Chapter 9

General discussion
As a complication of diabetes mellitus, diabetic foot disease is a well-established concept in which vascular, neurological, and biomechanical factors conspire to cause disorders that have a great impact on patient health, mobility, life-expectancy, and quality of life, and are a significant economic burden. The diabetic foot has in the last few decades received an increased amount of attention from both physicians and basic researchers. However, while the majority of studies on the diabetic foot have focused on treatment of ulceration, many aspects of its pathogenesis are still far from clear. The recent introduction of advanced technologies in the assessment of diabetic foot pathology such as \textit{in-vivo} imaging and biomechanical modeling has made it possible to study the factors believed to be responsible for foot ulceration in more detail. This thesis focused on several aspects of the pathogenesis of foot deformity, which is common in patients with diabetes, and on its role in elevating plantar pressures in patients with loss of protective sensation due to peripheral neuropathy. In particular, the putative chain of events linking motor neuropathy, intrinsic muscle atrophy, claw/hammer toe deformity, plantar fat-pad changes and increased levels of plantar pressures was analyzed on a quantitative basis using magnetic resonance imaging (MRI) and barefoot plantar pressure measurements.

\textbf{On the theory of toe deformity and elevated plantar pressures}

The studies in this thesis clearly show changes in the volume of the intrinsic muscles in the feet of diabetic patients with peripheral neuropathy. Both in chapter 2 and 4 we demonstrate remarkable degrees of intrinsic muscle atrophy, with a mean loss of more than 70\% of muscle tissue in neuropathic patients compared with matched healthy controls (chapter 2) and 10 of 18 neuropathic patients classified as having severe degrees of atrophy or almost no muscle tissue left (chapter 4). These findings support earlier studies showing significant muscle atrophy in the feet of neuropathic diabetic patients\textsuperscript{16,34} and lead us to conclude that substantial evidence is now available that loss of intrinsic muscle volume is a secondary effect of peripheral neuropathy in diabetes.

Distal displacement of the sub-metatarsal head (MTH) plantar fat pads has been suggested to result from toe deformity and cause elevated plantar pressures in the diabetic foot\textsuperscript{22,24,31}, but no study had ever quantified fat-pad displacement. We introduced a method to precisely address this topic using sagittal plane MR images of the forefoot. By dividing the measured fat-pad thickness under the MTH with the fat-pad thickness measured under the proximal phalanx, a thickness ratio indicating displacement was calculated. Thinner sub-MTH fat pads, thicker sub-phalangeal fat pads, and thus a lower thickness ratio were found in neuropathic patients with claw/hammer toe deformity when compared with matched patients with normally aligned toes (chapter 5). The average thickness ratio in the subjects

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with deformity was outside the normal limits (mean ± 2 standard deviations) for thickness ratio measured in the control subjects, demonstrating the remarkable difference between the subjects groups. Barefoot plantar pressures measured at the MTHs were nearly twice as high in the patients with toe deformity when compared with the patients without deformity. Together with the strong and significant associations found between variables of foot structure and foot function, the data presented in chapters 5 and 7 strongly support the long-held belief that claw/hammer toe deformity causes fat-pad displacement and elevated plantar pressures in the diabetic foot. These conditions increase the risk for plantar ulceration, which is supported by data showing that pressure ulcers indeed occur most frequently at sites of bony prominence, usually under the MTHs\(^7\), and by data showing that claw/hammer toe deformity is a significant independent predictor of plantar ulceration in patients with diabetes.\(^{14}\)

Although several other studies have shown a relationship between foot structure and plantar pressures in the diabetic foot\(^{26}\), including the association between sub-MTH tissue thickness and elevated plantar pressures\(^{1,39}\), ours was the first study to indicate that distal fat-pad displacement is a mechanistic factor in the association between claw/hammer toe deformity and increased levels of forefoot plantar pressure. Additionally, the explained variance of peak pressures by metatarsal-phalangeal (MTP) joint hyperextension (54%) is, to the best knowledge of the author, the largest found for a single factor to date.\(^ {1,2,26,39}\) This is rather surprising since the measure of toe angle is a static non-weight bearing measure, whereas plantar pressure is measured under dynamic weight-bearing conditions. The results suggest that assessments of foot structure may not necessarily have to be performed under the same circumstances as dynamic functional assessment, although we do not yet know how much the addition of dynamic factors may have further increased the level of explained variance in plantar pressure in our group of neuropathic subjects.\(^ {25}\)

The only part of the hypothesis regarding how motor neuropathy is related to elevated plantar pressure that was not supported by our results concerned the role of intrinsic muscle atrophy and muscle imbalance in explaining claw/hammer toe deformity. In chapter 2 we showed that intrinsic muscle atrophy does not necessarily imply clawing/hammering of the toes. The data presented in chapter 4 was in agreement with these findings. We further showed in chapter 4 that neither intrinsic muscle atrophy nor an imbalance between the intrinsic and extrinsic muscles could discriminate patients with claw/hammer toes from patients with normally aligned toes. These findings are contrary to the long held belief that intrinsic muscle atrophy is the causative factor in MTP joint instability leading to claw/hammer toe deformity.\(^ {12,21,22,24,33}\) Therefore, we suggest that this mechanical theory should be reconsidered. Based on abnormalities found in connective tissue structures involved in MTP joint stability, such as the plantar plate, collateral ligaments and the
plantar aponeurosis, which may be related to non-enzymatic glycosylation of proteins\(^{27,35}\), we suggested that these components may play a role in explaining why one diabetic patient develops deformity and another does not. However, we also found these factors to lack discriminatory power, leaving us with the provisional conclusion that claw/hammer toe deformity is idiopathic in nature, a conclusion that is supported by others stressing that the cause of claw/hammer toe deformity is often not known.\(^9,19\)

It is interesting to consider alternative mechanisms that were not investigated in this thesis which may cause a toe to become clawed or hammered in the diabetic neuropathic foot. In a comprehensive mechanical analysis of finger deformity in the hand, Brand and Hollister\(^{15}\) discuss the effects of removal or paralysis of muscles in the hand on the balance of joint moments when an external load is applied to the pulp of the finger tip. Because one muscle/tendon complex cannot itself control two finger joints when an external load is applied, additional muscles need to aid in balancing the external moment at more proximal joints. Without this aid, due to paralysis or atrophy, proximal joints will go into extension. To compensate for this, tension is added in the muscle controlling the distal joint but this will produce too much flexor torque at the distal joint. Over time, these unbalanced forces result in deformity. In the toes, the applied external loads are higher and more repetitive than in the hand. Therefore, in analogy to the mechanism in the hand, we proposed in chapter 4 that the repetitive application of increased pressures in the toes in a neuropathic patient with significant intrinsic muscle atrophy may result in joint moments at the MTP joint that cannot be sufficiently opposed, which, over time, will result in hyperextension of the MTP joint and flexion of the proximal inter-phalangeal joint (PIP). In support of this hypothesis, Coughlin and Mann\(^{19}\) state that “…the most important factor is probably the reactive force of the foot against the ground, pushing the MTP joints into extension.” Future studies should accept or reject this alternative theory of claw/hammer toe deformity pathogenesis in the diabetic foot. We suggest that a study designed at the long-term follow-up of a large group of neuropathic patients with normally aligned toes and known plantar foot pressures, and with the development of claw/hammer toe deformity as primary outcome, may provide the answer.

Reliability of measures of foot structure and function

The assessment of foot structure and function using quantitative methods such as MRI and plantar pressure measurement, whether in healthy individuals or in diabetic patients with peripheral neuropathy, requires that reliable data be obtained - since the validity of any result is limited by its reliability. Because we introduced several new measures of diabetic foot structure using MRI, we determined the intra-observer and inter-observer agreement of
these measurements. The reproducibility of obtaining barefoot plantar pressures in neuropathic diabetic patients had not been determined before, despite the wealth of plantar pressure studies performed in this group of patients. The results in chapters 3 and 6 show that assessment of intrinsic muscle atrophy, joint configuration, fat-pad thickness as well as barefoot plantar pressures can be done in a reproducible manner. This provides methodological support for the results obtained in the group comparison studies described in chapters 4, 5, and 7 and suggests that the conclusions drawn from these studies are methodologically robust. It is interesting to see that the intra- and inter-observer agreement for foot structure assessment using MRI is higher than reported for computed tomography\textsuperscript{18} and plane radiographs\textsuperscript{30}, suggesting that the superior tissue-contrast in MRI compared to other imaging techniques facilitates the measurement of soft- and hard-tissue structures in the neuropathic diabetic foot.

For many years, different approaches have been used in the assessment of barefoot plantar pressure in non-diabetic individuals as well as in diabetic patients, including a 1-step, 2-step, 3-step, and midgait approach. In chapter 6 we showed that, despite loss of kinesthetic information, neuropathic patients may be as consistent as non-diabetic healthy subjects in walking across a pressure platform for obtaining representative estimates of plantar pressure. We also demonstrated that reducing the number of steps before contact is made with the platform does not result in methodologically flawed results in this patient group. This finding is important in view of the risk for ulceration in patients with loss of protective sensation, who are advised not to walk on bare feet. Considering this result, it would be interesting to know what the effect of early termination of the follow-through after platform contact is on the validity and reproducibility of pressure data. We are currently investigating 1-step, 2-step, and 3-step termination protocols, in the first instance using non-neuropathic healthy volunteers.

**Plantar pressure measurements and footwear prescription**

This thesis shows that claw/hammer toe deformity is an important component in elevating plantar pressure in the foot, which emphasizes its role in increasing the risk of plantar ulceration. However, the deformity does not necessarily predict ulceration, because a clear threshold of barefoot plantar pressure above which ulceration occurs has not been established, despite several attempts to do so.\textsuperscript{8,17} In fact, barefoot plantar pressures have been found to be only 70\% sensitive and 65\% specific of causing ulceration.\textsuperscript{8} The peak barefoot pressures measured at the MTHs in the neuropathic patients studied in this thesis varied from 294 to 1257 kPa (chapters 7 and 8). But whether the patient with foot deformity and a peak pressure of 1257 kPa will ulcerate and the patient with no deformity
and a peak pressure of 294 kPa will not, is uncertain because barefoot plantar pressures do not predict the load that the foot is exposed to in normal daily living, which is dependent on activity level and footwear.\textsuperscript{17} These limitations of applying measured barefoot pressures to clinical decisions outcomes highlight the importance of measuring in-shoe plantar pressures in diabetic patients.

These results also reflect the importance of wearing protective and pressure-relieving footwear for primary and secondary ulcer prevention. In this thesis, we investigated the mechanical action of commonly prescribed custom-made insoles for diabetic feet by comparing pressure and load distribution while wearing both custom-made and flat insoles (chapter 8). We introduced an algorithm to assess the pattern in load transfer of one insole compared with another and showed that a built-in medial longitudinal arch support and cupping of the heel in custom-made insoles has a substantial load redistributing effect on the foot. On average, the custom-made insoles significantly reduced peak pressure at target sites in the foot (e.g. first MTH) but had a much larger effect in regions less susceptible for injury (e.g. heel). The finding that a third of patients wearing the particular custom-made insoles used in the study did not show reduced plantar pressures at the primary target area (first MTH) not only shows that fabricating efficacious devices in a predictable manner is very difficult, but also that reporting mean effects in these kind of comparison studies does not tell the full story. An individual approach is clearly warranted. But even where substantial pressure reductions with custom-made insoles are achieved, it should be kept in mind that only when the ulceration threshold has been defined in terms of a given pressure value for a given region it will be possible to prescribe insoles with precision.\textsuperscript{17} In the meantime, the efficacy of insoles can be judged only by whether an ulcer or skin abrasion can be prevented. It is believed, however, that the assessment of pressure and load distribution in combination with assessments of foot structure and biomechanical modeling will further improve our understanding of the principles of footwear prescription resulting in more appropriate interventions in the neuropathic patient with foot deformity.

**Staging and severity of motor neuropathy**

It has been suggested that motor neuropathy is more common and more profound in diabetic polyneuropathy than previously thought and may develop broadly in parallel with sensory neuropathy in many patients.\textsuperscript{4,13,20} These observations are based on recent data showing remarkable degrees of atrophy in the lower leg and in the intrinsic foot muscles, significant loss of strength in the muscles crossing the ankle joint, as well as a significant relationship between motor function and neuropathic severity.\textsuperscript{5,6,16,34} The remarkable loss of intrinsic muscle tissue as presented in chapters 2 and 4 support these suggestions. All
neuropathic subjects studied in this thesis for whom we examined the intrinsic foot musculature showed at least some degree of intrinsic muscle atrophy. *In-vivo* imaging tools such as MRI offer a unique opportunity to examine the most distal muscles in the foot in the same manner as quantitative testing (e.g. biothesiometry or monofilaments) can be used to assess protective sensation in the most distal foot regions. This is a step forward with respect to more traditional methods of assessing motor function for example by observing the presence of foot drop, inability to stand/walk on heels or toes, palpation of muscle bellies, or manual muscle testing, which are mostly non-quantitative or focus mainly on the muscles at the ankle joint. The number of subjects used in this thesis is too small to draw conclusions on the relative staging of motor and sensory neuropathy in diabetic polyneuropathy. A nerve-length dependency, however, has been demonstrated with more muscle atrophy present in the intrinsic muscles of the foot than in the extrinsic muscles located in the lower leg (*chapter 4*), which supports data from Andersen et al. Larger studies focused on the quantitative assessment of motor and sensory function in both distal and proximal regions should confirm or refute the suggested parallel development of motor and sensory neuropathy in the progress of diabetic neuropathy.

**Claw/hammer toe deformity assessment**

In clinical diabetic foot practice, claw and hammer toes are most often scored in a binary fashion (present or absent). It is unclear, however, which thresholds are used to determine the presence or absence of deformity. In fact, normal ranges of MTP and IP joint angles with which measures in the diabetic foot could be compared are not known. Standardized simple tools or methods that measure the angles in the MTP and IP joints currently do not exist. In a sectioning study of cadaver feet with claw and hammer toes by Myerson and Sheriff, the initial average MTP joint angles were 65, 60, 50, and 40 degrees extension in the second, third, fourth, and fifth MTP joint, respectively, as measured using goniometry, with a suggested precision of 5 degrees. From lateral weight-bearing radiographs, Smith et al. used the level of elevation of the PIP joint above the MTH to classify claw toes. They were graded as mild, moderate, or severe, respectively, when the PIP joints were seen below, through, or above a line drawn parallel to the foot sole and touching the top of the MTH. In our studies we used contact digitization on the dorsal surface with a three-dimensional pointer method (*chapter 2*) and sagittal plane MR images (*chapters 3, 4, 5, and 7*) to determine joint configuration in the forefoot. Using both methods, we classified claw/hammer toe deformity with respect to 95% normal limits (mean ± 2 standard deviations). This resulted in second ray MTP joint angles >54 degrees being classified as deformed using contact digitization. Using MRI, toe angles >13 degrees extension in the second or third ray were classified as deformed. However, all of the above analyses lack the
simplicity, number of subjects or cost-effectiveness to obtain reference values for normal
toe configuration that may be used in a clinical setting to assess claw/hammer toe deformity
in a valid and reliable way. The use of clinical tools such as goniometry may be validated
by comparison with in-vivo imaging techniques. Threshold values defining ‘clawed’ or
‘hammered’ using goniometric measures may then be established in population-based
studies. With such a classification system, the prevalence and incidence of these
deformities in different patient populations as well as healthy subjects may be determined
in a valid and reliable manner.

Interventions

A strong association was found between claw/hammer toe deformity and elevated plantar
pressure. This implies an increased risk for plantar ulceration, and suggests that strategies
should be developed for preventing this deformity from occurring in patients with loss of
protective sensation. Although foot exercises aimed at establishing a balance in muscle
action at the toes could be devised, the findings from chapter 4 suggest that these strategies
may at present be considered elusive until the key permissive factor in causing
claw/hammer toe deformity has been defined. Conservative treatment of patients with
claw/hammer toe deformity should be focused at reducing plantar pressures in the central
MTH regions of the foot. Custom-molded insoles, metatarsal pads, and rocker-bottom
footwear have been shown to have a significant positive effect on pressure in these
areas.\textsuperscript{3,23,28,29,36} Injections of liquid silicon in the areas under the MTHs have been shown to
give significant pressure relief that was maintained up to 12 months after treatment.\textsuperscript{37,38} If
shown to be medically safe, this procedure may offer a useful way to reduce plantar
pressures at MTH prominences caused by the distal displacement of the fat pads as a result
of toe deformity. Corrective surgery of toe deformity is not commonly performed in the
diabetic foot due to the presence of neuropathy, vascular complications, and a higher risk
for infection. But even if surgery is considered for rigid claw/hammer toe deformity, it may
be questioned, due to the multiple developed soft-tissue contractures in these toes, whether
with realignment of the toes the fat-pad cushions are repositioned under the MTHs and
regain proper function in protecting deeper structures.

Some limitations and further recommendations

This thesis consists of a series of cross-sectional studies from which cause-and-effect
relationships between foot structure and function in the neuropathic diabetic patient can not
be established. However, certain factors lead us to believe that cause-and-effect can at least
be suggested in several of the associations found. First, in the recruitment of subjects described in chapters 4, 5, and 7 we aimed at creating two groups that were similar in demographic and disease-related factors, such as age, gender, diabetes duration, severity of neuropathy, and differed primarily on one factor - the degree of MTP joint extension. Furthermore, in the examination of factors involved in MTP joint stability we chose to focus on flexible toe deformity, which is a pre-stage of more rigid deformity, because we believed that any difference found at this level would not be the result of disuse or stretching, as may be the case in rigid deformity. Finally, the theory on the pathogenesis of toe deformity and elevated plantar pressure describes a chronological chain of mechanical events that seems logical and not reversible in many aspects considering the known anatomical relationships in the foot. This supports us in our belief that, at least for the association found between deformity and elevated plantar pressure, deformity is the initiating event causing fat-pad displacement and, as a result, elevated plantar pressure.

The long-term follow-up of patients with flexible toe deformity or patients that may be ‘at risk’ of toe deformity may provide a definitive identification of the factor(s) involved in causing claw/hammer toe deformity and elevated plantar pressures in the diabetic foot. However, this approach is not free of limitations either. Several other structural changes or deformities that may develop over time could affect the sought after relationship between muscle imbalance, toe deformity, and elevated plantar pressure. Furthermore, because the natural history of claw/hammer toe deformity is not known, the patient who is suspected of risk for developing deformity may be very difficult to identify, requiring a large study that may be too costly, certainly if MRI and plantar pressure measurements are an integral part of the investigation. We suggest that cross-sectional studies incorporating additional techniques with which muscle or connective tissue can be examined in more detail such as MR spectroscopy, muscle biopsy, or histochemical examination, may further improve our basic understanding of how claw/hammer toes develop in diabetic neuropathic feet.

The conclusions in the studies of this thesis were based on results obtained in a relatively small sample of neuropathic subjects. Although this may be considered a limitation, many differences in the comparison of experimental and control groups were so substantial and consistent, that sufficient statistical power was obtained, despite these relatively small numbers. This specifically concerned the 73% loss of intrinsic muscle cross-sectional area found in neuropathic patients when compared with matched health controls (chapter 2), the 58% reduction in sub-MTH fat-pad thickness and 65% reduction in thickness ratio in neuropathic subjects with claw/hammer toe deformity compared with matched neuropathic controls (chapter 5), and the 1.7 fold increase in peak pressure at the MTH in these patients with toe deformity. The study on the pathogenesis of claw/hammer toe deformity (chapter 4) was explorative in design. Due to the nature of the problem (absence or presence of toe
deformity) we expected to find consistently different results between the experimental and control groups that may even show in a small sample of neuropathic patients. Larger group studies will enhance the statistical power for showing significant differences between patients with and without toe deformity and for determining the possible contributing role of different anatomical predisposing factors.

Finally, we did not measure shear pressure. Because abundant amounts of callus at the lesser MTHs is a frequent clinical finding in patients with claw/hammer toes, it is suggested that shear pressure (or in mechanical terms: shear stress) applied to the foot may be abnormally high in these regions, and may contribute to an increased risk of plantar ulceration. Pressure devices that can measure shear stress are currently not commercially available. When they are, studies in which both normal and shear stresses are measured in neuropathic subjects with clawing/hammering of the toes may lead to acceptance of this hypothesis. In any case, the addition of shear stress will improve the representation of the actual interaction between the foot and the floor (or insole), expressed by means of the resultant pressure. It will be interesting to determine how much of the variance in this resultant pressure may be explained by foot structure parameters.

**Conclusion**

This thesis describes several structural and functional aspects of foot deformity in a group of subjects with diabetes mellitus that are complicated with what may be considered one of the most intriguing and ambiguous lower-extremity deficits, namely peripheral neuropathy resulting in loss of pain and protective sensation. This thesis has shown remarkable degrees of intrinsic muscle atrophy secondary to peripheral neuropathy, identified a mechanistic link in associating toe deformity with elevated plantar pressure, demonstrated the clinical importance of claw/hammer toe deformity in neuropathic diabetic patients, led to some major reservations regarding long-advocated theories of toe deformity pathogenesis, shown good reproducibility of foot structure and plantar pressure measurements in neuropathic subjects, and elucidated the mechanical action of custom-made insoles in deformed neuropathic feet. The author hopes the findings in this thesis will entice researchers and clinicians to further explore and initiate studies on the structural and functional aspects of the neuropathic foot with the ultimate goal of preventing the occurrence of foot ulceration in patients with diabetes mellitus.
References


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