

Intrinsic Muscle Atrophy and Toe Deformity in the Diabetic Neuropathic Foot

A magnetic resonance imaging study

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OBJECTIVE— The objectives of this study were to compare intrinsic foot muscle cross-sectional area (CSA) in patients with diabetic polyneuropathy and nondiabetic control subjects and to examine the association between intrinsic muscle CSA and clawing/hammering of the toes in neuropathic feet.

RESEARCH DESIGN AND METHODS— High-resolution T2-weighted fast spin-echo images and parametric T2 multiple spin-echo images were acquired using multiple spin-echo magnetic resonance imaging (MRI) of frontal plane sections of the metatarsal region of the foot in a sample of eight individuals with diabetic polyneuropathy and eight age- and sex-matched nonneuropathic nondiabetic control subjects. The configuration of joints of the second toe was obtained using a three-dimensional contact digitizer.

RESULTS— Remarkable atrophy was found in all the intrinsic muscles of neuropathic subjects as compared with nondiabetic control subjects. Quantitative T2 analysis showed a 73% decrease in muscle tissue CSA distally in the neuropathic subjects. Muscle comprised only $8.3 \pm 2.9\%$ (means \pm SD) of total foot CSA compared with $30.8 \pm 3.9\%$ in control subjects. No significant differences were found between the groups in the metatarso-phalangeal and proximal and distal interphalangeal joint angles of the second ray. Moreover, clawing/hammering of the toes was found in only two of eight neuropathic subjects.

CONCLUSIONS— Although sensory neuropathy is often emphasized in considerations of diabetic foot pathology, our results show that the consequences of motor neuropathy in the feet are profound in people with diabetes. This has implications for foot function and may play a significant role in postural instability. However, intrinsic muscle atrophy does not necessarily appear to imply toe deformity.

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Abbreviations: CSA, cross-sectional area; DIP, distal interphalangeal; MNCV, motor nerve conduction velocity; MRI, magnetic resonance imaging; MT, magnetization transfer; MTH, metatarsal head; MTP, metatarso-phalangeal; PIP, proximal interphalangeal; TE, echo time; TR, repetition time; VPT, vibration perception threshold.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

It is well known that symmetrical distal diabetic polyneuropathy affects all three divisions of the peripheral nervous system (sensory, motor, and autonomic), but in the examination and management of the foot in diabetes, it is generally sensory neuropathy that receives the most attention. This is understandable because sensory neuropathy is known to be permissive for foot ulceration, which is often a precursor of amputation. However, there are indications that motor neuropathy can have important consequences in the lower extremities in the diabetic patient. Strength losses of ~16–21% in the plantar and dorsal flexors of the ankle have been reported by Andersen et al. (1). In a subsequent study using magnetic resonance imaging (MRI), Andersen et al. (2) found a 32% reduction in the volume of the dorsal and plantar flexors, with more atrophy apparent distally. The strength of the intrinsic muscles of the foot is more difficult to measure, and there are no reports in the literature of such measurement in diabetic patients. However, these muscles have been studied recently using MRI.

Using MRI magnetization transfer (MT) contrast sequence, Brash et al. (3) have shown qualitative changes in soft tissue (muscle and fat) under the first metatarsal head (MTH) in the feet of diabetic patients with neuropathy. The authors also found reductions in muscle MT activity, reflecting atrophy, with increasing severity of sensory neuropathy. Suzuki et al. (4), using magnetic resonance spectroscopy, have reported both biochemical and structural changes in the plantar foot muscles of diabetic patients with neuropathic ulcers, including a reduction in high-energy metabolites and an increase in fat content. Because significant relationships between motor nerve conduction velocity (MNCV) and these physiological variables were established, these results suggest atrophy in the intrinsic

sic musculature of the foot secondary to motor nerve dysfunction.

A number of authors believe that atrophy of the intrinsic muscles of the foot, as a consequence of motor neuropathy, leads to fixed claw and hammer toe deformities, which are common in the feet of neuropathic diabetic patients (5–9). Since the fat cushions under the MTHs are invested in the flexor tendons and originate from the plantar ligaments that are firmly attached to the proximal phalanges (10,11), clawing and hammering of the toes tends to cause this important soft tissue to migrate distally (9,10). This leads to prominent MTHs resulting in elevated plantar pressure during walking (7–9). For the past 30 years, this putative chain of causation has become an accepted theory in the pathogenesis of diabetic foot deformity (7). However, the relationship between intrinsic muscle atrophy and toe deformity currently remains a hypothesis because it has not been studied quantitatively.

The purpose of the present study was to use MRI to examine intrinsic muscle cross-sectional area (CSA) in the feet of patients with diabetic polyneuropathy and in age- and sex-matched nondiabetic control subjects and to examine the association between intrinsic muscle atrophy and toe deformity in neuropathic feet.

RESEARCH DESIGN AND METHODS

Eight diabetic subjects (six men and two women) with peripheral sensory-motor neuropathy (aged 51.6 ± 11.1 years, body mass 87.8 ± 16.2 kg, height 178 ± 8.8 cm, and diabetes duration 24.1 ± 9.8 years; means \pm SD) and eight healthy age- (± 5 years) and sex-matched nondiabetic control subjects (aged 53.1 ± 9.2 years, body mass 84.3 ± 10.8 kg, and height 174 ± 10.0 cm) were recruited for the study. All subjects were ambulatory. Sensory neuropathy was assessed using quantitative testing. Vibration perception threshold (VPT) at the fifth MTH of both feet was determined using a biothesiometer (Bio-Medical Instruments, Newbury, OH). The mean VPT in the diabetic patients was 40.4 ± 13.9 V, with three subjects having off-scale values of 50.0 V. The mean VPT in the control subjects was 10.8 ± 5.6 V. All neuropathic patients were outside the 95% age-appropriate CIs (12), and all control subjects were well within these normal limits. A full range of Semmes-

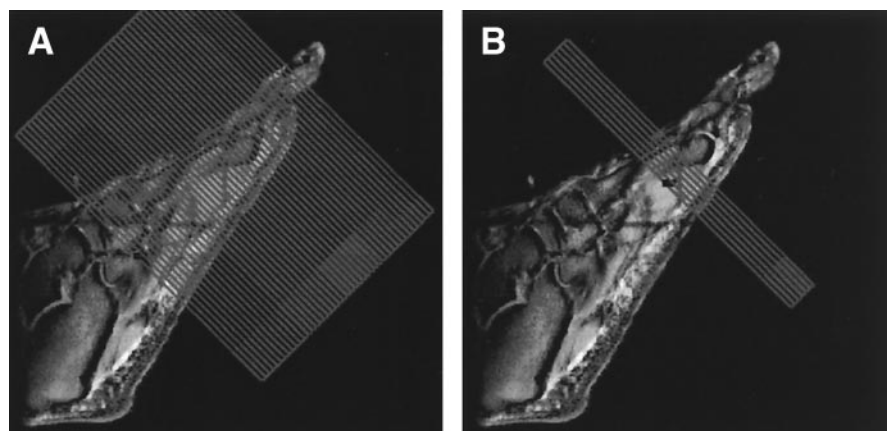


Figure 1—Orientation of the T2-weighted (A) and parametric T2 (B) frontal plane images in the foot. The number of T2-weighted slices per subject ranged from 40 to 46. Six slices were collected for parametric T2 imaging.

Weinstein monofilaments was used to test touch pressure sensation on the plantar and dorsal surface of the foot and at the lateral malleolus in both legs. Loss of protective sensation was confirmed in all neuropathic subjects by the inability to sense the 5.07 (10 g) monofilament at, at least, one of the sites tested in the foot. MNCV in the peroneal nerve was assessed according to standard methods (13). The mean values were 28.4 ± 5.4 and 48.0 ± 7.7 m/s for neuropathic and control subjects, respectively. (Three neuropathic subjects were unavailable for nerve conduction measurements.) Four neuropathic subjects had experienced a prior foot ulcer that was healed at the time of the experiments.

Subjects were excluded if they had a history of significant lower extremity injury, fracture (including Charcot neuroarthropathy), surgery, neurological disease (other than polyneuropathy in the diabetic subjects), or active disc disease. Subjects were also excluded for absent dorsalis pedis pulses or ankle-brachial systolic blood pressure index <0.75 . Significant hallux abducto-valgus, pes planus, or pes cavus were also causes for exclusion. Other exclusions were conditions precluding MRI. Subjects signed an institutional review board–approved informed consent form before participating in the study.

Experimental methods

The experimental data were acquired on a MEDSPEC S300 3.0 Tesla research whole-body imager (Bruker Instruments, Karlsruhe, Germany). Subjects lay supine

with their feet inserted into a quadrature birdcage head coil. Both feet were immobilized on a 45° wooden ramp using a pneumatic cuff and surgical tape to minimize motion artifacts during image acquisition.

Two different two-dimensional datasets were collected in the frontal plane using spin-echo sequencing. The first dataset consisted of 40–46 slices of T2-weighted fast spin-echo images with an effective echo time (TE) of 66 ms and a repetition time (TR) of 6,000–9,000 ms (depending on the number of slices). The T2-weighted image set was collected between the midtarsal joint proximally and the distal interphalangeal joint of the second toe distally (Fig. 1A). The second dataset consisted of 11 multiple spin-echo images, with TEs ranging from 12 to 132 ms and a TR of 1800 ms, collected from each of six slices from the distal metatarsal region of the foot (Fig. 1B). For both datasets, slice thickness was 3 mm, interslice gap was 0.15 mm (to minimize cross-talk between adjacent slices), field of view was 20×20 cm², and image matrix was 256×256 pixels. To improve visualization, the datasets were zero-filled to 512×512 pixels before image reconstruction. The collection of each dataset required ~15 min. From the six multiple spin-echo slices, one anatomically referenced slice passing through the head of the fifth metatarsal in the left foot was selected for quantitative analysis. The muscles that were typically included in this slice are identified in Fig. 2.

During a physical examination of the subjects, points on the dorsum of the

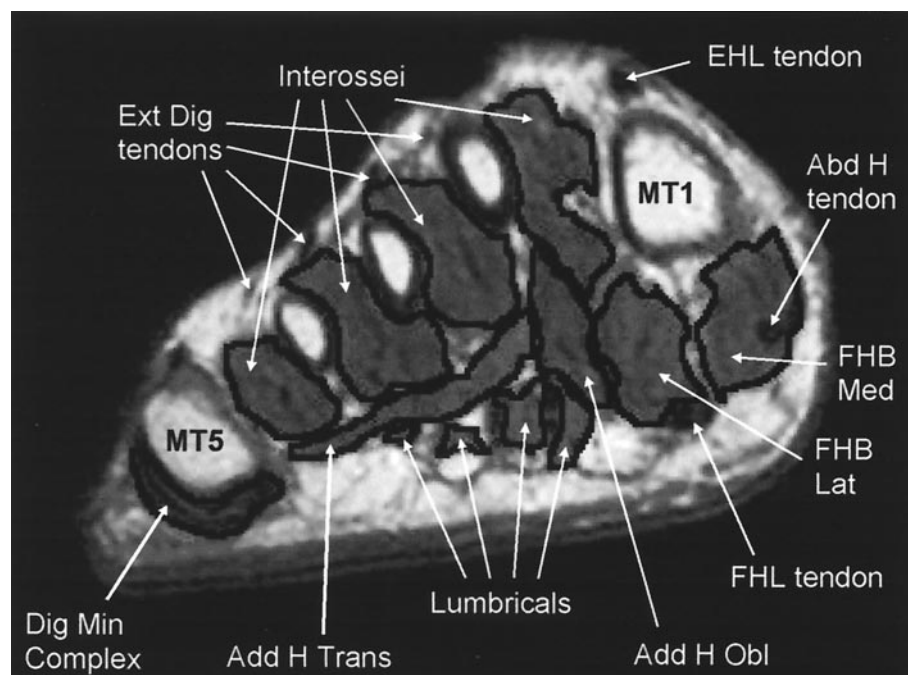


Figure 2—Annotated T2 frontal plane slice passing through the head of the fifth metatarsal from a nondiabetic subject in which the outlines of the intrinsic muscles of the foot are identified. Abd H, abductor hallucis; Add H Obl, adductor hallucis oblique head; Add H Trans, adductor hallucis transversal head; Dig Min Complex, digiti minimi complex including the flexor and opponens digiti minimi muscles; EHL, extensor hallucis longus; Ext Dig, extensor digitorum; FHB Lat, flexor hallucis brevis lateral head; FHB Med, flexor hallucis brevis medial head; FHL, flexor hallucis longus; MT, metatarsal.

left foot and the second toe [tarsometatarsal joint, metatarso-phalangeal (MTP) joint, proximal interphalangeal (PIP) and distal interphalangeal (DIP) joints, and tip of the toe] were located in a three-dimensional reference frame using a Microscribe contact digitizer (located at www.microscribe.com). The foot was non-weight bearing during this measurement. Joint angles were calculated from

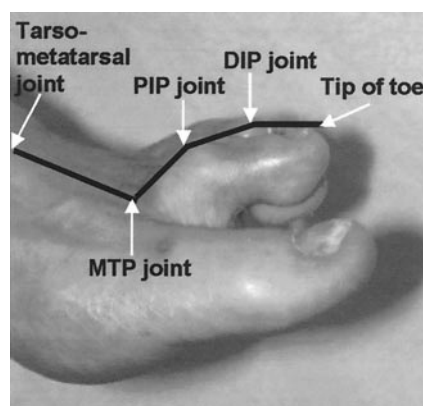


Figure 3—Toe joint configuration measured on the dorsum and second toe of the left foot during non-weight bearing.

these data to determine toe joint configuration in the study sample (Fig. 3).

Data analysis

Our original intention was to segment the T2-weighted images by digitizing the outlines of the intrinsic muscles in each slice, as shown in Fig. 2, and by calculating the volumes of individual muscles similar to the approach of Fukunaga et al. (14). However, as is apparent from Fig. 4A and B, which show the anatomically referenced T2 images of a nondiabetic control and neuropathic subject, respectively, muscle segmentation in the neuropathic subjects proved difficult or impossible because many of the structures were not clearly defined due to marked atrophy of muscle tissue. Therefore, the principal method of analysis used was a compositional analysis of soft tissue in the selected parametric T2 slice using CCHIPS software (15). Pixel-by-pixel parametric T2 color maps (Fig. 4C and D), with T2 relaxation times between 0 and 255 ms, were generated from the signal intensity levels of the 11 spin-echo images using a

nonlinear least-squares method, according to:

$$I_j = I_o \exp(-TE_j/T2)$$

where I_j is the pixel intensity in the image obtained, with an echo time TE_j , and I_o is a constant. A threshold of 30 ms was applied to the T2 map to filter background noise and to better visualize tissue with $T2 < 30$ ms (tendon and cortical bone). A multicomponent segmentation analysis, based on T2, was then used to determine the amount of muscle and other tissue in the image (Fig. 4E and F). Because skin tissue has approximately the same T2 as muscle tissue, it had to be excluded from the analysis. Normalized muscle CSA, expressed as a percentage of the total foot CSA in the image, was the dependent variable in this analysis. The resulting images were verified by visual inspection and comparison with the corresponding T2 color map. Histograms showing the number of pixels in the slice as a function of T2 were created from the parametric T2 maps (Fig. 5).

Independent *t* tests, using SPSS statistical software (SPSS, Chicago), assessed significance between the means of the subject groups for each dependent variable in the study ($P < 0.05$). Abnormality in muscle CSA and toe configuration values was defined as being outside the 95% CI of the mean of the nondiabetic subjects (i.e., >2 SDs from the mean).

RESULTS—A subjective analysis of the T2-weighted and parametric T2 images revealed a striking reduction or, in some cases, an absence of definable muscle cross sections in the majority of slices from the neuropathic subjects as compared with the nondiabetic control subjects. This can be observed in Fig. 6, in which the anatomically referenced T2 slices from matched nondiabetic control and neuropathic subjects are shown. The areas in which well-defined muscle bundles appear in the control subjects are replaced in the neuropathic subjects by somewhat disorganized tissue, with fatty infiltration showing markedly increased signal intensity. In most subjects, the interossei are generally absent, and only remnants of the other major intrinsic muscles such as flexor hallucis brevis and adductor hallucis are visible.

These subjective observations were

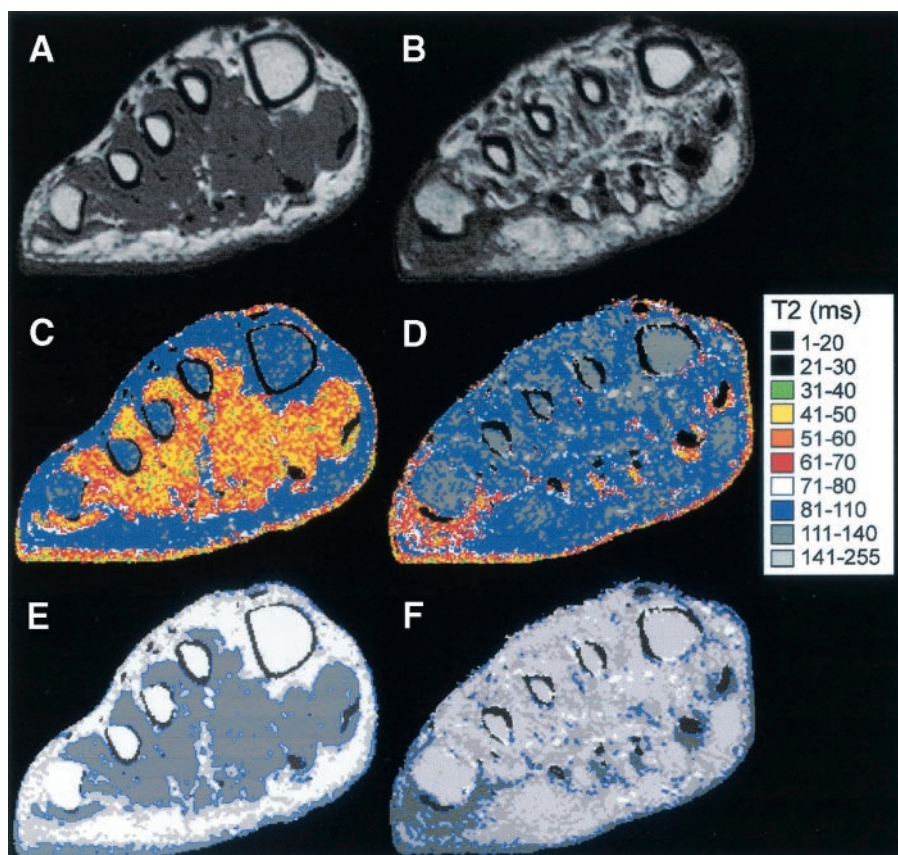


Figure 4—Images from the analysis of a nondiabetic control subject (A, C, and E) and an age- and sex-matched neuropathic subject (B, D, and F). A and B: single-echo anatomical T2 images of a metatarsal cross-section. C and D: T2 maps generated from all 11 echos with color-coding according to the adjacent legend. In these maps, tendon and cortical bone appear as black ($T2 < 30$ ms), muscle and skin as green, yellow, orange, and red ($31 \text{ ms} < T2 < 70$ ms), and fat and trabecular bone as white, blue, and dark gray ($71 \text{ ms} < T2 < 130$ ms). E and F: segmented images from the multicomponent analysis of the T2 maps, with muscle and skin tissue outlined in blue and shaded dark gray. Skin tissue was excluded in the quantification of muscle tissue.

confirmed by the quantitative tissue analysis. In the histograms shown in Fig. 5, all control subjects have a bimodal distribution with a first peak indicating mus-

cle tissue in the region of T2 relaxation times of 30–70 ms. This peak is absent in all of the neuropathic subjects, whereas the later peak (70–110 ms) representing

fat tissue is much higher in this group. The segmentation analysis revealed muscle CSA to be $8.3 \pm 2.9\%$ [means \pm SD] (range 3.7–11.8) in the neuropathic subjects and $30.8 \pm 3.9\%$ (range 24.4–36.8) in the nondiabetic control subjects. This was a highly significant ($P < 0.001$) 73% decrease in muscle tissue in the neuropathic subjects, who were all well outside the normal limits for muscle CSA.

The mean angle of the MTP joint in the second ray of the left foot was $46 \pm 16^\circ$ (range 27–70) of extension in the neuropathic subjects and $45 \pm 5^\circ$ (range 37–51) of extension in the control subjects (Fig. 7). Mean flexion at the PIP and DIP joints was 24 ± 8 and $28 \pm 7^\circ$, respectively, in the neuropathic subjects and 14 ± 11 and $30 \pm 7^\circ$, respectively, in the control subjects. None of the joints showed a significant difference between the two groups. Abnormal MTP joint hyperextension angles ($>54^\circ$), typical of clawing/hammering, were present in two of eight neuropathic subjects and in none of the control subjects.

As a preliminary confirmation that the changes were not related to diabetes per se, the midcalf section of the lower leg, where the effects of neuropathy are less marked, was imaged in one neuropathic patient and one matched control subject (Fig. 8) using the same parametric T2 protocol as described above. Total muscle CSA in the lower leg was not different between these two subjects (50.7 vs. 53.4%).

CONCLUSIONS— These data show that normal intrinsic muscle tissue is largely absent from the forefoot in all neuropathic subjects studied. This atrophy of

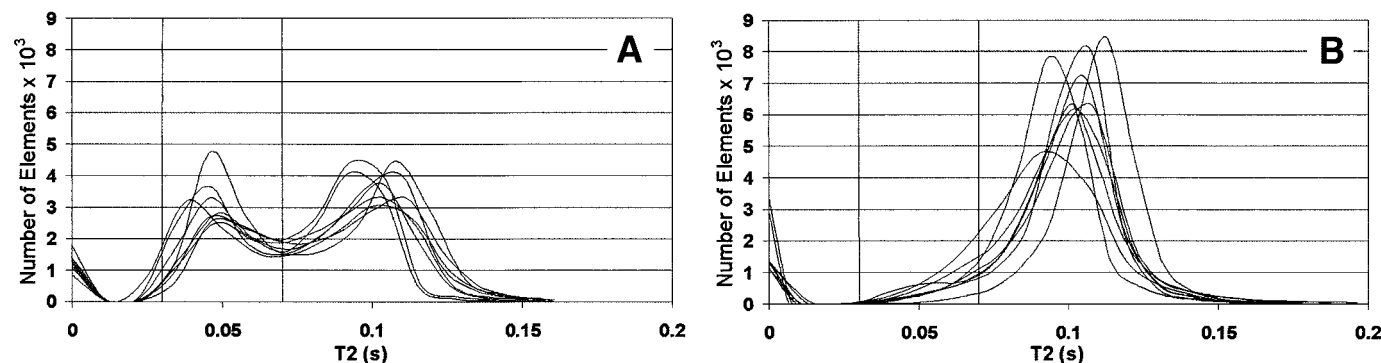


Figure 5—Histograms of the number of pixels at each value of T2 derived from the parametric T2 maps for all eight nondiabetic control subjects (A) and all eight neuropathic subjects (B). The limits for muscle tissue T2 relaxation times are marked by the vertical lines. Note the absence of the early T2 peak in all neuropathic patients reflecting muscle atrophy and the higher late peak reflecting fatty infiltration.

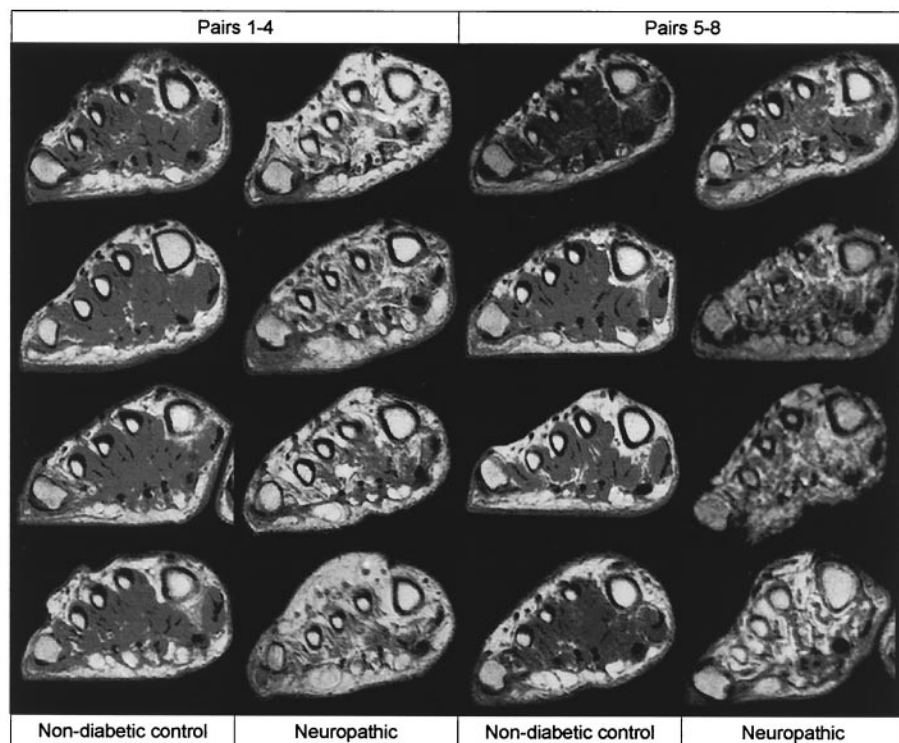


Figure 6—Anatomically referenced single echo parametric T2 images for eight pairs of age- and sex-matched nondiabetic control and neuropathic subjects.

the intrinsic muscles resulting from diabetic neuropathy is much more marked than had been expected. The present results extend the findings of Brash et al. (3) and Suzuki et al. (4). Brash et al. reported a significant reduction in MT activity, suggesting atrophy, in muscle adjacent to the first metatarsal in similar subjects. Suzuki et al. found a significant increase in the fat-to-water ratio and a significant decrease in the phosphocreatine-to-inorganic-phosphate ratio in the plantar muscles of diabetic patients with foot ulceration, indicating loss of muscle tissue with fatty infiltration. Phoenix et al. (16) used quantitative MRI analysis techniques similar to those used in the current study and demonstrated muscle depletion and fat infiltration in the lower-leg muscles of subjects with muscular dystrophy. Andersen et al. (2) demonstrated a distal-to-proximal gradient of muscle atrophy from cross sections in the proximal lower leg (no change), mid lower leg (43%), and distal lower leg (65%) in diabetic patients with neuropathy, suggesting that the changes would be even greater in foot muscles. This has been confirmed by our results showing 73% atrophy in the most distal foot muscles.

The implications of our findings are that muscle strength, and thus motor function in the feet of the neuropathic subjects studied, are apparently severely compromised. Although many of the actions of the intrinsic muscles (such as toe

flexion and extension) are complemented by extrinsic muscles, others, such as active ab/adduction of the digits and maintenance of forefoot integrity and stability, result only or largely from intrinsic muscle action (17–19). Thus, the mechanical action of these feet during foot-ground interaction must be substantially different from that of nonneuropathic feet. Balance is known to be compromised in neuropathic patients, and this has been assumed to be primarily due to loss of sensory feedback (20); however, altered action of intrinsic muscles may also be a significant contributor. Level walking on even ground may not be affected by such loss of force actuators, but walking on uneven surfaces or turning during walking may have to rely on more proximal muscle groups acting at the ankle rather than at the foot.

It is interesting that others have found toe function to be altered in patients with neuropathy (21,22), and the loss of intrinsic toe flexors and extensors may account for this finding. This effectively transfers more load to the MTHs during walking and increases the risk of plantar ulceration at the MTHs. The status of fascia and ligaments in neuropathic feet is not well known, although there are reports of rupture of the plantar fascia (23). Reduced or absent muscle force can be expected to increase the load on these passive structures.

The interossei and lumbricals are be-

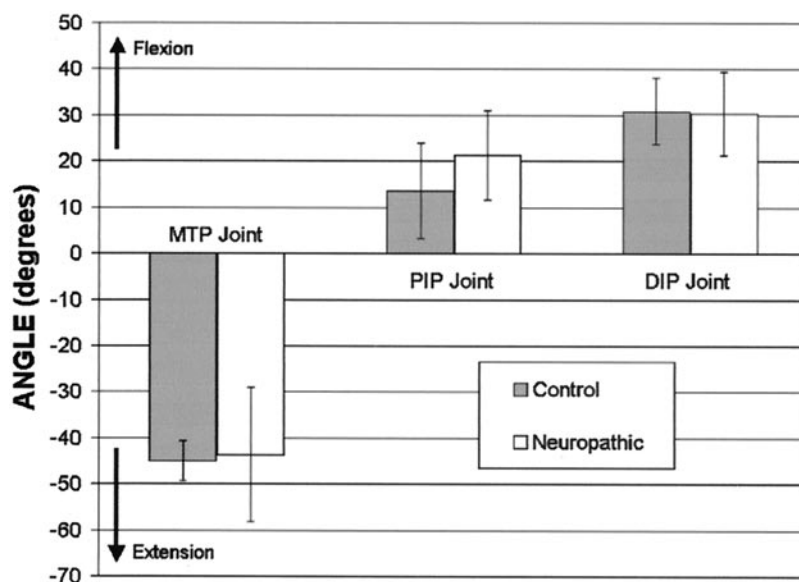


Figure 7—Configuration of the joints of the second toe during non-weight bearing in control and neuropathic subjects. No significant differences were found between the groups.

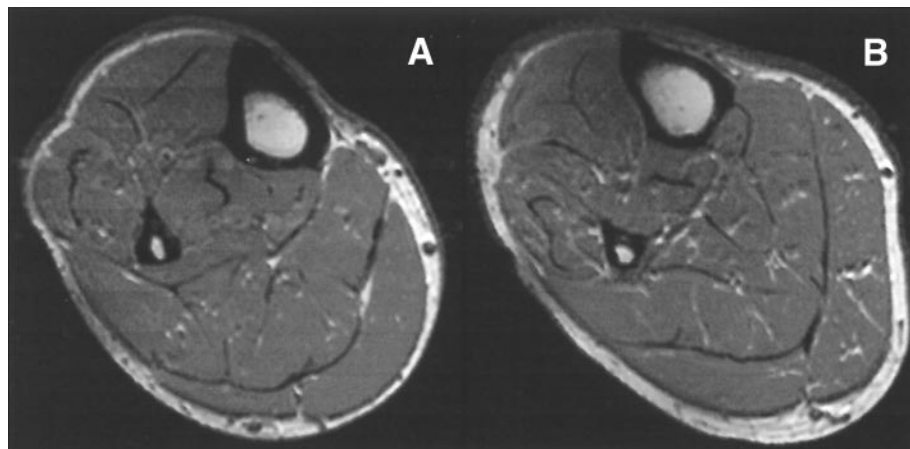


Figure 8—Midcalf single-echo parametric T2 scans of a nondiabetic control subject (A) and an age- and sex-matched neuropathic subject (B). No differences in the quantity of normalized muscle tissue between these two subjects could be found.

lied to play a major role in controlling the position of the proximal phalanx in relation to the respective metatarsal (8,24,25). It has been suggested that in neuropathic patients, these muscles are incapable of compensating for the mechanical advantage of contracted long extensor muscles at the MTP joint and contracted long flexor muscles at the interphalangeal joints (6,7). This would tend to drive the toes into a clawed or hammered position. Of all intrinsic foot muscles examined, it was our impression that the interossei showed the largest degree of atrophy in the neuropathic subjects. However, our measurements of toe-joint configuration indicate that the MTP joints of the neuropathic patients were not in more extension than those of the control subjects. Moreover, only two neuropathic subjects in this study exhibited abnormal MTP joint extension (>2 SD from control group mean) characteristic of clawing or hammering. Despite the fact that the state of the extrinsic muscles controlling the position of the toes was not examined, these results appear to cast major doubt on the role of intrinsic muscle atrophy in the hyperextension/subluxation deformity that is commonly seen in diabetic patients. Other intrinsic and extrinsic factors that have been reported to play a role in the development of claw or hammer toes in diabetic patients are ill-fitting shoes (6), contractures of the collateral ligaments of the MTP joint (25) and rupture of the plantar aponeurosis (which may both be caused by nonenzymatic glycosylation) (23). A comprehen-

sive and preferably prospective analysis of these factors, including examination of the status of the extrinsic toe flexors and extensors, should increase our understanding of the pathomechanics of lesser toe deformity in diabetic patients with neuropathy.

There is no reason to suggest that the subjects in this study represent an unusual subset of neuropathic diabetic individuals. The exclusion criteria used in subject selection and the matching of subjects on age and sex should have successfully eliminated individuals with muscle atrophy from causes other than distal symmetric polyneuropathy. We did not study nonneuropathic diabetic subjects; therefore, the influence of diabetes per se on signal intensity from intrinsic foot muscles could not be determined. However, the MRI examination of the midcalf region (where the effects of neuropathy are less marked) of a matched control and neuropathic subject demonstrated no difference in muscle CSA. Moreover, Andersen et al. (2) showed no differences in lower leg muscle volume between nonneuropathic diabetic patients and nondiabetic control subjects.

In conclusion, this study has shown remarkable atrophy of the intrinsic muscles of the foot secondary to diabetic neuropathy. Even though sensory neuropathy is often emphasized in considerations of diabetic foot pathology, these results show that the consequences of motor neuropathy in the feet are profound and are likely to have major consequences for foot function and mechanics.

The lack of toe deformity in the majority of our neuropathic subjects suggests that intrinsic muscle atrophy is not a primary causative factor in toe deformity as had been formerly hypothesized.

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