Foot deformity in diabetic neuropathy. A radiobiological and biomechanical analysis

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Introduction

Disorders of the foot are a major cause of morbidity and mortality in people with diabetes mellitus and are a leading cause of hospitalization among such patients. Diabetic patients have a 15-fold increased risk of lower-extremity amputation and as many as 40-70% of all non-traumatic lower-extremity amputations are performed on diabetic patients. Foot ulceration is frequently reported and considered one of the most serious complications of the foot. Foot ulcers precede the vast majority (85%) of lower-extremity amputations in patients with diabetes. Foot ulceration develops in approximately 15% of diabetic patients; its annual incidence is a little over 2% in diabetic patients but 5-7.5% in patients with peripheral neuropathy. The economic burden of diabetic foot ulceration is substantial. Prevention of ulceration has therefore emerged as a major goal in reducing the number of amputations and overall morbidity in these patients and in lowering health costs related to treatment of diabetic foot complications. Experts in the field have emphasized the need for more insight in the pathophysiology of diabetic foot ulceration in order to develop better prevention and management strategies.

Peripheral neuropathy, leading to a loss of protective sensation in the foot, is the key factor in diabetic foot ulceration and ultimately affects approximately 50% of patients with diabetes. Elevated plantar pressure during gait is frequently measured at sites of neuropathic ulceration and has been established prospectively as the major risk factor for plantar ulceration. In fact, it is now well-recognized that most diabetic foot ulcers are a consequence of mechanical trauma that is not recognized by the patient because of peripheral neuropathy. Deformity of the foot has been widely imputed as a major factor in elevating plantar pressure and ulceration in the diabetic neuropathic foot. There are, however, still many unproven hypotheses that try to explain how diabetic neuropathy affects foot structure and how foot deformity affects plantar pressures during walking.

One of these hypotheses is that atrophy of the intrinsic muscles in the foot secondary to motor neuropathy results in clawing and/or hammering of the toes, which causes a distal displacement of the protective plantar fat pads under the metatarsal heads (MTHs) and, subsequently, leads to elevated plantar pressures. This thesis aims at providing quantitative experimental data that supports or rejects this suggested mechanism. In this introductory chapter, different aspects related to this topic are discussed and put into a scientific context. This introduction will conclude with the aims and outline of this thesis.
Motor neuropathy and motor function

Distal symmetric polyneuropathy (DSPN) is the most common form of diabetic neuropathy. DSPN affects the left and right lower extremities in a similar way and its progression is a distal-to-proximal phenomenon ('stocking and glove' distribution), where the toes are affected before more proximal parts (lower leg) are involved. All components of the peripheral nervous system (i.e., sensory, motor, and autonomic) are involved. Motor neuropathy in diabetic polyneuropathy can be defined as the process in which segmental demyelination combined with axonal degeneration of motor nerve fibers limits the peripheral efferent stimulation of skeletal muscles in the lower and upper extremities.

Considerable debate exists on the prevalence and staging of motor neuropathy in diabetic patients. The conventional view is that DSPN is dominated by sensory and autonomic symptoms and deficits. However, this view has been largely based on clinical impressions or non-quantitative measures of muscle performance and has focused mainly on impairment at the ankle joint, where the distal-to-proximal progression of DSPN suggests that loss of function in the most distal muscles of the foot may be present before any obvious changes occur in more proximal areas.

Others have pointed out that DSPN is more a mixed motor and sensory neuropathy. Electrophysiological testing shows reduction or absence of action potentials recorded from the intrinsic muscles. In further support of this view, standardized and quantitative studies of motor performance by isokinetic dynamometry and magnetic resonance imaging (MRI) have shown muscular atrophy in the feet and lower legs and significant decreases in muscle strength varying from 16-45% in diabetic patients with neuropathy, where muscle atrophy and weakness are considered markers for motor nerve degeneration. Furthermore, significant relationships have been established between muscle atrophy, weakness, and severity of neuropathy. Finally, foot ulceration has been associated with significant impairment of motor nerve conduction velocity as sub-clinical feature of neuropathy.

Sensory neuropathy is usually emphasized in considerations of diabetic foot pathology. This is understandable because sensory neuropathy is known to be permissive for ulceration. However, the above review of the literature shows a significant motor component to diabetic neuropathy and suggests that motor neuropathy is more common in
DSPN than previously thought and develops broadly in parallel with sensory neuropathy in many patients.

**Foot deformity**

Foot deformity is commonly observed in patients with diabetes. Prevalence values of 66% have been reported. The deformities seen include callus, hallux valgus, clawing or hammering of the toes, Charcot neuro-osteoarthropathy, partial foot amputation, forefoot varus or valgus, and limited joint mobility. The prevalence of each deformity varies, with Charcot deformity not being very common but certainly the most devastating foot deformity, and callus being the most prevalent abnormality found in the diabetic foot (51%).

Claw toes and hammer toes are the most common toe deformities in patients with diabetes; prevalence values of 32% and 46% have been reported. A claw toe presents as hyperextension of the metatarsal-phalangeal (MTP) joint and hyperflexion of the proximal inter-phalangeal (PIP) and distal inter-phalangeal (DIP) joints. A hammer toe is characterized by a hyperextended MTP joint, hyperflexed PIP joint and a hyperextended or neutral DIP joint. These are the most commonly reported definitions of claw and hammer toes and will be used in this thesis. The most important characteristic of both claw toes and hammer toes from a biomechanical point of view is the hyperextended MTP joint. For this reason, we will not make a distinction between these toe deformities in this thesis and speak of a claw/hammer toe deformity.

Claw/hammer toe deformity can involve one toe or multiple toes. Progressive subluxation of the proximal phalanx and even dislocation of the MTP joint, the most severe complication, may be present. Claw/hammer toes can be classified as flexible or rigid. In a flexible state, the toes are deformed while non-weight bearing but are realigned when applying pressure on the ball of the foot (e.g. in standing). In a rigid state, joint mobility is severely compromised and the toes cannot be realigned. In time, flexible deformities nearly always become fixed. In diabetic foot practice, claw and hammer toes are generally scored in a binary fashion (present or absent), most often based on dorsal extension seen in the proximal phalanx. However, there are no known thresholds used to determine the presence or absence of deformity, and therefore its diagnosis is strongly subjective.

All the above-mentioned deformities affect normal gait and have been associated with increased levels of plantar pressure in the diabetic foot. Moreover, hallux valgus,
claw/hammer toe deformity and Charcot deformity have been identified as significant predictors of plantar ulceration showing their importance in diabetic foot disease.\textsuperscript{22,54}

**Functional anatomy**

For this thesis, the metatarsal-phalangeal joints of second and third ray are the primary regions of interest in the foot. Several structures contribute to stability at these joints, including the intrinsic and extrinsic toe muscles, the plantar aponeurosis (fascia) and the joint capsule consisting of plantar plate and collateral ligaments. Therefore, these muscles and connective tissue structures may also be involved in MTP joint instability leading to claw/hammer toe deformity. What follows is a concise description of the functional anatomy of foot and lower-leg structures that are considered relevant for the topic of this thesis. For a detailed anatomical description the reader is referred to other texts.\textsuperscript{15,16,37,58,74,85,86,100}

The intrinsic and extrinsic muscles controlling the lesser toes (2-4) are the flexor digitorum longus (FDL), flexor digitorum brevis (FDB), extensor digitorum longus (EDL), extensor digitorum brevis (EDB), the plantar and dorsal interossei, and the lumbricals. The FDL muscle passes plantar to the MTP joint in a groove created by the joint capsule and inserts into the distal phalanx. The FDL is a strong flexor of the DIP joint. The FDB inserts into the middle phalanx and flexes the PIP joint. There is no insertion of these muscles on the proximal phalanx, so the flexor influence at the MTP joint is minimal.\textsuperscript{33,57} The flexors are active throughout the second half of stance phase in walking to resist extension of the MTP joint and the IP joints, thereby increasing the surface area contacting the ground and the rigidity of the foot.\textsuperscript{49,54,77,96} The EDL muscle is part of the dorsal extensor expansion\textsuperscript{60,86} (also called extensor sling\textsuperscript{33} or hood\textsuperscript{57}) at the MTP joint and inserts into the middle and distal phalanges. It effectively extends the MTP joint and has little extensor power over the IP joints.\textsuperscript{33,34} EDL pull produces a passive tension in the long and short flexors resulting in IP joint flexion while the EDL extends the MTP joint.\textsuperscript{57} The EDL is active from just before toe-off until just after heel strike, in order to lift the toes to clear the ground during swing phase.\textsuperscript{49,54,77,96} The EDB is a thin muscle that joins the tendons of the EDL distally to form the extensor expansion\textsuperscript{57,86} and inserts into the middle phalanx. The EDB assists the EDL in phalangeal extension at the IP and MTP joints.\textsuperscript{50,57} The EDB is active during the second half of forefoot contact in walking.\textsuperscript{106}

The deep intrinsic muscles (interossei and lumbricals) and their function have only rarely been studied. The tendons of the interossei muscles pass plantar to the axis of the MTP joint. The tendons insert into the plantar ligament and on the base of the proximal
Accounts vary as to whether there are connections to the extensor expansion. The interossei flex the proximal phalanx at the MTP joint^ and may extend the IP joints. Abduction and adduction of the toes is also controlled by the dorsal and plantar interossei, respectively. The lumbricals are unique muscles in that they originate from the tendons of the FDL. The lumbricals pass plantar to the MTP joint and curve sharply dorsally to insert partly in the proximal phalanx and partly in the extensor hood. On isolation, the lumbricals contribute to MTP joint plantar flexion and IP joint extension. In the intact foot, they are unable to contribute to the flexor torque at the MTP joint by virtue of their attachment to the FDL; the force applied by the lumbricals would be subtracted from the flexor force. The lumbricals can, however, serve to equilibrate the flexor and extensor torques across the MTP and IP joints and contribute to stabilization by reducing the flexor pull at the MTP joint (slackening of the FDL) while simultaneously increasing the extensor torque across the IP joints. Dynamically, the deep intrinsic muscles of the foot are mid to late stance phase muscles that function as stabilizers of the MTP joints before push-off, and help maintain the toes flat on the ground until lift-off has occurred. The actual dynamic function of the interossei and, in particular, the lumbricals are, however, far from clear.

The plantar aponeurosis is considered one of the most important soft-tissue structures in the foot as it supports the longitudinal arch of the foot and contributes to MTP joint stability. The plantar aponeurosis is a complex connective tissue structure consisting of longitudinally oriented collagen and elastic fibers. It originates from the postero-medial calcaneal tuberosity. The most prominent and important central component of the aponeurosis divides into five bands at the mid-metatarsal level as it courses distally, with each band dividing into a deep tract inserting into the plantar plate and a superficial tract inserting into the skin. According to the windlass mechanism described by Hicks, extension of the MTP joint during the propulsive phase of gait causes the plantar aponeurosis to tighten and to draw the calcaneus and the MTH together resulting in a raised longitudinal arch and rearfoot supination, thereby making the foot a stable rigid lever in propulsion. On weight bearing, during standing or foot flat in gait, the arch tends to flatten, increasing tension in the plantar aponeurosis. This tension unwinds the windlass causing plantar flexion at the MTP joint. This stabilizing action disappears when the plantar aponeurosis is ruptured.

The joint capsule consisting of the plantar plate and the collateral ligaments is a central structure of the MTP joint with many attachments to other soft-tissue structures. The plantar plate is a firm but flexible fibro-cartilage structure of predominantly type 1 collagen with no elastin present. Distally, the plate is firmly attached to the proximal phalanx. The proximal attachments of the plantar plate are the collateral ligaments and the plantar
aponeurosis. The collateral ligaments are fibrous structures along the medial and lateral surfaces of the MTP joint that form the attachment of the plantar plate to the MTHs. The collateral ligaments also insert into the proximal phalanx. The plantar plate functions by sustaining both tensile and compressive loads. Claw/hammer toe deformity in combination with substantial plantar pressures during gait may cause stretching or attenuation and, eventually, rupture of the plantar plate or the plantar aponeurosis.

The subcutaneous plantar fat tissue serves as primary source of cushioning in order to protect the skin and more deeply located bony and soft-tissue structures from the forces that are transmitted through the foot during standing and gait. The sub-calcaneal fat pad is relatively thick (2 cm), tightly bound with fibroelastic septae arranged in a closed-cell configuration (chambers) and thus not very mobile. The fat-pad cushions located under the MTHs are considerably thinner. They are entrapped by vertical fibers that arise from the fibrous flexor sheaths and plantar ligaments and insert in the plantar skin. The sub-MTH fat-pad cushions are mobile due to their investment in the tendons of the toe flexors and their attachment to the plantar ligaments which connect with the proximal phalanx. Therefore, these cushions are pulled distally and around the MTHs in cases of claw/hammer toe deformity.

Theories of toe deformity and elevated plantar pressure in the diabetic foot

One of the most commonly referenced theories explaining elevated plantar pressures in diabetic feet is related to claw/hammer toe deformity. Historically, this deformity is believed to be caused by an imbalance between the intrinsic and extrinsic muscles controlling the toes resulting from intrinsic muscle atrophy secondary to motor neuropathy. Subsequently, this deformity is suggested to cause distal displacement of the sub-MTH fat pads exposing the MTHs to increased levels of plantar pressure during walking. In the presence of sensory neuropathy, this may cause plantar ulceration (Figure 1, see Appendix, p. 179).

The problem is thought to lie in the inability of the intrinsic muscles, due to atrophy and weakness, to balance the flexor and extensor pulls of the extrinsic muscles across the MTP and IP joints. By virtue of their insertions into the middle and distal phalangeal bones, the flexor muscles have a greater mechanical advantage over the extensors at the IP joints, but minimal flexor force at the MTP joint. The extensors, through their investment in the extensor hood, have a greater mechanical advantage over the flexors at the MTP joint, but no real extensor power at the IP joints. If the
interossei and lumbral muscles are functioning correctly, they can compensate for this by flexing at the MTP joint and by simultaneously ‘slackening’ the flexor pull while contributing to extension across the IP joints. However, with loss of intrinsic muscle function, the long toe flexors (FDL) are opposed only by the decidedly weaker intrinsics dorsally at the IP joints, whereas the long extensors of the toes (EDL) are unopposed by the intrinsics at the MPT joint. Over time, this mismatch will result in hyperextension at the MTP joint and hyperflexion at the IP joints (Figure 1, see Appendix, p. 179).

Although not reported specifically for the diabetic foot, some authors believe that simultaneous contractures of the extrinsic toe flexor and extensor muscles primarily cause the imbalance in agonist and antagonist muscle action at the MTP and IP joints forcing the toes in a clawed/hammered position. In any case, as the deformity sets in, the interossei muscles will subluxate dorsally and pass through or even dorsal to the MTP joint axis, loosing their flexion effect, and accentuating the deformity. The lumbricals do not subluxate dorsally because they are tethered by the deep transverse metatarsal ligament. However, MTP joint hyperextension may also render these muscles less efficient in flexing this joint, aggravating the hyperextension deformity. Because the sub-MTH soft-tissue cushions that help to reduce MTH pressures are invested in the flexor tendons and originate from the plantar ligaments that are firmly attached to the proximal phalanges, hyperextension of the MTP joint in claw/hammer toes is believed to displace these pads distally, leaving the MTHs ‘exposed’ to bear increased plantar pressures (Figure 1, see Appendix, p. 179).

Several other factors not related to muscle atrophy and imbalance that might cause claw/hammer toe deformity have been reported. Restrictive footwear has been widely reported to mechanically deform the toes into a clawed or hammered appearance. Taylor et al. have shown discontinuity of plantar aponeurosis on MRI indicating rupture in diabetic patients with dorsiflexed toes and have suggested that non-enzymatic glycosylation of connective tissue may render the plantar aponeurosis less compliant and more prone to rupture. By sequentially sectioning claw and hammer toes in non-diabetic cadaver feet, Myerson and Sheriff showed the release of collateral ligaments at the MTP joint to have the most significant effect on joint mobility and realignment of the toes, suggesting an important role for these structures in toe deformity pathogenesis.

Objective evidence that supports or rejects the muscle balance theory of claw/hammer toe deformity does not exist. Only recently parts of this theory were studied quantitatively. Significant degrees of intrinsic muscle atrophy have been shown in neuropathic diabetic patients and the degree of atrophy was found to correlate significantly with the severity of
neuropathic impairment. A comprehensive analysis of the above-mentioned mechanisms is lacking in the scientific literature. The quantitative in-vivo examination of intrinsic and extrinsic muscle status and plantar fat-pad thickness combined with assessments of plantar aponeurosis and MTP joint capsule and the measurement of barefoot plantar pressures in neuropathic diabetic patients with claw/hammer toe deformity may advance our basic understanding of the pathogenesis of foot deformity and further elucidate the mechanisms that eventually lead to breakdown of the skin.

**Imaging and plantar pressure measurement in the diabetic foot**

*In-vivo* imaging tools have become increasingly used for studying the diabetic foot in the last two decades. Quantitative assessments of changes in anatomical structure and deformity in the diabetic foot have been reported using ultrasound, radiography, computed tomography (CT), and magnetic resonance imaging (MRI). The plantar soft-tissue structures in the heel and forefoot have been studied by several authors using ultrasound and CT. The bony configuration in the foot has been examined with radiography and CT. Detailed studies of the muscles in the foot and lower leg of diabetic patient have been performed using MRI.

Due to its inherent superiority in tissue contrast, MRI is considered the method of choice for evaluating soft-tissue structures in the foot, including fat, muscle and connective tissue. Bone tissue is clearly distinguishable on MRI images so that the configuration of the joints in the foot can be assessed too using this technique. Furthermore, MRI does not involve the use of ionizing radiation and has no known harmful effects on the patient under examination. Although MRI is, at present, not cost-effective in the clinical diagnosis of foot structure changes or deformity in patients with diabetes, it can be ideally used for research purposes with the goal of establishing associations between structural abnormalities and, in combination with plantar pressure measurements, for determining the relationships between structure and function in the diabetic foot.

Already in the early 1960's, Brand and his colleagues emphasized the role of repetitive plantar pressures in causing foot ulceration. Since these early reports, a number of retrospective and prospective studies have shown that barefoot plantar pressures measured during gait are elevated in diabetic patients with neuropathy and that these elevated pressures are a major risk factor for plantar ulceration. Variables that are commonly used in dynamic pressure analysis are the maximum pressure measured by any sensor of the pressure system in contact with the foot (peak pressure) and the integral of the peak pressure over time (pressure-time integral). Normative data on barefoot peak pressure
is not available. In healthy non-diabetic individuals values may range from zero to about 600 kPa across all regions in the foot (= mean ± 2 standard deviations from study by Rosenbaum\textsuperscript{11}). Average peak pressures reported for diabetic patients using the same pressure measuring device (EMED, Novel, Munchen, Germany) vary from around 450 kPa to about 1000 kPa, dependent on the presence of neuropathy, ulceration and foot deformity\textsuperscript{9,11}, with patients exceeding the 1275 kPa measuring limit of the platform not being uncommon. It should be stressed that in this thesis we refer to pressures measured perpendicular to the supporting surface (normal stress); the measurement of shear stress has to date not been possible in commercially available systems.

Although barefoot plantar pressures measured in a laboratory can predict the risk of ulceration in the diabetic foot, it does not predict the load that the foot is exposed to in normal daily living, which is mostly dependent on activity level and footwear.\textsuperscript{30} Therefore, barefoot plantar pressures cannot predict the occurrence of ulceration. There may be patients with low barefoot pressures that ulcerate because they wear inferior footwear or are very active, and there may be patients with high barefoot pressures who do not ulcerate because they are sedentary or wear effective pressure-reducing footwear. Because most patients wear shoes and probably ulcerate while wearing these shoes, the measurement of pressure inside the shoe is an important extension of barefoot pressure measurement. In-shoe plantar pressures can be used to assess the effect of footwear on reducing pressure at high-risk areas in the foot and therefore refine the process of footwear prescription to diabetic patients with foot problems with the ultimate goal of preventing (recurrence of) ulceration.

Summary

The above review of the literature shows that several (so far unproven) hypotheses have emerged in the last four decades trying to explain how claw/hammer toe deformity develops and how this deformity affects plantar pressures in diabetic patients with peripheral neuropathy. It is striking to see that many early-developed theories, which have been based mainly on clinical observation and anecdotal evidence, have been considered by many authors as accepted mechanisms in diabetic foot ulcer etiology while quantitative experimental data that may prove or reject these theories is largely absent. Recently, several studies have emerged in which parts of the above-mentioned mechanisms have been examined quantitatively, but many unresolved aspects remain. Quantitative techniques such as MRI and plantar pressure measurement are available to objectively detect changes in muscle status, soft-tissue integrity and biomechanical function, which could provide insight in the sequence of events that are believed to be important in the genesis of plantar ulcers.
General introduction

Aims

The general aim of this thesis was to provide insight in the associations between structural changes in the foot and their effects on foot function in diabetic patients with peripheral neuropathy. Specific aims were to determine in these patients (1) the association between peripheral neuropathy and intrinsic muscle atrophy, (2) the role of intrinsic and extrinsic muscle factors and connective tissue structures in clawing and/or hammering of the toes, (3) the association between changes in foot structure and dynamic plantar pressures, and (4) the effect of custom-made insoles on pressure and load distribution during gait.

Outline of this thesis

In chapter 2, a study is presented in which the degree of intrinsic muscle atrophy is quantified using a special MRI technique in diabetic patients with peripheral neuropathy and compared with matched healthy non-diabetic subjects. Intrinsic muscle atrophy is also associated with joint configuration in the forefoot in order to define its role in claw/hammer toe deformity.

When using MRI for assessing foot structure it is imperative that reproducible data is obtained. In chapters 4, 5, and 7 MRI is used to assess intrinsic muscle atrophy, plantar fat-pad thickness, and joint configuration in the diabetic neuropathic foot. The intra-observer and inter-observer reliability of these assessments is described in chapter 3.

Several components are believed to be involved in the pathogenesis of claw/hammer toe deformity in neuropathic diabetic patients. These include intrinsic muscle atrophy leading to muscle imbalance, and abnormalities in plantar aponeurosis and MTP joint capsule. In chapter 4 we evaluate these factors using MRI in a group of neuropathic subjects with claw/hammer toe deformity and in a matched group without deformity.

The effect of claw/hammer toe deformity on the plantar fat pads and on dynamic barefoot plantar pressures is described in chapter 5 and chapter 7, respectively. In chapter 5, fat-pad thickness under the metatarsal heads and the proximal phalanx is measured in a group of neuropathic patients with claw/hammer toe deformity and compared with a matched group of patients with normally aligned toes. The ratio of sub-MTH and sub-phalangeal fat-pad thickness is introduced as measure to identify fat-pad displacement.

Barefoot plantar pressures in neuropathic diabetic patients are often collected on multiple repeated trials of walking across a platform using a 1-step or 2-step gait approach. In
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Chapter 6 we describe the validity and reproducibility of using a 1-step or 2-step protocol in comparison with a 3-step reference protocol for obtaining barefoot plantar pressure data in the diabetic neuropathic foot.

In the same sample of subjects described in chapter 5, the plantar pressures measured during barefoot walking are described in chapter 7. Peak pressures measured at the MTHs are related to the degree of toe deformity and plantar fat-pad changes in order to obtain quantitative support for the importance of this deformity as risk factor for plantar ulceration in neuropathic feet.

Where chapters 2 through 7 focus on providing more insight in the factors that may lead to elevated plantar pressures in the diabetic neuropathic foot, chapter 8 deals with interventions meant for reducing plantar pressures and risk of (recurrent) ulceration. By measuring in-shoe plantar pressures, the mechanical action of custom-made insoles as compared with simple flat insoles is evaluated in neuropathic patients with foot deformity.

Finally, in chapter 9 a general overview and discussion of the findings in the previous chapters is presented followed by a brief discussion on the clinical implications of these findings and some recommendations for future research.
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References


10. Armstrong DG, Lavery LA: Plantar pressures are higher in diabetic patients following partial foot amputation. *Ostomy Wound Manage* 44:30-2, 34, 36 passim, 1998


16. Bojsen-Moller F, Flagstad KE: Plantar aponeurosis and internal architecture of the ball of
the foot. *J Anat* 121:599-611, 1976


Suppl 1:S12-6, 1996

Dynamic foot pressure and other studies as diagnostic and management aids in diabetic


study of risk factors for diabetic foot ulcer. The Seattle Diabetic Foot Study. *Diabetes
Care* 22:1036-42, 1999

W.B. Saunders Co., 1982, p. 622-658

micro-haemorrhage in the feet of diabetic patients with a history of ulceration. *Diabet Med*
13:973-8, 1996


nerve conduction velocity predict foot problems in diabetic subjects over a 6-year outcome
period? *Diabetes Care* 25:2010-5, 2002


29. Cavanagh PR, Morag E, Boulton AJM, Young MJ, Deffner KT, Pammer SE: The

30. Cavanagh PR, Ulbrecht JS, Caputo GM: The biomechanics of the foot in diabetes

abnormalities in the feet of patients with diabetic neuropathy. *Diabetes Care* 17:201-9, 1994

32. Corbin DOC, Young RJ, Morrison DC, et al.: Blood flow in the foot, polyneuropathy and


61. Lippmann HI: Must loss of limb be a consequence of diabetes mellitus? *Diabetes Care* 2:432-6, 1979


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