; Mayer J.; O'Connor A.B.; Rice A.S.C.; Stacey B.

Source: EMBASE

Full Text: Available from *Elsevier* in *Mayo Clinic Proceedings*

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175. Duloxetine versus placebo in the treatment of patients with diabetic neuropathic pain in China

Citation: Chinese Medical Journal, November 2010, vol./is. 123/22(3184-3192), 0366-6999 (November 20, 2010)

Author(s): Gao Y.; Ning G.; Jia W.-P.; Zhou Z.-G.; Xu Z.-R.; Liu Z.-M.; Liu C.; Ma J.-H.; Li Q.; Cheng L.-L.; Wen C.-Y.; Zhang S.-Y.; Zhang Q.; Desaiah D.; Skljarevski S.

Source: EMBASE

176. Characteristics of Older Adults Receiving Opioids in Primary Care: Treatment Duration and Outcomes

Citation: Pain Medicine, July 2010, vol./is. 11/7(1063-1071), 1526-2375;1526-4637 (July 2010)

Author(s): Reid M.C.; Henderson Jr C.R.; Papaleontiou M.; Amanfo L.; Olkhovskaya Y.; Moore A.A.; Parikh S.S.; Turner B.J.

Source: EMBASE

Full Text: Available from *EBSCOhost* in *Pain Medicine*

Available from *Wiley* in *Pain Medicine*

177. Approach to the patient with type 2 diabetes and progressive kidney disease

Citation: Journal of Clinical Endocrinology and Metabolism, July 2010, vol./is. 95/7(3103-3110), 0021-972X;0021-972X (July 2010)

Author(s): Seaquist E.R.; Ibrahim H.N.

Source: EMBASE

Full Text: Available from *JOURNAL OF CLINICAL ENDOCRINOLOGY AND METABOLISM* in

178. Management of paclitaxel-induced neurotoxicity

Citation: Oncology Reviews, June 2010, vol./is. 4/2(107-115), 1970-5557;1970-5565 (June 2010)

Author(s): Bhutani M.; Colucci P.M.; Laird-Fick H.; Conley B.A.

Source: EMBASE

179. Efficacy of weight reduction program on obese patients with diabetic peripheral neuropathy

Citation: Egyptian Journal of Neurology, Psychiatry and Neurosurgery, October 2010, vol./is. 47/4(673-679), 1110-1083;1687-8329 (October 2010)

Author(s): Ahmed G.M.; Mostafa M.; Farouk M.; El-Gohary A.

Source: EMBASE

180. Identification, treatment, and clinical outcomes of neuropathic pain for the primary care physician

Citation: Journal of Clinical Outcomes Management, August 2010, vol./is. 17/8(37-54), 1079-6533 (August 2010)

Author(s): Berry J.D.; Cochrane T.I.

Source: EMBASE

181. Realignment and extended fusion with use of a medial column screw for midfoot deformities secondary to

diabetic neuropathy: Surgical technique

Citation: Journal of Bone and Joint Surgery - Series A, March 2010, vol./is. 92/SUPPL. 1 PART 1(20-31), 0021-9355;1535-1386 (01 Mar 2010)

Author(s): Assal M.; Ray A.; Stern R.

Source: EMBASE

Full Text: Available from *Elsevier* in *Journal of Bone and Joint Surgery*

Available from *Ovid* in *Journal of Bone and Joint Surgery - American Volume*

Available from *EBSCOhost* in *Journal of Bone & Joint Surgery, American Volume*

182. Lower-limb risk factors for falls in people with diabetes mellitus

Page 40

Citation: Diabetic Medicine, February 2010, vol./is. 27/2(162-168), 0742-3071;1464-5491 (February 2010)

Author(s): MacGilchrist C.; Paul L.; Ellis B.M.; Howe T.E.; Kennon B.; Godwin J.

Source: EMBASE

Full Text: Available from *EBSCOhost* in *Diabetic Medicine*

Available from *EBSCOhost* in *Diabetic Medicine*

Available from *Wiley* in *Diabetic Medicine*

183. A pain in the bone

Citation: Journal of Hospital Medicine, February 2010, vol./is. 5/2(107-112),

1553-5592;1553-5606 (February 2010)

Author(s): Srour J.F.; Braza J.; Smetana G.W.

Source: EMBASE

184. Hypothermia-induced acute kidney injury in a diabetic patient with nephropathy and neuropathy

Citation: Internal Medicine, 2010, vol./is. 49/2(171-174), 0918-2918;1349-7235 (2010)

Author(s): Yamada S.; Shimomura Y.; Ohsaki M.; Fujisaki A.; Tsuruya K.; Iida M.

Source: EMBASE

185. Prolonged activity of knee extensors and dorsal flexors is associated with adaptations in gait in diabetes and

diabetic polyneuropathy

Citation: Clinical Biomechanics, June 2010, vol./is. 25/5(468-475), 0268-0033 (June 2010)

Author(s): Savelberg H.H.C.M.; Ilgin D.; Angin S.; Willems P.J.B.; Schaper N.C.; Meijer K.

Source: EMBASE

Full Text: Available from *Elsevier* in *Clinical Biomechanics*

186. Relationships between segmental foot mobility and plantar loading in individuals with and without diabetes and

neuropathy

Citation: Gait and Posture, February 2010, vol./is. 31/2(251-255), 0966-6362 (February 2010)

Author(s): Rao S.; Saltzman C.L.; Yack H.J.

Source: EMBASE

Full Text: Available from *Elsevier* in *Gait and Posture*

187. Opioids for the treatment of chronic neuropathic pain: The evidence

Citation: European Journal of Pain Supplements, April 2010, vol./is. 4/1(34), 1754-3207 (April 2010)

Author(s): Raja S.

Source: EMBASE

Full Text: Available from *Elsevier* in *European Journal of Pain Supplements*

188. Quantitative sensory test: Normal range in Korean adults and application to diabetic polyneuropathy

Citation: Clinical Neurophysiology, October 2010, vol./is. 121/(S110), 1388-2457 (October 2010)

Author(s): Kim S.H.; Kim J.E.; Ahn S.W.; Kim S.M.; Hong Y.-H.; Sung J.J.; Park K.S.; Lee K.W.

Source: EMBASE

Full Text: Available from *Elsevier* in *Clinical Neurophysiology*

Appendix ROM and Variability

```
Stair Ascent

Parameter
"Table Analyzed" "Ankle frontal"

"One-way analysis of variance"
"  P value" 0.0830
"  P value summary"     ns
"  Are means signif. different? (P < 0.05)"   No
"  Number of groups"   3
"  F" 2.572
"  R square"      0.06261

"Bartlett's test for equal variances"
"  Bartlett's statistic (corrected)"    2.675
"  P value" 0.2625
"  P value summary"    ns
"  Do the variances differ signif. (P < 0.05)"     No

"ANOVA Table"    SS    df    MS
"  Treatment (between columns)"   17.18 2    8.589
"  Residual (within columns)"     257.2 77   3.340
"  Total"   274.4 79

"Newman-Keuls Multiple Comparison Test" "Mean Diff."    q
     "Significant? P < 0.05?"      Summary
"  Ctrl vs DPN"  -1.160      3.110 No    ns
"  Ctrl vs DM"   -0.2654     ---   No    ns
"  DM vs DPN"    -0.8949     ---   No    ns

Table Analyzed"  "Ankle sagittal"

"One-way analysis of variance"
"  P value" 0.0060
"  P value summary"    **
"  Are means signif. different? (P < 0.05)"   Yes
"  Number of groups"   3
"  F" 5.472
"  R square"      0.1244

"Bartlett's test for equal variances"
"  Bartlett's statistic (corrected)"    2.233
"  P value" 0.3274
"  P value summary"    ns
"  Do the variances differ signif. (P < 0.05)"     No

"ANOVA Table"    SS    df    MS
"  Treatment (between columns)"   318.8 2    159.4
"  Residual (within columns)"     2243  77   29.13
```

```
"  Total"   2562  79

"Newman-Keuls Multiple Comparison Test" "Mean Diff."      q
      "Significant? P < 0.05?"     Summary
"  DPN vs DM"    -4.574      4.241 Yes   *
"  DPN vs Ctrl"  -4.495      4.080 Yes   **
"  Ctrl vs DM"   -0.07960    0.07999    No    ns




Parameter
"Table Analyzed" "Ankle trans"

"One-way analysis of variance"
"  P value" 0.7374
"  P value summary"     ns
"  Are means signif. different? (P < 0.05)"   No
"  Number of groups"   3
"  F" 0.3058
"  R square"      0.007880

"Bartlett's test for equal variances"
"  Bartlett's statistic (corrected)"    1.378
"  P value" 0.5022
"  P value summary"     ns
"  Do the variances differ signif. (P < 0.05)"     No

"ANOVA Table"     SS     df     MS
"  Treatment (between columns)"   2.551 2     1.276
"  Residual (within columns)"     321.2 77    4.171
"  Total"   323.7 79

"Newman-Keuls Multiple Comparison Test" "Mean Diff."      q
      "Significant? P < 0.05?"     Summary
"  DM vs Ctrl"   -0.4101    1.089 No    ns
"  DM vs DPN"    -0.1242    ---   No    ns
"  DPN vs Ctrl"  -0.2859    ---   No    ns

Table Analyzed"  "Ankle sagittal"

"One-way analysis of variance"
"  P value" 0.0001
"  P value summary"    ***
"  Are means signif. different? (P < 0.05)"   Yes
"  Number of groups"   3
"  F" 10.39
"  R square"      0.2216

"Bartlett's test for equal variances"
"  Bartlett's statistic (corrected)"    0.7815
"  P value" 0.6765
"  P value summary"     ns
```

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```
"  Do the variances differ signif. (P < 0.05)"        No

"ANOVA Table"     SS      df      MS
"  Treatment (between columns)"     767.9 2      384.0
"  Residual (within columns)"       2698  73     36.96
"  Total"   3466  75

"Newman-Keuls Multiple Comparison Test" "Mean Diff."      q
      "Significant? P < 0.05?"       Summary
"  DPN vs Ctrl"   -7.921       6.099 Yes    ***
"  DPN vs DM"     -6.927       5.405 Yes    ***
"  DM vs Ctrl"    -0.9934      0.8794      No     ns



Parameter
"Table Analyzed" "Ankle transverse"

"One-way analysis of variance"
"  P value" 0.4950
"  P value summary"     ns
"  Are means signif. different? (P < 0.05)"   No
"  Number of groups"   3
"  F" 0.7100
"  R square"       0.01908

"Bartlett's test for equal variances"
"  Bartlett's statistic (corrected)"    0.2477
"  P value" 0.8835
"  P value summary"     ns
"  Do the variances differ signif. (P < 0.05)"        No

"ANOVA Table"     SS      df      MS
"  Treatment (between columns)"     6.755 2      3.377
"  Residual (within columns)"       347.2 73     4.757
"  Total"   354.0 75

"Newman-Keuls Multiple Comparison Test" "Mean Diff."      q
      "Significant? P < 0.05?"       Summary
"  Ctrl vs DPN"   -0.7841      1.683 No     ns
"  Ctrl vs DM"    -0.3389      ---   No     ns
"  DM vs DPN"     -0.4452      ---   No     ns
ROM ANKLE STAIR ASCENT

Parameter
"Table Analyzed" "Ankle sagittal"

"One-way analysis of variance"
"  P value" 0.0060
"  P value summary"    **
"  Are means signif. different? (P < 0.05)"   Yes
"  Number of groups"   3
```

```
"  F"  5.472
"  R square"        0.1244

"Bartlett's test for equal variances"
"  Bartlett's statistic (corrected)"    2.233
"  P value" 0.3274
"  P value summary"     ns
"  Do the variances differ signif. (P < 0.05)"     No

"ANOVA Table"      SS     df     MS
"  Treatment (between columns)"    318.8 2      159.4
"  Residual (within columns)"      2243  77    29.13
"  Total"   2562  79

"Newman-Keuls Multiple Comparison Test" "Mean Diff."      q
      "Significant? P < 0.05?"      Summary
"  DPN vs DM"      -4.574      4.241 Yes     *
"  DPN vs Ctrl"  -4.495      4.080 Yes     **
"  Ctrl vs DM"   -0.07960    0.07999     No     ns



Parameter
"Table Analyzed" "Ankle trans"

"One-way analysis of variance"
"  P value" 0.7374
"  P value summary"     ns
"  Are means signif. different? (P < 0.05)"   No
"  Number of groups"   3
"  F" 0.3058
"  R square"        0.007880

"Bartlett's test for equal variances"
"  Bartlett's statistic (corrected)"    1.378
"  P value" 0.5022
"  P value summary"     ns
"  Do the variances differ signif. (P < 0.05)"     No

"ANOVA Table"      SS     df     MS
"  Treatment (between columns)"    2.551 2      1.276
"  Residual (within columns)"      321.2 77    4.171
"  Total"   323.7 79

"Newman-Keuls Multiple Comparison Test" "Mean Diff."      q
      "Significant? P < 0.05?"      Summary
"  DM vs Ctrl"   -0.4101      1.089 No     ns
"  DM vs DPN"    -0.1242      ---   No     ns
"  DPN vs Ctrl"  -0.2859      ---   No     ns

Parameter
"Table Analyzed" "Hip frontal"
```

```
"One-way analysis of variance"
"  P value" 0.4311
"  P value summary"     ns
"  Are means signif. different? (P < 0.05)"   No
"  Number of groups"   3
"  F" 0.8508
"  R square"        0.02162

"Bartlett's test for equal variances"
"  Bartlett's statistic (corrected)"    3.075
"  P value" 0.2149
"  P value summary"     ns
"  Do the variances differ signif. (P < 0.05)"      No

"ANOVA Table"     SS    df    MS
"  Treatment (between columns)"   15.43 2     7.713
"  Residual (within columns)"      698.0 77   9.065
"  Total"   713.5 79

"Newman-Keuls Multiple Comparison Test" "Mean Diff."      q
      "Significant? P < 0.05?"     Summary
"  Ctrl vs DPN"   -1.131      1.841 No    ns
"  Ctrl vs DM"    -0.4266      ---    No    ns
"  DM vs DPN"     -0.7048      ---    No    ns




Parameter
"Table Analyzed" "Hip Sagittal"

"One-way analysis of variance"
"  P value" 0.0054
"  P value summary"     **
"  Are means signif. different? (P < 0.05)"   Yes
"  Number of groups"   3
"  F" 5.593
"  R square"        0.1268

"Bartlett's test for equal variances"
"  Bartlett's statistic (corrected)"    1.146
"  P value" 0.5637
"  P value summary"     ns
"  Do the variances differ signif. (P < 0.05)"      No

"ANOVA Table"     SS    df    MS
"  Treatment (between columns)"   228.9 2     114.5
"  Residual (within columns)"      1576  77   20.46
```

```
"  Total"   1805  79

"Newman-Keuls Multiple Comparison Test" "Mean Diff."        q
      "Significant? P < 0.05?"      Summary
"  Ctrl vs DM"    -3.821      4.582 Yes    **
"  Ctrl vs DPN"   -2.962      3.208 Yes    *
"  DPN vs DM"     -0.8586     0.9497    No     ns

Parameter
"Table Analyzed"  "Hip trans"

"One-way analysis of variance"
"   P value" 0.0520
"   P value summary"     ns
"   Are means signif. different? (P < 0.05)"    No
"   Number of groups"    3
"   F" 3.073
"   R square"      0.07391

"Bartlett's test for equal variances"
"   Bartlett's statistic (corrected)"    1.941
"   P value" 0.3790
"   P value summary"     ns
"   Do the variances differ signif. (P < 0.05)"       No

"ANOVA Table"     SS     df     MS
"   Treatment (between columns)"    88.43 2     44.22
"   Residual (within columns)"      1108   77     14.39
"   Total"   1197  79

"Newman-Keuls Multiple Comparison Test" "Mean Diff."        q
      "Significant? P < 0.05?"      Summary
"  Ctrl vs DPN"   -2.712      3.503 Yes    *
"  Ctrl vs DM"    -1.072      1.532 No     ns
"  DM vs DPN"     -1.641      2.164 No     ns

Parameter
"Table Analyzed"  "Knee frontal"

"One-way analysis of variance"
"   P value" 0.0005
"   P value summary"     ***
"   Are means signif. different? (P < 0.05)"    Yes
"   Number of groups"    3
"   F" 8.482
"   R square"      0.1805

"Bartlett's test for equal variances"
"   Bartlett's statistic (corrected)"    1.424
```

```
"  P value" 0.4906
"  P value summary"    ns
"  Do the variances differ signif. (P < 0.05)"        No


"ANOVA Table"    SS    df    MS
"  Treatment (between columns)"    357.0 2    178.5
"  Residual (within columns)"    1621  77    21.05
"  Total"  1978  79

"Newman-Keuls Multiple Comparison Test" "Mean Diff."    q
      "Significant? P < 0.05?"    Summary
"  Ctrl vs DPN"    -5.354    5.717 Yes    ***
"  Ctrl vs DM"    -3.123    3.693 Yes    *
"  DM vs DPN"    -2.231    2.433 No    ns

Parameter
"Table Analyzed" "Knee sagittal"

"One-way analysis of variance"
"  P value" 0.0241
"  P value summary"    *
"  Are means signif. different? (P < 0.05)"   Yes
"  Number of groups"    3
"  F" 3.912
"  R square"    0.09223

"Bartlett's test for equal variances"
"  Bartlett's statistic (corrected)"    3.195
"  P value" 0.2024
"  P value summary"    ns
"  Do the variances differ signif. (P < 0.05)"       No

"ANOVA Table"    SS    df    MS
"  Treatment (between columns)"    400.2 2    200.1
"  Residual (within columns)"    3939  77    51.15
"  Total"  4339  79

"Newman-Keuls Multiple Comparison Test" "Mean Diff."    q
      "Significant? P < 0.05?"    Summary
"  Ctrl vs DM"    -5.212    3.953 Yes    *
"  Ctrl vs DPN"    -2.546    1.744 No    ns
"  DPN vs DM"    -2.666    1.865 No    ns




Parameter
"Table Analyzed" "Knee trans"

"One-way analysis of variance"
"  P value" 0.4929
"  P value summary"    ns
```

```
"  Are means signif. different? (P < 0.05)"   No
"  Number of groups"   3
"  F" 0.7141
"  R square"       0.01821

"Bartlett's test for equal variances"
"  Bartlett's statistic (corrected)"    1.192
"  P value" 0.5510
"  P value summary"    ns
"  Do the variances differ signif. (P < 0.05)"      No

"ANOVA Table"    SS    df    MS
"  Treatment (between columns)"    11.78 2    5.889
"  Residual (within columns)"      635.0 77   8.247
"  Total"   646.8 79

"Newman-Keuls Multiple Comparison Test" "Mean Diff."      q
      "Significant? P < 0.05?"      Summary
"  DM vs DPN"    -0.9146    1.594 No    ns
"  DM vs Ctrl"   -0.6372    ---   No    ns
"  Ctrl vs DPN"  -0.2774    ---   No    ns
```

Stair Descent

```
Parameter
"Table Analyzed" "Ankle frontal"

"One-way analysis of variance"
"  P value" 0.0067
"  P value summary"    **
"  Are means signif. different? (P < 0.05)"   Yes
"  Number of groups"   3
"  F" 5.363
"  R square"       0.1281

"Bartlett's test for equal variances"
"  Bartlett's statistic (corrected)"    0.6495
"  P value" 0.7227
"  P value summary"    ns
"  Do the variances differ signif. (P < 0.05)"      No

"ANOVA Table"    SS    df    MS
"  Treatment (between columns)"    42.35 2    21.18
"  Residual (within columns)"      288.3 73   3.949
"  Total"   330.6 75

"Newman-Keuls Multiple Comparison Test" "Mean Diff."      q
      "Significant? P < 0.05?"      Summary
```

```
"  Ctrl vs DPN"  -1.676      3.949 Yes    *
"  Ctrl vs DM"   -1.454      3.938 Yes    **
"  DM vs DPN"    -0.2222     0.5304      No    ns
Parameter
"Table Analyzed" "Ankle sagittal"

"One-way analysis of variance"
"  P value" 0.0001
"  P value summary"     ***
"  Are means signif. different? (P < 0.05)"   Yes
"  Number of groups"   3
"  F" 10.39
"  R square"      0.2216

"Bartlett's test for equal variances"
"  Bartlett's statistic (corrected)"    0.7815
"  P value" 0.6765
"  P value summary"    ns
"  Do the variances differ signif. (P < 0.05)"      No

"ANOVA Table"    SS    df    MS
"  Treatment (between columns)"   767.9 2    384.0
"  Residual (within columns)"     2698  73   36.96
"  Total"   3466  75

"Newman-Keuls Multiple Comparison Test" "Mean Diff."     q
     "Significant? P < 0.05?"     Summary
"  DPN vs Ctrl"  -7.921      6.099 Yes    ***
"  DPN vs DM"    -6.927      5.405 Yes    ***
"  DM vs Ctrl"   -0.9934     0.8794      No    ns

Parameter
"Table Analyzed" "Ankle transverse"

"One-way analysis of variance"
"  P value" 0.4950
"  P value summary"    ns
"  Are means signif. different? (P < 0.05)"   No
"  Number of groups"   3
"  F" 0.7100
"  R square"      0.01908

"Bartlett's test for equal variances"
"  Bartlett's statistic (corrected)"    0.2477
"  P value" 0.8835
"  P value summary"    ns
"  Do the variances differ signif. (P < 0.05)"      No

"ANOVA Table"    SS    df    MS
"  Treatment (between columns)"   6.755 2    3.377
"  Residual (within columns)"     347.2 73   4.757
"  Total"   354.0 75
```

```
"Newman-Keuls Multiple Comparison Test" "Mean Diff."      q
      "Significant? P < 0.05?"      Summary
"  Ctrl vs DPN"  -0.7841      1.683 No    ns
"  Ctrl vs DM"   -0.3389      ---   No    ns
"  DM vs DPN"    -0.4452      ---   No    ns
Parameter
"Table Analyzed" "Hip frontal"

"One-way analysis of variance"
"  P value" 0.0003
"  P value summary"     ***
"  Are means signif. different? (P < 0.05)"   Yes
"  Number of groups"   3
"  F" 9.215
"  R square"       0.2016

"Bartlett's test for equal variances"
"  Bartlett's statistic (corrected)"    2.579
"  P value" 0.2755
"  P value summary"     ns
"  Do the variances differ signif. (P < 0.05)"      No

"ANOVA Table"     SS    df    MS
"  Treatment (between columns)"    183.7 2     91.83
"  Residual (within columns)"      727.4 73    9.965
"  Total"    911.1 75

"Newman-Keuls Multiple Comparison Test" "Mean Diff."      q
      "Significant? P < 0.05?"      Summary
"  Ctrl vs DPN"  -4.032      5.979 Yes   ***
"  Ctrl vs DM"   -2.131      3.633 Yes   *
"  DM vs DPN"    -1.901      2.857 Yes   *


Parameter
"Table Analyzed" "Hip frontal"

"One-way analysis of variance"
"  P value" 0.0003
"  P value summary"     ***
"  Are means signif. different? (P < 0.05)"   Yes
"  Number of groups"   3
"  F" 9.215
"  R square"       0.2016

"Bartlett's test for equal variances"
"  Bartlett's statistic (corrected)"    2.579
"  P value" 0.2755
"  P value summary"     ns
"  Do the variances differ signif. (P < 0.05)"      No

"ANOVA Table"     SS    df    MS
```

```
"  Treatment (between columns)"   183.7 2    91.83
"  Residual (within columns)"     727.4 73   9.965
"  Total"  911.1 75


"Newman-Keuls Multiple Comparison Test" "Mean Diff."      q
     "Significant? P < 0.05?"      Summary
"  Ctrl vs DPN"  -4.032      5.979 Yes    ***
"  Ctrl vs DM"   -2.131      3.633 Yes    *
"  DM vs DPN"    -1.901      2.857 Yes    *
Parameter
"Table Analyzed" "Hip Sagittal"

"One-way analysis of variance"
"  P value" 0.0873
"  P value summary"    ns
"  Are means signif. different? (P < 0.05)"   No
"  Number of groups"   3
"  F" 2.522
"  R square"       0.06463


"Bartlett's test for equal variances"
"  Bartlett's statistic (corrected)"    3.957
"  P value" 0.1383
"  P value summary"    ns
"  Do the variances differ signif. (P < 0.05)"      No


"ANOVA Table"     SS    df    MS
"  Treatment (between columns)"   58.14 2    29.07
"  Residual (within columns)"     841.3 73   11.53
"  Total"  899.5 75

"Newman-Keuls Multiple Comparison Test" "Mean Diff."      q
     "Significant? P < 0.05?"      Summary
"  Ctrl vs DM"   -1.973      3.128 No    ns
"  Ctrl vs DPN"  -1.378      --- No    ns
"  DPN vs DM"    -0.5949     --- No    ns

Parameter
"Table Analyzed" "Hip transverse"

"One-way analysis of variance"
"  P value" "< 0.0001"
"  P value summary"    ****
"  Are means signif. different? (P < 0.05)"   Yes
"  Number of groups"   3
"  F" 11.57
"  R square"       0.2406


"Bartlett's test for equal variances"
"  Bartlett's statistic (corrected)"    1.936
"  P value" 0.3798
"  P value summary"    ns
```

```
"  Do the variances differ signif. (P < 0.05)"      No


"ANOVA Table"     SS     df     MS
"  Treatment (between columns)"    378.2 2     189.1
"  Residual (within columns)"      1193  73    16.35
"  Total"   1572  75

"Bonferroni's Multiple Comparison Test" "Mean Diff."      t
     "Significant? P < 0.05?"     Summary     "95% CI of diff"
"  Ctrl vs DM"    -1.668     1.570 No    ns     "-4.271 to 0.9356"
"  Ctrl vs DPN"   -5.822     4.767 Yes   ****   "-8.815 to -2.829"
"  DM vs DPN"     -4.154     3.446 Yes   **     "-7.108 to -1.201"

Parameter
"Table Analyzed" "Knee frontal"

"One-way analysis of variance"
"  P value" 0.0007
"  P value summary"    ***
"  Are means signif. different? (P < 0.05)"   Yes
"  Number of groups"   3
"  F" 8.119
"  R square"      0.1820

"Bartlett's test for equal variances"
"  Bartlett's statistic (corrected)"    0.09664
"  P value" 0.9528
"  P value summary"    ns
"  Do the variances differ signif. (P < 0.05)"      No

"ANOVA Table"     SS     df     MS
"  Treatment (between columns)"    184.6 2     92.29
"  Residual (within columns)"      829.8 73    11.37
"  Total"   1014  75

"Newman-Keuls Multiple Comparison Test" "Mean Diff."     q
     "Significant? P < 0.05?"     Summary
"  Ctrl vs DPN"   -3.435     4.769 Yes   **
"  Ctrl vs DM"    -3.089     4.932 Yes   ***
"  DM vs DPN"     -0.3454    0.4860    No    ns

Parameter
"Table Analyzed" "Knee sagittal"

"One-way analysis of variance"
"  P value" 0.0539
"  P value summary"    ns
"  Are means signif. different? (P < 0.05)"   No
"  Number of groups"   3
"  F" 3.041
"  R square"      0.07691
```

```
"Bartlett's test for equal variances"
"  Bartlett's statistic (corrected)"    0.5000
"  P value" 0.7788
"  P value summary"    ns
"  Do the variances differ signif. (P < 0.05)"      No

"ANOVA Table"    SS    df    MS
"  Treatment (between columns)"   164.8 2    82.41
"  Residual (within columns)"     1978  73   27.10
"  Total"   2143  75

"Newman-Keuls Multiple Comparison Test" "Mean Diff."      q
      "Significant? P < 0.05?"      Summary
"  Ctrl vs DM"   -3.308      3.420 Yes    *
"  Ctrl vs DPN"  -1.034      0.9296     No    ns
"  DPN vs DM"    -2.275      2.073 No    ns

Parameter
"Table Analyzed" "Knee transverse"

"One-way analysis of variance"
"  P value" 0.0546
"  P value summary"    ns
"  Are means signif. different? (P < 0.05)"   No
"  Number of groups"    3
"  F" 3.026
"  R square"      0.07656

"Bartlett's test for equal variances"
"  Bartlett's statistic (corrected)"    2.949
"  P value" 0.2289
"  P value summary"    ns
"  Do the variances differ signif. (P < 0.05)"      No

"ANOVA Table"    SS    df    MS
"  Treatment (between columns)"   45.22 2    22.61
"  Residual (within columns)"     545.4 73   7.471
"  Total"   590.6 75

"Newman-Keuls Multiple Comparison Test" "Mean Diff."      q
      "Significant? P < 0.05?"      Summary
"  Ctrl vs DPN"  -2.031      3.478 Yes    *
"  Ctrl vs DM"   -0.7471     1.471 No    ns
"  DM vs DPN"    -1.283      2.227 No    ns




Ascent Variability

Parameter
"Table Analyzed" "Ankle frontal"
```

"One-way analysis of variance"
"   P value" 0.0965
"   P value summary"   ns
"   Are means signif. different? (P < 0.05)"   No
"   Number of groups"   3
"   F" 2.411
"   R square"   0.05893

"Bartlett's test for equal variances"
"   Bartlett's statistic (corrected)"   17.39
"   P value" 0.0002
"   P value summary"   ***
"   Do the variances differ signif. (P < 0.05)"   Yes

"ANOVA Table"   SS   df   MS
"   Treatment (between columns)"   6.693 2   3.346
"   Residual (within columns)"   106.9 77   1.388
"   Total"   113.6 79

"Newman-Keuls Multiple Comparison Test" "Mean Diff."   q
       "Significant? P < 0.05?"   Summary
"   DM vs DPN"   -0.6971   2.961 No   ns
"   DM vs Ctrl"   -0.09858   ---   No   ns
"   Ctrl vs DPN"   -0.5985   ---   No   ns

Parameter
"Table Analyzed" "Ankle sagittal"

"One-way analysis of variance"
"   P value" 0.0764
"   P value summary"   ns
"   Are means signif. different? (P < 0.05)"   No
"   Number of groups"   3
"   F" 2.659
"   R square"   0.06461

"Bartlett's test for equal variances"
"   Bartlett's statistic (corrected)"   46.88
"   P value" "< 0.0001"
"   P value summary"   ****
"   Do the variances differ signif. (P < 0.05)"   Yes

"ANOVA Table"   SS   df   MS
"   Treatment (between columns)"   26.18 2   13.09
"   Residual (within columns)"   379.0 77   4.922
"   Total"   405.2 79

"Newman-Keuls Multiple Comparison Test" "Mean Diff."   q
       "Significant? P < 0.05?"   Summary

```
"  Ctrl vs DPN"  -1.421       3.138 No    ns
"  Ctrl vs DM"   -0.2893      ---   No    ns
"  DM vs DPN"    -1.132       ---   No    ns




Parameter
"Table Analyzed" "Ankle trans"

"One-way analysis of variance"
"  P value" 0.5680
"  P value summary"    ns
"  Are means signif. different? (P < 0.05)"   No
"  Number of groups"   3
"  F" 0.5699
"  R square"      0.01459

"Bartlett's test for equal variances"
"  Bartlett's statistic (corrected)"    10.90
"  P value" 0.0043
"  P value summary"    **
"  Do the variances differ signif. (P < 0.05)"      Yes

"ANOVA Table"     SS     df     MS
"  Treatment (between columns)"   1.718 2      0.8591
"  Residual (within columns)"      116.1 77    1.508
"  Total"   117.8 79

"Newman-Keuls Multiple Comparison Test" "Mean Diff."      q
      "Significant? P < 0.05?"      Summary
"  DM vs Ctrl"   -0.3301      1.458 No    ns
"  DM vs DPN"    -0.2429      ---   No    ns
"  DPN vs Ctrl" -0.08725      ---   No    ns




Parameter
"Table Analyzed" "Hip frontal"

"One-way analysis of variance"
"  P value" 0.1768
"  P value summary"    ns
"  Are means signif. different? (P < 0.05)"   No
"  Number of groups"   3
"  F" 1.772
"  R square"      0.04400


"Bartlett's test for equal variances"
"  Bartlett's statistic (corrected)"    0.1973
"  P value" 0.9061
"  P value summary"    ns
```

```
"  Do the variances differ signif. (P < 0.05)"       No

"ANOVA Table"      SS      df      MS
"  Treatment (between columns)"    3.011 2      1.506
"  Residual (within columns)"      65.42 77    0.8496
"  Total"   68.43 79

"Newman-Keuls Multiple Comparison Test" "Mean Diff."     q
     "Significant? P < 0.05?"      Summary
"  Ctrl vs DPN"   -0.4997    2.656 No    ns
"  Ctrl vs DM"    -0.1859      ---   No    ns
"  DM vs DPN"     -0.3138      ---   No    ns




Parameter
"Table Analyzed" "Hip Sagittal"

"One-way analysis of variance"
"  P value" 0.2775
"  P value summary"    ns
"  Are means signif. different? (P < 0.05)"   No
"  Number of groups"   3
"  F" 1.303
"  R square"       0.03275

"Bartlett's test for equal variances"
"  Bartlett's statistic (corrected)"    15.25
"  P value" 0.0005
"  P value summary"    ***
"  Do the variances differ signif. (P < 0.05)"       Yes

"ANOVA Table"      SS      df      MS
"  Treatment (between columns)"    23.81 2      11.90
"  Residual (within columns)"      703.2 77    9.132
"  Total"   727.0 79

"Newman-Keuls Multiple Comparison Test" "Mean Diff."     q
     "Significant? P < 0.05?"      Summary
"  Ctrl vs DPN"   -1.350     2.189 No    ns
"  Ctrl vs DM"    -0.2604      ---   No    ns
"  DM vs DPN"     -1.090       ---   No    ns




Parameter
"Table Analyzed" "Hip trans"

"One-way analysis of variance"
"  P value" 0.7841
"  P value summary"    ns
```

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```
"  Are means signif. different? (P < 0.05)"   No
"  Number of groups"   3
"  F" 0.2439
"  R square"        0.006296


"Bartlett's test for equal variances"
"  Bartlett's statistic (corrected)"    9.464
"  P value" 0.0088
"  P value summary"     **
"  Do the variances differ signif. (P < 0.05)"      Yes

"ANOVA Table"     SS     df     MS
"  Treatment (between columns)"    4.968 2     2.484
"  Residual (within columns)"      784.1 77    10.18
"  Total"   789.1 79

"Newman-Keuls Multiple Comparison Test" "Mean Diff."      q
      "Significant? P < 0.05?"      Summary
"  DM vs DPN"    -0.6008     0.9420      No    ns
"  DM vs Ctrl"   -0.3998     ---   No    ns
"  Ctrl vs DPN"  -0.2010     ---   No    ns


Parameter
"Table Analyzed" "Knee frontal"

"One-way analysis of variance"
"  P value" 0.9414
"  P value summary"    ns
"  Are means signif. different? (P < 0.05)"   No
"  Number of groups"   3
"  F" 0.06039
"  R square"      0.001566

"Bartlett's test for equal variances"
"  Bartlett's statistic (corrected)"    3.923
"  P value" 0.1407
"  P value summary"    ns
"  Do the variances differ signif. (P < 0.05)"      No

"ANOVA Table"     SS     df     MS
"  Treatment (between columns)"    1.265 2     0.6324
"  Residual (within columns)"      806.4 77    10.47
"  Total"   807.7 79

"Newman-Keuls Multiple Comparison Test" "Mean Diff."      q
      "Significant? P < 0.05?"      Summary
"  DM vs DPN"    -0.3152     0.4874      No    ns
"  DM vs Ctrl"   -0.1613     ---   No    ns
"  Ctrl vs DPN"  -0.1540     ---   No    ns
```

```
Parameter
"Table Analyzed" "Knee sagittal"

"One-way analysis of variance"
"  P value" 0.0732
"  P value summary"    ns
"  Are means signif. different? (P < 0.05)"   No
"  Number of groups"   3
"  F" 2.706
"  R square"        0.06566

"Bartlett's test for equal variances"
"  Bartlett's statistic (corrected)"    41.57
"  P value" "< 0.0001"
"  P value summary"    ****
"  Do the variances differ signif. (P < 0.05)"      Yes

"ANOVA Table"     SS    df    MS
"  Treatment (between columns)"    41.50 2      20.75
"  Residual (within columns)"      590.5 77    7.669
"  Total"   632.0 79

"Newman-Keuls Multiple Comparison Test" "Mean Diff."      q
     "Significant? P < 0.05?"       Summary
"  DM vs DPN"    -1.753      3.168 No    ns
"  DM vs Ctrl"  -0.3010      ---   No    ns
"  Ctrl vs DPN" -1.452       ---   No    ns




Parameter
"Table Analyzed" "Knee trans"

"One-way analysis of variance"
"  P value" 0.6992
"  P value summary"    ns
"  Are means signif. different? (P < 0.05)"   No
"  Number of groups"   3
"  F" 0.3595
"  R square"        0.009251

"Bartlett's test for equal variances"
"  Bartlett's statistic (corrected)"    0.1150
"  P value" 0.9441
"  P value summary"    ns
"  Do the variances differ signif. (P < 0.05)"      No

"ANOVA Table"     SS    df    MS
"  Treatment (between columns)"    4.257 2      2.129
"  Residual (within columns)"      455.9 77    5.921
"  Total"   460.2 79
```

```
"Newman-Keuls Multiple Comparison Test" "Mean Diff."     q
    "Significant? P < 0.05?"     Summary
"  DM vs Ctrl"   -0.5194     1.158 No    ns
"  DM vs DPN"    -0.1102     ---   No    ns
"  DPN vs Ctrl"  -0.4093     ---   No    ns




Descent Variability

Parameter
"Table Analyzed" "Ankle frontal"

"One-way analysis of variance"
"  P value" 0.1429
"  P value summary"     ns
"  Are means signif. different? (P < 0.05)"   No
"  Number of groups"   3
"  F" 1.998
"  R square"     0.05191

"Bartlett's test for equal variances"
"  Bartlett's statistic (corrected)"     8.330
"  P value" 0.0155
"  P value summary"     *
"  Do the variances differ signif. (P < 0.05)"     Yes

"ANOVA Table"     SS     df     MS
"  Treatment (between columns)"   2.477 2     1.238
"  Residual (within columns)"      45.24 73    0.6198
"  Total"   47.72 75

"Newman-Keuls Multiple Comparison Test" "Mean Diff."     q
    "Significant? P < 0.05?"     Summary
"  Ctrl vs DPN"  -0.4610     2.741 No    ns
"  Ctrl vs DM"   -0.08984    ---   No    ns
"  DM vs DPN"    -0.3711     ---   No    ns




Parameter
"Table Analyzed" "Ankle sagittal"

"One-way analysis of variance"
"  P value" 0.1233
"  P value summary"     ns
"  Are means signif. different? (P < 0.05)"   No
"  Number of groups"   3
"  F" 2.154
"  R square"     0.05573
```

```
"Bartlett's test for equal variances"
"  Bartlett's statistic (corrected)"     5.482
"  P value" 0.0645
"  P value summary"      ns
"  Do the variances differ signif. (P < 0.05)"      No

"ANOVA Table"      SS      df     MS
"  Treatment (between columns)"   15.93 2      7.965
"  Residual (within columns)"      269.9 73    3.698
"  Total"    285.9 75

"Newman-Keuls Multiple Comparison Test"  "Mean Diff."      q
      "Significant? P < 0.05?"      Summary
"  DM vs DPN"      -1.142       2.816 No    ns
"  DM vs Ctrl"    -0.1604      ---    No    ns
"  Ctrl vs DPN"   -0.9812      ---    No    ns




Parameter
"Table Analyzed" "Ankle transverse"

"One-way analysis of variance"
"  P value" 0.4655
"  P value summary"      ns
"  Are means signif. different? (P < 0.05)"   No
"  Number of groups"    3
"  F" 0.7728
"  R square"        0.02073

"Bartlett's test for equal variances"
"  Bartlett's statistic (corrected)"     9.245
"  P value" 0.0098
"  P value summary"      **
"  Do the variances differ signif. (P < 0.05)"       Yes

"ANOVA Table"      SS      df     MS
"  Treatment (between columns)"    1.497 2      0.7484
"  Residual (within columns)"      70.70 73    0.9685
"  Total"    72.20 75

"Newman-Keuls Multiple Comparison Test"  "Mean Diff."      q
      "Significant? P < 0.05?"      Summary
"  DM vs DPN"      -0.3439      1.657 No    ns
"  DM vs Ctrl"    -0.03191     ---    No    ns
"  Ctrl vs DPN"   -0.3120      ---    No    ns

Parameter
"Table Analyzed" "Hip frontal"

"One-way analysis of variance"
"  P value" 0.4178
```

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```
"  P value summary"      ns
"  Are means signif. different? (P < 0.05)"    No
"  Number of groups"    3
"  F" 0.8832
"  R square"        0.02363

"Bartlett's test for equal variances"
"  Bartlett's statistic (corrected)"      1.737
"  P value" 0.4196
"  P value summary"      ns
"  Do the variances differ signif. (P < 0.05)"       No

"ANOVA Table"     SS     df     MS
"  Treatment (between columns)"    1.229 2      0.6145
"  Residual (within columns)"      50.79 73    0.6958
"  Total"    52.02 75

"Newman-Keuls Multiple Comparison Test" "Mean Diff."      q
      "Significant? P < 0.05?"      Summary
"  DM vs DPN"     -0.3019      1.717 No     ns
"  DM vs Ctrl"    -0.005913   ---   No     ns
"  Ctrl vs DPN"   -0.2960      ---   No     ns

Parameter
"Table Analyzed" "Hip sagittal"

"One-way analysis of variance"
"  P value" 0.2908
"  P value summary"     ns
"  Are means signif. different? (P < 0.05)"    No
"  Number of groups"    3
"  F" 1.256
"  R square"        0.03327

"Bartlett's test for equal variances"
"  Bartlett's statistic (corrected)"      2.159
"  P value" 0.3398
"  P value summary"     ns
"  Do the variances differ signif. (P < 0.05)"       No

"ANOVA Table"     SS     df     MS
"  Treatment (between columns)"    3.795 2      1.898
"  Residual (within columns)"      110.3 73    1.511
"  Total"    114.1 75

"Newman-Keuls Multiple Comparison Test" "Mean Diff."      q
      "Significant? P < 0.05?"      Summary
"  DM vs DPN"     -0.5267      2.033 No     ns
"  DM vs Ctrl"    -0.002136   ---   No     ns
"  Ctrl vs DPN"   -0.5245      ---   No     ns

Parameter
```

```
"Table Analyzed" "Hip transverse"

"One-way analysis of variance"
"  P value" 0.0257
"  P value summary"    *
"  Are means signif. different? (P < 0.05)"   Yes
"  Number of groups"   3
"  F" 3.851
"  R square"       0.09544

"Bartlett's test for equal variances"
"  Bartlett's statistic (corrected)"    3.803
"  P value" 0.1493
"  P value summary"    ns
"  Do the variances differ signif. (P < 0.05)"      No

"ANOVA Table"     SS    df    MS
"  Treatment (between columns)"   19.05 2    9.523
"  Residual (within columns)"      180.5 73   2.473
"  Total"   199.6 75

"Newman-Keuls Multiple Comparison Test" "Mean Diff."     q
     "Significant? P < 0.05?"      Summary
"  Ctrl vs DPN"  -1.268     3.775 Yes   *
"  Ctrl vs DM"   -0.2155    0.7376     No    ns
"  DM vs DPN"    -1.052     3.175 Yes   *

Parameter
"Table Analyzed" "Knee frontal"

"One-way analysis of variance"
"  P value" 0.2404
"  P value summary"    ns
"  Are means signif. different? (P < 0.05)"   No
"  Number of groups"   3
"  F" 1.454
"  R square"       0.03830

"Bartlett's test for equal variances"
"  Bartlett's statistic (corrected)"    16.22
"  P value" 0.0003
"  P value summary"    ***
"  Do the variances differ signif. (P < 0.05)"      Yes

"ANOVA Table"     SS    df    MS
"  Treatment (between columns)"   12.20 2    6.100
"  Residual (within columns)"      306.4 73   4.197
"  Total"   318.6 75

"Newman-Keuls Multiple Comparison Test" "Mean Diff."     q
     "Significant? P < 0.05?"      Summary
"  DM vs DPN"    -1.024     2.372 No    ns
```

```
"  DM vs Ctrl"   -0.2342     ---    No    ns
"  Ctrl vs DPN"  -0.7901     ---    No    ns


Parameter
"Table Analyzed" "Knee sagittal"

"One-way analysis of variance"
"  P value" 0.4987
"  P value summary"     ns
"  Are means signif. different? (P < 0.05)"   No
"  Number of groups"    3
"  F" 0.7024
"  R square"       0.01888

"Bartlett's test for equal variances"
"  Bartlett's statistic (corrected)"    1.737
"  P value" 0.4196
"  P value summary"     ns
"  Do the variances differ signif. (P < 0.05)"      No

"ANOVA Table"      SS    df    MS
"  Treatment (between columns)"   2.392 2    1.196
"  Residual (within columns)"     124.3 73    1.703
"  Total"   126.7 75

"Newman-Keuls Multiple Comparison Test" "Mean Diff."      q
      "Significant? P < 0.05?"       Summary
"  DM vs Ctrl"   -0.3649    1.505 No    ns
"  DM vs DPN"    -0.3599      ---   No    ns
"  DPN vs Ctrl"  -0.004936   ---   No    ns

Parameter
"Table Analyzed" "Knee transverse"

"One-way analysis of variance"
"  P value" 0.0446
"  P value summary"     *
"  Are means signif. different? (P < 0.05)"   Yes
"  Number of groups"    3
"  F" 3.247
"  R square"       0.08170

"Bartlett's test for equal variances"
"  Bartlett's statistic (corrected)"    7.551
"  P value" 0.0229
"  P value summary"     *
"  Do the variances differ signif. (P < 0.05)"      Yes

"ANOVA Table"      SS    df    MS
"  Treatment (between columns)"   12.62 2    6.308
"  Residual (within columns)"     141.8 73    1.943
"  Total"   154.4 75
```
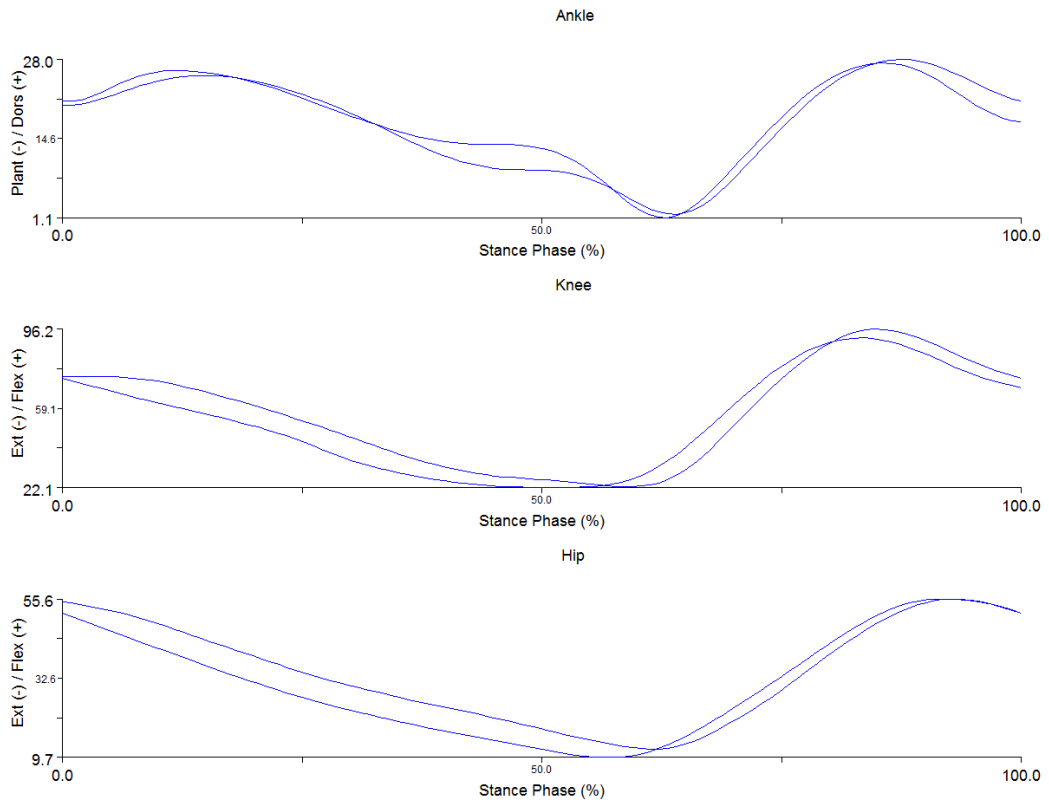
```
"Newman-Keuls Multiple Comparison Test" "Mean Diff."      q
       "Significant? P < 0.05?"      Summary
"  Ctrl vs DPN"   -1.071      3.598 Yes    *
"  Ctrl vs DM"    -0.4667     1.802 No     ns
"  DM vs DPN"     -0.6047     2.058 No     ns
```
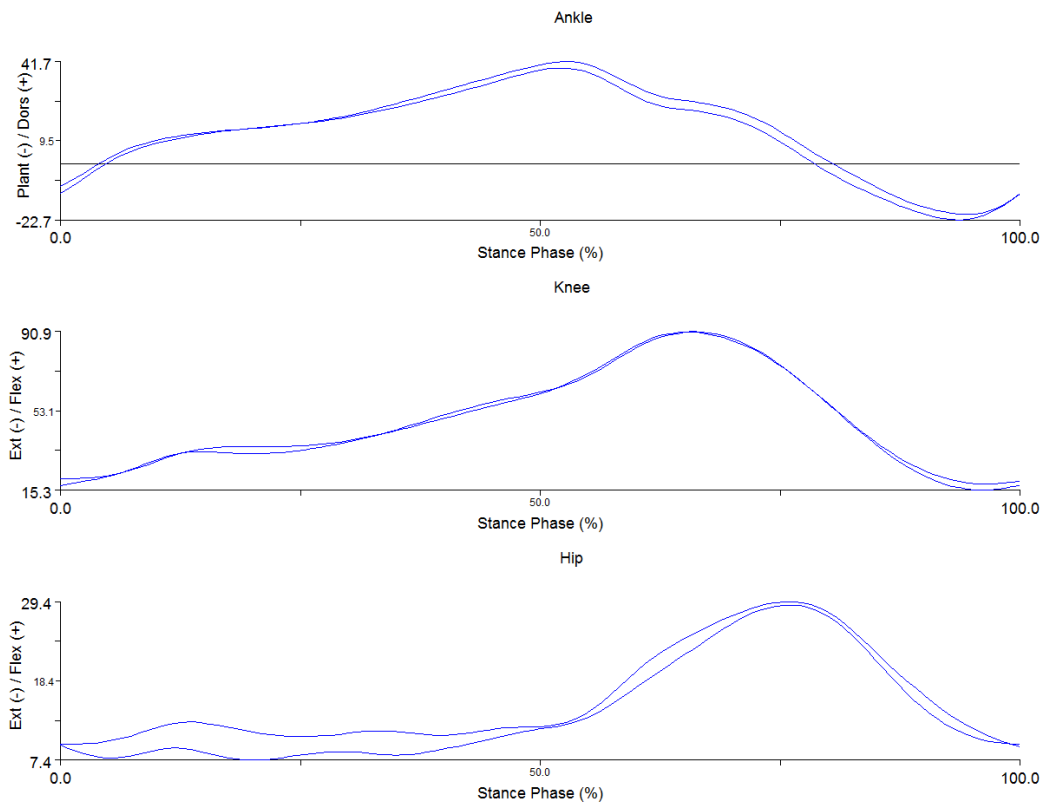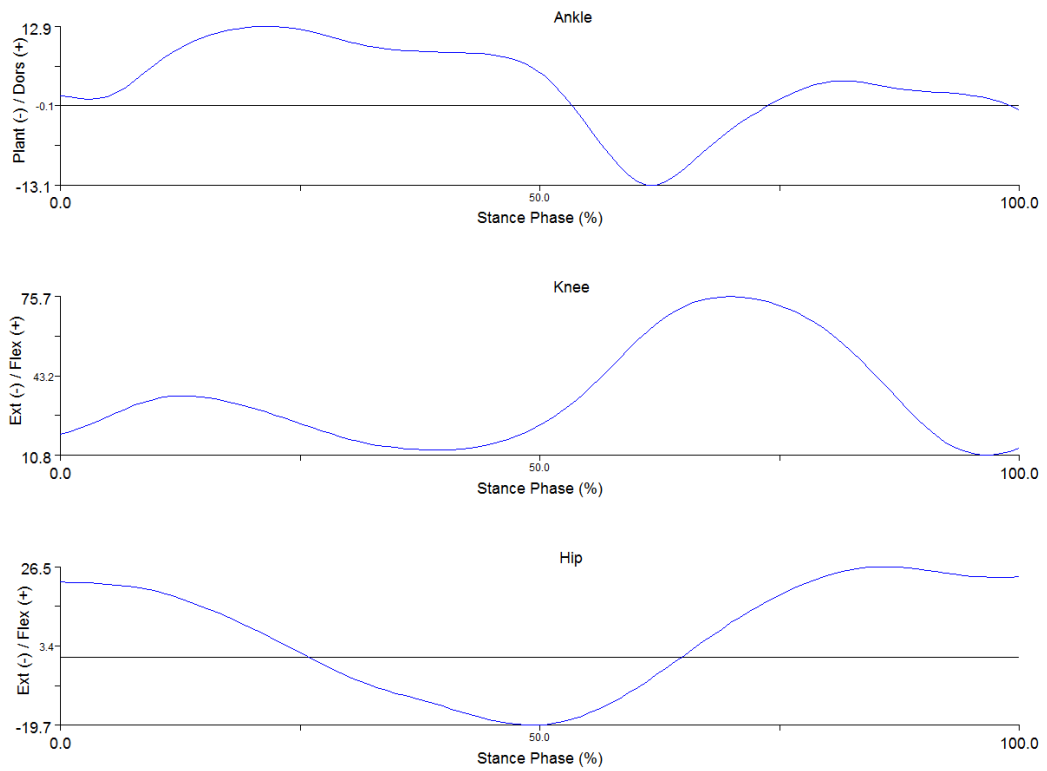
Stair ascent

Joint Angles (Degrees)

Ankle

Knee

Hip

Stair descent

Joint Angles (Degrees)

Level walking
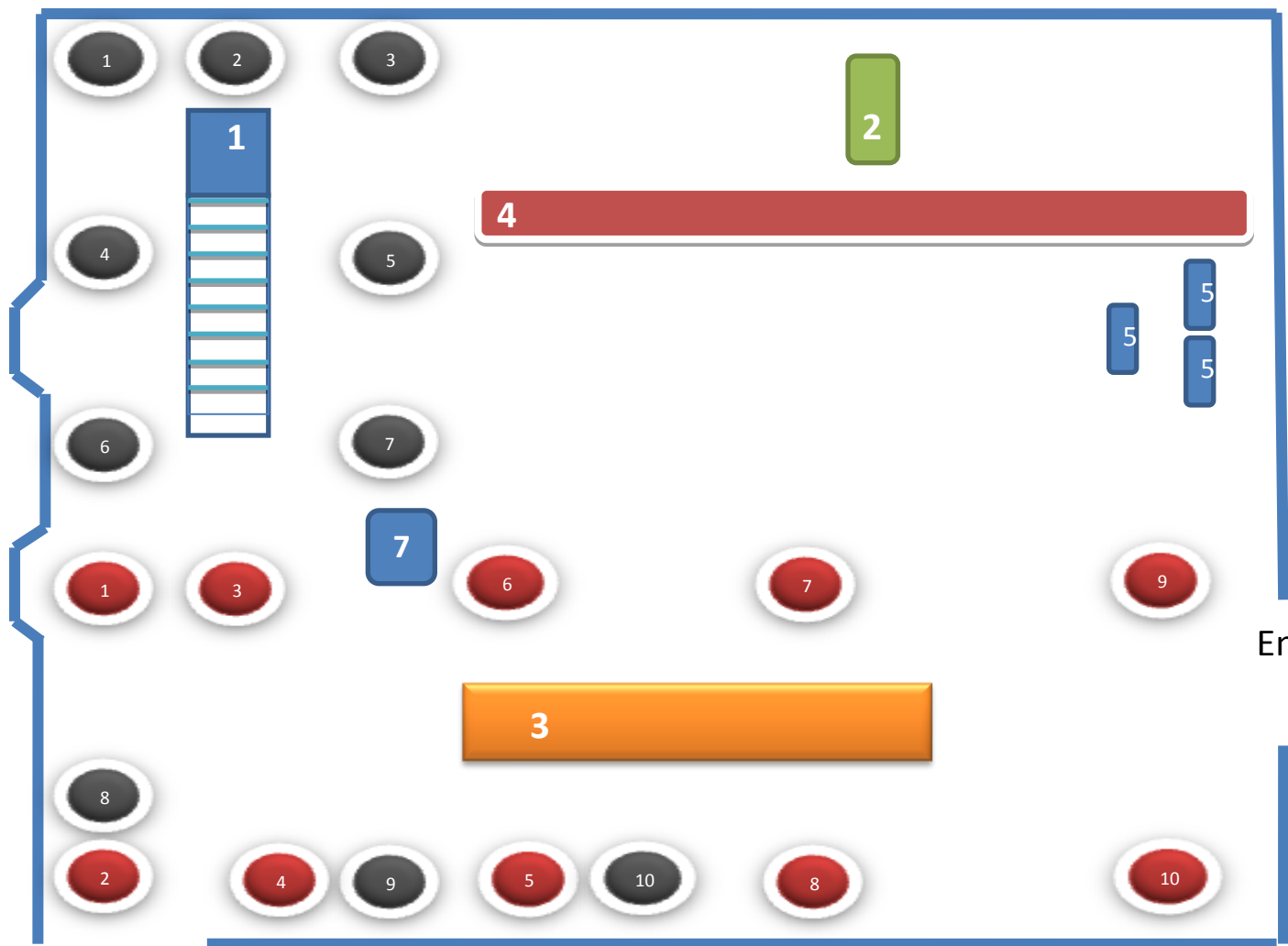
Joint Angles (Degrees)

Floor plan gait laberotory

Windows

1 Stairs
2 Tread mill
3 Level walking
4 Arial platform
5 PC workstations
6 Cameras 1,2,3,4, 5,6,7,8,9,10 7 [Grey Stairs, Red level waliking]
7 Column

Door

Entrance

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