



REVIEW

Diabetic Neuropathy and Gait: A Review

Uazman Alam · David R. Riley · Ravinder S. Jugdey · Shazli Azmi ·
Satyan Rajbhandari · Kristiaan D'Août · Rayaz A. Malik

Received: July 19, 2017

© The Author(s) 2017. This article is an open access publication

ABSTRACT

Diabetic peripheral neuropathy (DPN) is a major sequela of diabetes mellitus and may have a detrimental effect on the gait of people with this complication. DPN causes a disruption in the body's sensorimotor system and is believed to affect up to 50% of patients with diabetes mellitus, dependent on the duration of diabetes. It has a major effect on morbidity and mortality. The peripheral nervous system controls the complex series of events in gait through somatic and autonomic functions, careful balancing of eccentric and concentric

muscle contractions and a reliance on the sensory information received from the planter surface. In this literature review focussing on kinetics, kinematics and posture during gait in DPN patients, we have identified an intimate link between DPN and abnormalities in gait and demonstrated an increased risk in falls for older patients with diabetes. As such, we have identified a need for further research on the role of gait abnormalities in the development of diabetic foot ulceration and subsequent amputations.

Keywords: Diabetic neuropathy; Gait; Kinetics; Kinematics; Plantar pressure; Posture; Ulceration

Enhanced content To view enhanced content for this article go to <http://www.medengine.com/Redeem/F2FBF06014967C5E>.

U. Alam (✉)
Diabetes and Endocrinology Research, Department of Eye and Vision Sciences, Institute of Ageing and Chronic Disease, University of Liverpool and Aintree University Hospital NHS Foundation Trust, Liverpool, UK
e-mail: Uazman.alam@liverpool.ac.uk;
Uazman.alam@manchester.ac.uk

U. Alam · S. Azmi · R. A. Malik
Division of Diabetes, Endocrinology and Gastroenterology, Institute of Human Development, University of Manchester and the Manchester Royal Infirmary, Central Manchester Hospital Foundation Trust, Manchester, UK

R. S. Jugdey
Department of Orthopaedics, Royal Bolton Hospital, Bolton, UK

D. R. Riley · S. Rajbhandari
Lancashire Teaching Hospitals, Chorley, UK

K. D'Août
Evolutionary Morphology and Biomechanics Group, Department of Musculoskeletal Biology, Institute of Ageing and Chronic Disease, University of Liverpool, Liverpool, UK

R. A. Malik
Weill Cornell Medicine-Qatar, Doha, Qatar

INTRODUCTION

Diabetic peripheral neuropathy (DPN) is a symmetrical, length-dependent sensorimotor polyneuropathy which is attributed to metabolic and microvessel alterations due to hyperglycaemia and concomitant cardiovascular risk covariates [1]. The occurrence of other diabetic microvascular complications in a given patient strengthens the case that DPN is attributable to diabetes [1]. The prevalence of DPN in diabetes can be as high as 50% dependent on age and duration of diabetes [2], and symptomatic painful DPN can affect up to 30% of diabetic patients with neuropathy [3]. Traditionally, DPN symptoms can be either positive (aching, burning, sharp or pressure pains) or negative (numbness or dead feeling), or both simultaneously. Although, DPN affects the sensory, motor and autonomic components of the nervous system, manifesting as a loss of protective sensation, intrinsic foot muscle dysfunction may lead to an alteration in gait [4].

Normal walking is the end-product of a healthy neuro-musculo-skeletal system, which requires both sensory input to modify learned motor patterns and muscular output to execute the desired action. Walking is a critical component of physical function. An intact central and peripheral nervous system to initiate and control the movement, adequate muscle strength and bones and joints moving in full range are essential for normal locomotion, which is the most natural daily activity for humans. Moreover, the majority of falls occur during situations in which the individual is walking [5]. Hence, DPN may have a significant interplay with gait disorders and the risk of falls [6].

This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

PATHOPHYSIOLOGY OF DPN

The pathogenesis of DPN is yet to be fully elucidated. The pathological changes are mediated through competing or parallel pathways:

glucose-induced activation of protein kinase C isoforms; increased formation of advanced-glycation end-products; increased glucose flux through the aldose reductase pathway [7–9]. Both metabolic and microvascular factors play important roles [10, 11].

PREVALENCE OF DPN

The prevalence of DPN is thought to be around 50% [2, 12] and increases with a longer duration of the disease and poor glycaemic control [13]. When diabetes has been present for >25 years the prevalence rises to approximately 50% [12]. The Rochester Diabetic Neuropathy Study reported a prevalence of 54 and 45% for patients with type 1 and type 2 diabetes mellitus (T1DM, T2DM), respectively, among 380 patients, with the majority not exhibiting neuropathic symptoms [14]. The 1989 National Health Interview Survey consisted of a representative sample of 84,572 persons in the USA aged ≥ 18 years [15]. Those with diabetes mellitus ($n = 2405$) were identified and asked to complete a questionnaire to define the prevalence of symptoms of sensory neuropathy, which was found to be 30.2% among subjects with T1DM. Symptoms of sensory neuropathy affect 30–40% of diabetic patients, and the prevalence of these symptoms increases with longer duration of diabetes, with hypertension and hyperglycaemia with motor involvement being more pronounced in those with a longer duration of diabetes [15].

GAIT

Gait is the forward propulsion of the human skeleton through a series of movements. One gait cycle is measured from heel-strike to heel-strike on the ipsilateral side. The gait cycle consists of 60% stance and 40% swing phase, with the latter further subdivided into eight distinct phases. The prerequisites of normal gait are stability in stance; toe clearance in swing phase; swing phase pre-positioning; adequate step length; a good mechanical and metabolic efficiency. A healthy gait pattern depends on an

array of biomechanical features that are orchestrated by the central nervous system for economy and stability [16]. Gait is a complex sequence of events that involves both somatic and autonomic functions. Locomotion involves a combination of eccentric and concentric muscular contractions in order to resist gravity and achieve forward propulsion of the body's centre of gravity.

In addition to efferent motor action resulting in muscular contractions, plantar cutaneous sensation and joint position sensation are important factors in standing balance and ambulation [17–19]. Plantar skin receptors are sensitive to pressure and vibration. The plantar surface of the foot is described as a “sensory map” that provides the central nervous system with information on the position of the body, based on the distribution of activated receptors [20, 21].

MECHANICS OF GAIT

Forward propulsion of the body's centre of gravity involves the voluntary contraction of muscles within the lower limbs and the rest of the body, including trunk rotation and arm swinging [22]. Upon heel-strike there is an eccentric contraction of the tibialis anterior muscle. During mid-stance the gastro-soleus complex contracts eccentrically, followed by contraction concentrically in terminal stance. The swing phase involves concentric contractions of the tibialis anterior for adequate ground clearance. The hamstrings and quadriceps also play an important role in gait, as do the proprioceptive feedback mechanisms within the body, in order to maintain both static and dynamic balance. This is regulated through an intact central and peripheral nervous system [23], resulting in a walking gait that can be modelled as an “inverted pendulum”, conserving about 70% of energy.

STATIC AND DYNAMIC BALANCE

The ability to remain upright involves an intricate sequence of motor and sensory feedback

mechanisms. Sensory detection of the body in space from visual, vestibular, proprioceptive and auditory cues provide feedback to allow autonomous mechanical adjustments in posture [24, 25]. Stresses and strains within the plantar foot activate various mechanoreceptors. The perception of a limb position and movement is mediated via muscle spindle, cutaneous and joint receptors. Furthermore, the proprioceptive feedback of muscular contraction is mediated by tendon organ receptors [26]. This creates a feedback loop using A β myelinated fibres via the dorsal root ganglia to the nuclei gracilis within the brainstem [27, 28]. In a recent study by Almurthi et al. [29], people with impaired glucose tolerance, but not those with T2DM, had a significantly higher dynamic mediolateral sway during walking, suggesting alterations in gait may occur very early, even in the pre-diabetes phase.

DIABETIC NEUROPATHY AND GAIT DISORDERS

This section addresses the changes in gait associated with diabetic neuropathy and evaluates factors that contribute to the development of diabetic foot ulcers. Numerous abnormalities, including sensory loss (impaired vibration and protective sensation), decreased lower-extremity strength (force-producing capacity) and alterations in the central nervous system contribute to impaired gait in diabetes [30–33].

Abnormalities in gait have an effect on patients beyond simple functional impairments. For example, Vileikyte et al. demonstrated that unsteadiness in gait was the strongest association with symptoms of depression in patients with diabetes [34]. Furthermore, both mood and cognition may alter the relationship between diabetes and gait [35].

People with diabetic neuropathy are at far greater risk of falling than those with intact sensation [36, 37]. That most falls occur during locomotion [36, 38] suggests that these patients may have difficulty maintaining dynamic stability while walking. In one study these patients showed greater deviation of their central mass

from the centre of pressure during staircase and level walking [39]. It has been suggested that sensory feedback may play a pivotal role in smoothing unintended irregularities that occur during unperturbed movements [40] and in adjusting step-to-step limb trajectories to maintain balance during locomotion [41]. In a study assessing autonomic function in relation to gait, people with diabetes took additional steps when walking in a linear path and during turns [30]. Reduced walking speed, cadence and step length and fewer acceleration patterns have been noted in subjects with diabetic neuropathy [32]. To our knowledge only one previous non-interventional study has assessed painful diabetic neuropathy and gait [42]. The authors of this study concluded that people with painful diabetic neuropathy had greater variation in step length and step velocity but also tended to walk more [42]. The painful diabetic neuropathy group also self-reported an increased number of falls with subsequent hospitalisations for injuries sustained, as well as a greater fear of falling [42]. However, the method used to analyse gait in this study was a portable device attached to the patient; thus, the complexities of alterations in gait strategy in patients with painful diabetic neuropathy were not fully elucidated [42]. Furthermore, the authors did not investigate any associations/relationships between painful diabetic neuropathy and quality of life and depression, despite the patients report this increased fear of falling [42]. Interestingly, in another study, intervention with pregabalin in painful diabetic neuropathy did not improve gait stability of the patients; rather, it caused increasing variability in gait speed and step length [43], possibly reflecting a higher risk of falling.

Individuals with DPN walk slower than age-matched healthy controls [32, 44]. Dingwell et al. [45] and Menz et al. [32] demonstrated that those with greater DPN-related loss of plantar cutaneous sensation tended to walk with a slower preferred walking speed. However, increases in gait variability are linked to reductions in self-selected walking speed rather than sensory loss per se [44]. Gait speed is positively correlated to survival advantage in the aged population [46]. Presence of neuropathy has

been shown to be an independent risk factor for death among patients with diabetes [47].

Diabetic neuropathy is a recognised risk factor for diabetic foot ulceration [6, 48, 49], and patients who develop diabetic foot ulceration are at increased risk of amputation [50, 51]. Foot amputation is usually the sequela of a cascade of events, including the development of neuropathy, microangiopathy and vascular disease and abnormal plantar pressures and gait, all of which lead to foot ulcers [52]. Once ulceration is present, the gait may alter further [53], leading to a self-perpetuating situation of ulcer formation and lack of healing.

There are large variations in the results of studies addressing these aspects of DPN due to the heterogeneous population and small numbers of subjects enrolled.

KINEMATICS

Locomotion is a fundamental component of many activities that are critical to the maintenance of an independent lifestyle. Dynamic gait evaluation allows examination of the intrinsic and extrinsic factors affecting an individual's ability to walk or run. The aim of this section is to identify specific differences in lower limb kinematics between patients with diabetic neuropathy and non-diabetic patients.

The range of movement at joints is altered in diabetes, and patients with DPN have a reduced motion at the ankle in dorsiflexion and plantar flexion and a reduced range of motion at the knee in both flexion and extension compared to non-diabetic individuals [54, 55]. Alterations in ankle joint motion and mobility occur in relation to plantar pressure changes [56]. The range of motion at the metatarsal heads is reduced in patients with DPN when compared to that in non-diabetic patients [57]. This reduction has been found to be most prominent at the first metatarsophalangeal joint in diabetic patients with a history of ulceration [58, 59].

A relatively increased magnitude of stride-to-stride variability and decreased magnitude of local instability are viewed as impairments because of their association with aging and disease [45, 60]. The impact of diabetic

neuropathy on the range of motion at the hip is unclear. Gomes et al. [61] found an increase in flexion at the hip in patients with DPN, which they believed was due to a compensatory effect for the loss of motion at distal joints. However, two studies by Rasporic et al. [58] and Yavuzer et al. [62] found a decrease in the range of hip flexion in patients with DPN when compared with non-diabetic individuals.

Interestingly, Hazari et al. [54] recently found no significant difference between the range of motion at the hip, knee or ankle joints when comparing patients with and without diabetic neuropathy. These authors reported that the passive range of motion at the ankle joint complex during gait differed between diabetic patients and non-diabetic patients. However, there were no differences between patients with and without DPN during gait; nor were there differences in the range of motion of the ankle joint complex in the three groups during gait. The glycation of collagen may lead to periarticular structures becoming thickened and may confound differences in ankle motion due to neuropathy [59].

There are only a few studies that compare kinematics in patients with DPN to patients without DPN. Those that do have small sample sizes, and there is a significant variation in results between them [58, 61, 62]. Larger, more robust studies are therefore required to identify if there are any specific kinematic changes due to neuropathy.

KINETICS

Kinetics looks at the forces involved in the gait cycle; in this case ground reaction forces and joint moments.

Ground reaction forces seem to differ between patients with DPN, without DPN and controls at either the initial contact or toe-off stage of gait [54, 55]. However, available studies are limited by small sample sizes, and there is considerable variation among the findings. Based on the limited data currently available, ground reaction forces do not appear to differ in the purely diabetic neuropathic gait [54, 55]. However, in a recent cross-sectional case control

study of those with DPN and a cerebrovascular accident, there were alterations of medial–lateral forces of the non-paretic side and vertical forces of the paretic side in stroke survivors with DPN compared to stroke survivors without DPN and healthy controls [63].

There are limited data available on the moments at the hip or knee. Savelberg et al. [64] and Yavuzer et al. [62] observed no significant differences in joint moments at the hip or the knee when comparing diabetic patients with or without neuropathy to non-diabetic patients. Sacco et al. [65] did demonstrate that people with diabetes have an increased hip flexion moment at push off and decreased extensor moment at initial contact when compared to those without diabetes, but they found no significant difference between patients with and without DPN [56]. Paradoxically, Fernando et al. [55] showed a decrease in hip flexion moment and an increase in extensor moment in patients with DPN. Taken together, these results show that there is a lack of good evidence to suggest differences in joint moments at the hip and knee between patients with diabetic neuropathy compared to healthy individuals and those with and without DPN [54].

Peak plantar flexion moments are reduced in patients with DPN [62, 66, 67]. Savelberg et al. showed that abnormal plantar pressure patterns are associated with a redistribution of joint moments in those with DPN and a consequently reduced capacity to control forward velocity at heel-strike [68]. However, there are a paucity of data comparing patients with and without DPN.

MUSCLE STRENGTH

Sarcopenia is atrophy and progressive loss of function of skeletal muscle associated with aging and there is clear evidence that states of hyperglycaemia accelerate this loss in muscle size [69] and strength [70].

Previous studies of muscle strength (assessed through use of a dynamometer) in DPN have shown reduced power including plantar flexor torque [71] and reduced ankle and knee maximal isokinetic muscle strength [72].

In relation to muscle size, of the intrinsic foot muscles can be quite pronounced in DPN and appears to be related to the severity of neuropathy [73–75]. Muscular atrophy is thought to underlie motor weakness at the ankle in patients with DPN [74]. The atrophy is most pronounced in distal muscles of the lower leg indicating a length dependent neuropathic process [74]. In a follow up study by Andreassen et al. [76], muscle atrophy in long-term DPN occurred early in the feet, progressed steadily up the lower legs and was related to the severity of neuropathy leading to weakness at the ankle. Recently, Almurthi et al. [77], showed that patients with type 2 diabetes have a significant reduction in proximal and distal leg muscle strength and a proximal reduction in muscle volume, not seen in the distal muscles due an increase in intramuscular fat. Furthermore, in a case–control study patients with DPN possessed less endurance than controls, and a failure of neuromuscular transmission may have contributed to greater muscle fatigability [78]. People with DPN have also demonstrated decreased muscle strength and slower dorsiflexion contractile properties for both evoked and voluntary contractions which may contribute to reduced muscle quality as well as contractile slowing [79].

PLANTAR PRESSURES

Compensatory musculoskeletal mechanisms may develop in patients with DPN to compensate for their sensory deficits and in part may lead to altered plantar pressures. Diabetic neuropathy causes atrophy of the small muscles in the foot, leading to a loss of support surface and an increase in bony prominences. These changes are thought to result in higher peak plantar pressures at the mid-foot and forefoot when compared to patients with and without DPN [49, 50, 54, 55, 80]. There are conflicting data for peak plantar pressure at the hind foot. Fernando et al. [55] found a significant increase in peak plantar pressure at the hind foot, but the more recent meta-analysis by Hazari et al. [54] found no significant difference.

Other factors that have been identified to cause a raised plantar pressure are the

development of hallux valgus and hallux rigidus deformities, which cause increased pressures in the medial forefoot. Although intrinsic muscular foot atrophy does not necessarily imply foot deformity [75]. A high body mass index causes increased plantar pressure in the lateral forefoot which is independent of diabetic neuropathy [81].

Peak plantar pressure (PPP) is used as a surrogate measure of trauma to the plantar foot. While mild DPN may not raise plantar pressures [81], they are clearly elevated in those with severe DPN [82] and those with obvious foot deformity [81, 83]. High plantar pressures are a key risk factor in the development of foot ulcers, and high foot pressures and neuropathy are independently associated with ulceration in patients with diabetes [52]. A foot pressure of $> 6 \text{ N/cm}^2$ is associated with foot ulceration [52], increased morbidity and an increased risk of limb amputation [50, 80, 81].

Most research in the field has focused on assessing plantar pressures before the development, or after the healing, of diabetic foot ulcers [53, 84–87]. The results of these studies suggest that reducing plantar pressures prevents diabetic foot ulcers from occurring and allows optimal healing if they do develop [88, 89]. Elevated plantar pressures during gait in the presence of sensory DPN increases plantar tissue trauma and predisposes people to diabetic foot ulcers [4, 90]. Previous studies also suggest that the mechanical loading on the ulcerated limb is substantially increased during gait [50]. Treatment of diabetic foot ulcer by offloading it using a total contact cast or removable cast walker significantly alters the gait and affects balance, but there is hardly any published literature in this field.

A more precise formulation of tailored treatments that include existing recommendations to reduce plantar pressure in conjunction with novel interventions to promote changes in gait may help in the prevention and recurrence of diabetic foot ulcers. A multi-modal target strategy is required in the prevention of diabetic foot ulcers. Future strategies should include an analysis of gait; however, until biomechanics laboratories are more widely available in clinical settings, this remains an unmet need.

CHARCOT FOOT, PLANTAR PRESSURES AND GAIT

Charcot neuropathic osteoarthropathy or ‘Charcot foot’ occurs in patients with peripheral neuropathy, and diabetes is the commonest cause [91]. It is a process of sensory loss and inappropriate inflammation in the foot that causes bone subluxation and dislocation with bone destruction and new bone formation, culminating in deformity [92, 93]. The typical deformity is a mid-foot collapse, often described as “rocker-bottom” foot.

These deformities cause a rise in PPP and thereby lead to an increased risk of ulceration [92, 94, 95]. Studies assessing bone mineral density as a marker of disease have found an increased turnover of bone in the affected foot [95]. This increased turnover is not present in any other lower limb joint, suggesting that the inflammatory process that underpins Charcot foot is a localised phenomenon [96]. The current imaging modalities most commonly used in the diagnosis and management of acute Charcot foot are X-ray and magnetic resonance imaging (MRI) [97], with MRI considered to be superior to X-ray in terms of diagnostics; the former may show early osteomyelitic changes [91].

The mainstay of treatment for Charcot foot involves offloading pressure areas [98]. An alternative is surgical correction of the deformity, particularly in those with a rocker-bottom foot; however, a high complication rate of > 40% limits wide use of the surgical option [94]. Offloading pressure areas has been shown to improve mobilisation when used in conjunction with orthopaedic shoes [95], and when undertaken appropriately it achieves limb salvage in 97% of patients [94]. Currently, the data related to Charcot foot and gait disorders are limited; therefore, further research is needed.

INTERVENTIONAL STUDIES ON GAIT DISORDERS IN DIABETES

The focus of interventional studies on patients with a gait disorder in diabetes has been on

reducing the risk of falls and preventing diabetic foot ulcer. Aerobic and resistance training exercise regimes for diabetic patients can improve gait stability through increased muscle strength and range of joint motion, as well as generally improving their blood sugar control, blood pressure and serum lipid levels [49, 99–101]. Allet et al. [99] showed that older individuals with diabetes had impaired balance, slower reactions and, consequently, a higher risk of falling than age-matched control subjects. All of these variables improved after resistance/balance training through a structured exercise programme. However, the follow-up period for all studies was relatively short, with the longest being just 6 months. An exercise intervention in older people with T2DM with mild to moderate DPN demonstrated improvements in balance, proprioception, lower-limb strength, reaction time, and, consequently, a decreased risk of falling [102]. However, gait was not specifically assessed in this study [102]. There are a paucity of studies evaluating whether these improvements in gait are maintained long term and if they actually reduce the incidence of falls. While a structured exercise programme may be beneficial in terms of physiological function in people with T2DM and DPN, better-designed longitudinal studies are required to evaluate the frequency and duration of any programme and to assess if the effects are sustainable.

With a view to diabetic ulcer prevention and treatment, a key in addressing the detrimental effect of gait disorders in people with diabetes is the reduction or redistribution of plantar pressure as this is known to be a significant risk factor in ulcer formation [50, 54, 81, 103]. Redistribution looks at recruiting areas of the foot or lower leg that are not normally weight bearing or that are normally under lower pressure in order to redistribute the plantar pressure across a wider area and, as a result, reduce the peak pressure in any one area. This can be done through the application of various insoles, braces, casts or rigid soles, depending on where the clinician wishes to transfer the pressure to or from [50, 103]. Total contact casts are the most effective method of off-loading plantar pressure in the presence of an ulcer to aid healing [104].

Another possible method of reducing plantar pressures is to reduce gait speed; this strategy has been shown to reduce the plantar pressures across the foot [105]. However, in practical terms, it may be difficult to get patients to consistently walk slower. Very recent relevant meta-analyses confirm the limited benefits of reducing gait speed, but the authors also conclude that larger studies need to be carried out [54, 55].

CONCLUSIONS

Abnormalities in gait occur in patients with DPN and are intimately linked to alterations in kinetics, kinematics and posture. Sarcopenia related to the severity of DPN also appears to play a pivotal role. These conditions may lead to an increased risk of falls and be a significant cause of morbidity and mortality in older people with diabetes. Further detailed evaluation of gait disorders in DPN is required, particularly in terms of accurately phenotyping neuropathy in relation to gait disorders. Further research on the role of gait abnormalities in the development of diabetic foot ulcers and subsequent amputations needs is urgently required.

ACKNOWLEDGEMENTS

No funding or sponsorship was received for this study or publication of this article. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole and have given final approval for the version to be published.

Disclosures. Uazman Alam, David R. Riley, Ravinder S. Jugdey, Shazli Azmi, Satyan Rajbhandari, Kristiaan D'Août and Rayaz A. Malik have nothing to disclose

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

Data Availability. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors. As such there were no datasets generated and/or analysed during this paper.

Open Access. This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits any non-commercial use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

REFERENCES

1. Tesfaye S, Boulton AJ, Dyck PJ, Freeman R, Horowitz M, Kempler P, et al. Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. *Diabetes Care*. 2010;33(10):2285–93.
2. Shaw J, Zimmet P. The epidemiology of diabetic neuropathy. *Diabetes Rev*. 1999;7:245–52.
3. Skljarevski V, Malik RA. Clinical diagnosis of diabetic neuropathy. In: Veves A, Malik RA, editors. *Diabetic neuropathy: clinical management*. 2nd edn. Totowa: Humana Press; 2007.
4. Boulton AJ. The diabetic foot: from art to science. The 18th Camillo Golgi lecture. *Diabetologia*. 2004;47(8):1343–53.
5. Timsina LR, Willetts JL, Brennan MJ, Marucci-Wellman H, Lombardi DA, Courtney TK, et al. Circumstances of fall-related injuries by age and gender among community-dwelling adults in the United States. *PLoS One*. 2017;12(5):e0176561.
6. Pop-Busui R, Boulton AJM, Feldman EL, Bril V, Freeman R, Malik RA, et al. Diabetic neuropathy: a position statement by the American Diabetes Association. *Diabetes Care*. 2017;40(1):136–54.
7. Malik RA. Current and future strategies for the management of diabetic neuropathy. *Treat Endocrinol*. 2003;2(6):389–400.
8. Brownlee M. The pathobiology of diabetic complications: a unifying mechanism. *Diabetes*. 2005;54(6):1615–25.

9. Malik RA. The pathology of human diabetic neuropathy. *Diabetes*. 1997;46:50–3.
10. Malik RA, Veves A, Walker D, Siddique I, Lye RH, Schady W, et al. Sural nerve fibre pathology in diabetic patients with mild neuropathy: relationship to pain, quantitative sensory testing and peripheral nerve electrophysiology. *Acta Neuropathol*. 2001;101(4):367–74.
11. Ward JD, Tesfaye S. Pathogenesis of human diabetic neuropathy. In: Pickup J, Williams G, editors. *Textbook of diabetes*. Oxford: Blackwell Science; 1997. p. 49.1–49.
12. Boulton AJM, Vinik AI, Arezzo JC, Bril V, Feldman EL, Freeman R, et al. Diabetic neuropathies: a statement by the American Diabetes Association. *Diabetes Care*. 2005;28(4):956–62.
13. Nathan DM. The diabetes control and complications trial/epidemiology of diabetes interventions and complications study at 30 years: overview. *Diabetes Care*. 2014;37(1):9–16.
14. Dyck PJ, Kratz KM, Karnes JL, Litchy WJ, Klein R, Pach JM, et al. The prevalence by staged severity of various types of diabetic neuropathy, retinopathy, and nephropathy in a population-based cohort: the Rochester Diabetic Neuropathy Study. *Neurology*. 1993;43(4):817–24.
15. Harris M, Eastman R, Cowie C. Symptoms of sensory neuropathy in adults with NIDDM in the US population. *Diabetes Care*. 1993;16(11):1446–52.
16. Kuo AD, Donelan JM. Dynamic principles of gait and their clinical implications. *Phys Ther*. 2010;90(2):157–74.
17. Hendrickson J, Patterson KK, Inness EL, McIlroy WE, Mansfield A. Relationship between asymmetry of quiet standing balance control and walking post-stroke. *Gait Posture*. 2014;39(1):177–81.
18. Marigold DS, Eng JJ, Tokuno CD, Donnelly CA. Contribution of muscle strength and integration of afferent input to postural instability in persons with stroke. *Neurorehabil Neural Repair*. 2004;18(4):222–9.
19. Tyson SF, Hanley M, Chillala J, Selley A, Tallis RC. Balance disability after stroke. *Phys Ther*. 2006;86(1):30–8.
20. Alfuth M, Rosenbaum D. Effects of changes in plantar sensory feedback on human gait characteristics: a systematic review. *Footwear Sci*. 2012;4(1):1–22.
21. Kavounoudias A, Roll R, Roll JP. The plantar sole is a 'dynamometric map' for human balance control. *Neuroreport*. 1998;9(14):3247–52.
22. Winter DA. Biomechanics of normal and pathological gait: implications for understanding human locomotor control. *J Mot Behav*. 1989;21(4):337–55.
23. Whittle MW. Clinical gait analysis: a review. *Hum Mov Sci*. 1996;15(3):369–87.
24. Aruin AS. Enhancing anticipatory postural adjustments: a novel approach to balance rehabilitation. *J Nov Physiother*. 2016;6(2):e144.
25. Takakusaki K. Functional neuroanatomy for posture and gait control. *J Mov Disord*. 2017;10(1):1–17.
26. Jones LA. Perception of force and weight: theory and research. *Psychol Bull*. 1986;100(1):29–42.
27. Abraira VE, Ginty DD. The sensory neurons of touch. *Neuron*. 2013;79(4):618–39.
28. Burgess PR, Perl ER. Cutaneous mechanoreceptors and nociceptors. In: Iggo A, editor. *Somatosensory system*. Berlin: Springer; 1973. p. 29–78.
29. Almurthi MM, Brown SJ, Bowling FL, Boulton AJM, Jeziorska M, Malik RA, et al. Altered walking strategy and increased unsteadiness in participants with impaired glucose tolerance and type 2 diabetes relates to small-fibre neuropathy but not vitamin D deficiency. *Diabet Med*. 2017;34(6):839–45.
30. Petrofsky J, Lee S, Macnider M, Navarro E. Autonomic, endothelial function and the analysis of gait in patients with type 1 and type 2 diabetes. *Acta Diabetol*. 2005;42(1):7–15.
31. Sacco IC, Amadio AC. A study of biomechanical parameters in gait analysis and sensitive chronaxie of diabetic neuropathic patients. *Clin Biomech (Bristol, Avon)*. 2000;15(3):196–202.
32. Menz HB, Lord SR, St George R, Fitzpatrick RC. Walking stability and sensorimotor function in older people with diabetic peripheral neuropathy. *Arch Phys Med Rehabil*. 2004;85(2):245–52.
33. Arvanitakis Z, Wilson RS, Schneider JA, Bienias JL, Evans DA, Bennett DA. Diabetes mellitus and progression of rigidity and gait disturbance in older persons. *Neurology*. 2004;63(6):996–1001.
34. Vileikyte L, Leventhal H, Gonzalez JS, Peyrot M, Rubin RR, Ulbrecht JS, et al. Diabetic peripheral neuropathy and depressive symptoms. *Diabetes Care*. 2005;28(10):2378–83.
35. Brach JS, Talkowski JB, Strotmeyer ES, Newman AB. Diabetes mellitus and gait dysfunction: possible explanatory factors. *Phys Ther*. 2008;88(11):1365–74.

-
36. Cavanagh PR, Derr JA, Ulbrecht JS, Maser RE, Orchard TJ. Problems with gait and posture in neuropathic patients with insulin-dependent diabetes mellitus. *Diabet Med*. 1992;9(5):469–74.
37. Richardson JK, Ching C, Hurvitz EA. The relationship between electromyographically documented peripheral neuropathy and falls. *J Am Geriatr Soc*. 1992;40(10):1008–12.
38. Blake AJ, Morgan K, Bendall MJ, Dallosso H, Ebrahim SB, Arie TH, et al. Falls by elderly people at home: prevalence and associated factors. *Age Ageing*. 1988;17(6):365–72.
39. Brown SJ, Handsaker JC, Bowling FL, Boulton AJ, Reeves ND. Diabetic peripheral neuropathy compromises balance during daily activities. *Diabetes Care*. 2015;38(6):1116–22.
40. Gandevia SC, Burke D. Does the nervous system depend on kinesthetic information to control natural limb movements? In: Cordo P, Harnad S, editors. *Movement control*. Cambridge: Cambridge University Press; 1994. p. 12–30.
41. Ferber R, Osternig LR, Woollacott MH, Wasielewski NJ, Lee JH. Reactive balance adjustments to unexpected perturbations during human walking. *Gait Posture*. 2002;16(3):238–48.
42. Lalli P, Chan A, Garven A, Midha N, Chan C, Brady S, et al. Increased gait variability in diabetes mellitus patients with neuropathic pain. *J Diabetes Complicat*. 2013;27(3):248–54.
43. Karmakar S, Rashidian H, Chan C, Liu C, Toth C. Investigating the role of neuropathic pain relief in decreasing gait variability in diabetes mellitus patients with neuropathic pain: a randomized, double-blind crossover trial. *J Neuroeng Rehabil*. 2014;11:125.
44. Dingwell JB, Cavanagh PR. Increased variability of continuous overground walking in neuropathic patients is only indirectly related to sensory loss. *Gait Posture*. 2001;14(1):1–10.
45. Dingwell JB, Cusumano JP, Cavanagh PR, Sternad D. Local dynamic stability versus kinematic variability of continuous overground and treadmill walking. *J Biomech Eng*. 2000;123(1):27–32.
46. Studenski S, Perera S, Patel K, et al. Gait speed and survival in older adults. *JAMA*. 2011;305(1):50–8.
47. Forsblom CM, Sane T, Groop PH, Totterman KJ, Kallio M, Saloranta C, et al. Risk factors for mortality in type II (non-insulin-dependent) diabetes: evidence of a role for neuropathy and a protective effect of HLA-DR4. *Diabetologia*. 1998;41(11):1253–62.
48. Wang H, Ramakrishnan A, Fletcher S, Prochownik EV. A quantitative, surface plasmon resonance-based approach to evaluating DNA binding by the c-Myc oncoprotein and its disruption by small molecule inhibitors. *J Biol Methods*. 2015;2(2):e18.
49. Andersen H. Motor dysfunction in diabetes. *Diabetes Metab Res Rev*. 2012;28[Suppl 1]:89–92.
50. van Deursen R. Mechanical loading and off-loading of the plantar surface of the diabetic foot. *Clin Infect Dis*. 2004;39[Suppl 2]:S87–91.
51. Pham H, Armstrong DG, Harvey C, Harkless LB, Giurini JM, Veves A. Screening techniques to identify people at high risk for diabetic foot ulceration: a prospective multicenter trial. *Diabetes Care*. 2000;23(5):606–11.
52. Frykberg RG, Lavery LA, Pham H, Harvey C, Harkless L, Veves A. Role of neuropathy and high foot pressures in diabetic foot ulceration. *Diabetes Care*. 1998;21:1714.
53. Fernando ME, Crowther RG, Lazzarini PA, Sangla KS, Buttner P, Golledge J. Gait parameters of people with diabetes-related neuropathic plantar foot ulcers. *Clin Biomech*. 2016;37:98–107.
54. Hazari A, Maiya AG, Shivashankara KN, Agouris I, Monteiro A, Jadhav R, et al. Kinetics and kinematics of diabetic foot in type 2 diabetes mellitus with and without peripheral neuropathy: a systematic review and meta-analysis. *Springerplus*. 2016;5(1):1819.
55. Fernando M, Crowther R, Lazzarini P, Sangla K, Cunningham M, Buttner P, et al. Biomechanical characteristics of peripheral diabetic neuropathy: a systematic review and meta-analysis of findings from the gait cycle, muscle activity and dynamic barefoot plantar pressure. *Clin Biomech (Bristol, Avon)*. 2013;28(8):831–45.
56. Sacco ICN, Hamamoto AN, Gomes AA, Onodera AN, Hirata RP, Hennig EM. Role of ankle mobility in foot rollover during gait in individuals with diabetic neuropathy. *Clin Biomech*. 2009;24(8):687–92.
57. DiLiberto FE, Tome J, Baumhauer JF, Houck J, Nawoczenski DA. Individual metatarsal and forefoot kinematics during walking in people with diabetes mellitus and peripheral neuropathy. *Gait Posture*. 2015;42(4):435–41.
58. Raspovic A. Gait characteristics of people with diabetes-related peripheral neuropathy, with and without a history of ulceration. *Gait Posture*. 2013;38(4):723–8.
59. Turner DE, Helliwell PS, Burton AK, Woodburn J. The relationship between passive range of motion and
-

- range of motion during gait and plantar pressure measurements. *Diabet Med.* 2007;24(11):1240–6.
60. Buzzi UH, Stergiou N, Kurz MJ, Hageman PA, Heidel J. Nonlinear dynamics indicates aging affects variability during gait. *Clin Biomech (Bristol, Avon).* 2003;18(5):435–43.
61. Gomes AA, Onodera AN, Otuzi ME, Pripas D, Mezarane RA, Sacco IC. Electromyography and kinematic changes of gait cycle at different cadences in diabetic neuropathic individuals. *Muscle Nerve.* 2011;44(2):258–68.
62. Yavuzer G, Yetkin I, Toruner FB, Koca N, Bolukbasi N. Gait deviations of patients with diabetes mellitus: looking beyond peripheral neuropathy. *Eura Medicophys.* 2006;42(2):127–33.
63. Mustapa A, Justine M, Mustafah NM, Manaf H. The effect of diabetic peripheral neuropathy on ground reaction forces during straight walking in stroke survivors. *Rehabil Res Pract.* 2017;2017:9.
64. Savelberg HH, Schaper NC, Willems PJ, de Lange TL, Meijer K. Redistribution of joint moments is associated with changed plantar pressure in diabetic polyneuropathy. *BMC Musculoskelet Disord.* 2009;03(10):16.
65. Sacco IC, Picon AP, Macedo DO, Butugan MK, Watari R, Sartor CD. Alterations in the lower limb joint moments precede the peripheral neuropathy diagnosis in diabetes patients. *Diabetes Technol Ther.* 2015;17(6):405–12.
66. DiLiberto FE, Tome J, Baumhauer JF, Quinn JR, Houck J, Nawoczenski DA. Multi-joint foot kinetics during walking in people with diabetes mellitus and peripheral neuropathy. *J Biomech.* 2015;48(13):3679–84.
67. Rao S, Saltzman CL, Yack HJ. Relationships between segmental foot mobility and plantar loading in individuals with and without diabetes and neuropathy. *Gait Posture.* 2010;31(2):251–5.
68. Savelberg HH, Schaper NC, Willems PJ, de Lange TL, Meijer K. Redistribution of joint moments is associated with changed plantar pressure in diabetic polyneuropathy. *BMC Musculoskelet Disord.* 2009;10(1):16.
69. Umegaki H. Sarcopenia and diabetes: hyperglycemia is a risk factor for age-associated muscle mass and functional reduction. *J Diabetes Investig.* 2015;6(6):623–4.
70. Jang HC. Sarcopenia, frailty, and diabetes in older adults. *Diabetes Metab J.* 2016;40(3):182–9.
71. Mueller MJ, Minor SD, Sahrman SA, Schaaf JA, Strube MJ. Differences in the gait characteristics of patients with diabetes and peripheral neuropathy compared with age-matched controls. *Phys Ther.* 1994;74:299.
72. Andersen H, Gadeberg PC, Brock B, Jakobsen J. Muscular atrophy in diabetic neuropathy: a stereological magnetic resonance imaging study. *Diabetologia.* 1997;40(9):1062–9.
73. Andersen H, Gjerstad MD. Atrophy of foot muscles: a measure of diabetic neuropathy. *Diabetes Care.* 2004;27:2382.
74. Andersen H, Gadeberg PC, Brock B, Jakobsen J. Muscular atrophy in diabetic neuropathy: a stereological magnetic resonance imaging study. *Diabetologia.* 1997;40:1062.
75. Bus SA, Yang QX, Wang JH, Smith MB, Wunderlich R, Cavanagh PR. Intrinsic muscle atrophy and toe deformity in the diabetic neuropathic foot. A magnetic resonance imaging study. *Diabetes Care.* 2002;25(8):1444–50.
76. Andreassen CS, Jakobsen J, Ringgaard S, Ejksjaer N, Andersen H. Accelerated atrophy of lower leg and foot muscles—a follow-up study of long-term diabetic polyneuropathy using magnetic resonance imaging (MRI). *Diabetologia.* 2009;52(6):1182–91.
77. Almurthi MM, Reeves ND, Bowling FL, Boulton AJ, Jeziorska M, Malik RA. Reduced lower-limb muscle strength and volume in patients with type 2 diabetes in relation to neuropathy, intramuscular fat, and vitamin D levels. *Diabetes Care.* 2016;39(3):441–7.
78. Allen MD, Kimpinski K, Doherty TJ, Rice CL. Decreased muscle endurance associated with diabetic neuropathy may be attributed partially to neuromuscular transmission failure. *J Appl Physiol.* 2015;118(8):1014–22.
79. Allen MD, Major B, Kimpinski K, Doherty TJ, Rice CL. Skeletal muscle morphology and contractile function in relation to muscle denervation in diabetic neuropathy. *J Appl Physiol.* 2014;116(5):545–52.
80. Fernando ME, Crowther RG, Pappas E, Lazzarini PA, Cunningham M, Sangla KS, et al. Plantar pressure in diabetic peripheral neuropathy patients with active foot ulceration, previous ulceration and no history of ulceration: a meta-analysis of observational studies. *PLoS One.* 2014;9(6):e99050.
81. Tang UH, Zugner R, Lisovskaja V, Karlsson J, Hagberg K, Tranberg R. Foot deformities, function in the lower extremities, and plantar pressure in patients with diabetes at high risk to develop foot ulcers. *Diabet Foot Ankle.* 2015;6:27593.

-
82. Lavery LA, Armstrong DG, Vela SA, Quebedeaux TL, Fleischli JG. Practical criteria for screening patients at high risk for diabetic foot ulceration. *Arch Intern Med.* 1998;158(2):157–62.
 83. Crawford F, Anandan C, Chappell FM, Murray GD, Price JF, Sheikh A, et al. Protocol for a systematic review and individual patient data meta-analysis of prognostic factors of foot ulceration in people with diabetes: the international research collaboration for the prediction of diabetic foot ulcerations (PODUS). *BMC Med Res Methodol.* 2013;15(13):22.
 84. Fernando M, Crowther R, Lazzarini P, Sangla K, Cunningham M, Buttner P, et al. Biomechanical characteristics of peripheral diabetic neuropathy: a systematic review and meta-analysis of findings from the gait cycle, muscle activity and dynamic barefoot plantar pressure. *Clin Biomech.* 2013;28(8):831–45.
 85. Akashi PMH, Sacco ICN, Watari R, Hennig E. The effect of diabetic neuropathy and previous foot ulceration in EMG and ground reaction forces during gait. *Clin Biomech.* 2008;23(5):584–92.
 86. Sacco ICN, Akashi PMH, Hennig EM. A comparison of lower limb EMG and ground reaction forces between barefoot and shod gait in participants with diabetic neuropathic and healthy controls. *BMC Musculoskelet Disord.* 2010;11:24.
 87. Savelberg HH, Schaper NC, Meijer K. The vertical component of the ground reaction force does not reflect horizontal braking or acceleration per se. *Clin Biomech (Bristol, Avon).* 2009;24(6):527–8.
 88. Wrobel JS, Najafi B. Diabetic foot biomechanics and gait dysfunction. *J Diabetes Sci Technol.* 2010;4(4):833–45.
 89. Cavanagh PR, Bus SA. Off-loading the diabetic foot for ulcer prevention and healing. *J Vasc Surg.* 2010;52[3 Suppl]:375–435.
 90. Wu SC, Driver VR, Wrobel JS, Armstrong DG. Foot ulcers in the diabetic patient, prevention and treatment. *Vasc Health and Risk Manag.* 2007;3(1):65–76.
 91. Chantelau E, Onvlee GJ. Charcot foot in diabetes: farewell to the neurotrophic theory. *Horm Metab Res.* 2006;38(6):361–7.
 92. Rogers LC, Frykberg RG, Armstrong DG, Boulton AJ, Edmonds M, Van GH, et al. The Charcot foot in diabetes. *Diabetes Care.* 2011;34(9):2123–9.
 93. Uccioli L, Sinistro A, Almerighi C, Ciaprini C, Cavazza A, Giurato L, et al. Proinflammatory modulation of the surface and cytokine phenotype of monocytes in patients with acute Charcot foot. *Diabetes Care.* 2010;33(2):350–5.
 94. Wukich DK, Raspovic KM, Hobizal KB, Sadoskas D. Surgical management of Charcot neuroarthropathy of the ankle and hindfoot in patients with diabetes. *Diabetes Metab Res Rev.* 2016;32[Suppl 1]:292–6.
 95. Illgner U, Podella M, Rummler M, Wuhr J, Busch HG, Wetz HH. Reconstructive surgery for Charcot foot. Long-term 5-year outcome. *Orthopade.* 2009;38(12):1180–6.
 96. Christensen TM, Bulow J, Simonsen L, Holstein PE, Svendsen OL. Bone mineral density in diabetes mellitus patients with and without a Charcot foot. *Clin Physiol Funct Imaging.* 2010;30(2):130–4.
 97. Ergen FB, Sanverdi SE, Oznur A. Charcot foot in diabetes and an update on imaging. *Diabet Foot Ankle.* 2013;4:21884.
 98. Bus SA, Valk GD, van Deursen RW, Armstrong DG, Caravaggi C, Hlaváček P, et al. The effectiveness of footwear and offloading interventions to prevent and heal foot ulcers and reduce plantar pressure in diabetes: a systematic review. *Diabetes Metab Res Rev.* 2008;24[Suppl 1]:S162–80.
 99. Allet L, Armand S, de Bie RA, Golay A, Monnin D, Aminian K, et al. The gait and balance of patients with diabetes can be improved: a randomised controlled trial. *Diabetologia.* 2010;53(3):458–66.
 100. Francia P, Gulisano M, Anichini R, Seghieri G. Diabetic foot and exercise therapy: step by step the role of rigid posture and biomechanics treatment. *Curr Diabetes Rev.* 2014;10(2):86–99.
 101. Taveggia G, Villafane JH, Vavassori F, Lecchi C, Borboni A, Negrini S. Multimodal treatment of distal sensorimotor polyneuropathy in diabetic patients: a randomized clinical trial. *J Manip Physiol Ther.* 2014;37(4):242–52.
 102. Morrison S, Colberg SR, Mariano M, Parson HK, Vinik AI. Balance training reduces falls risk in older individuals with type 2 diabetes. *Diabetes Care.* 2010;33(4):748–50.
 103. van Netten JJ, Price PE, Lavery LA, Monteiro-Soares M, Rasmussen A, Jubiz Y, et al. Prevention of foot ulcers in the at-risk patient with diabetes: a systematic review. *Diabetes Metab Res Rev.* 2016;32[Suppl 1]:84–98.
 104. Kashefsky H, Marston W. Total contact casting combined with human fibroblast-derived dermal tissue in 15 DFU patients. *J Wound Care.* 2012;21(5):236.
 105. Ko M, Hughes L, Lewis H. Walking speed and peak plantar pressure distribution during barefoot walking in persons with diabetes. *Physiother Res Int.* 2012;17(1):29–35.
-