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# STRUCTURAL CHANGES IN THE FOREFOOT OF INDIVIDUALS WITH DIABETES AND A PRIOR PLANTAR ULCER

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*Investigation performed at Washington University School of Medicine, St. Louis, Missouri*

**Background:** Plantar ulcers produced by diabetic foot disease are devastating and costly. Better understanding of the ulcer-producing process is important to improve detection of feet that are at risk and to improve intervention. We identified and quantified soft-tissue and osseous structural changes in the forefoot of diabetic patients with a prior plantar ulcer.

**Methods:** Thirty-two individuals with a mean age (and standard deviation) of  $57 \pm 11$  years were studied; sixteen had diabetes (of a mean of  $20 \pm 11$  years' duration), peripheral neuropathy, and a prior plantar ulcer, and sixteen were matched controls. Computed tomography was used to evaluate forefoot structure, including the plantar soft-tissue (muscle) density, soft-tissue thickness beneath the metatarsal heads, metatarsophalangeal joint angle, metatarsal bone density, and metatarsophalangeal joint arthropathy.

**Results:** Plantar soft-tissue (muscle) density was lower in the individuals with diabetes (mean, 1 HU [Hounsfield unit]) than it was in the controls (mean, 18 HU). There was no difference in the soft-tissue thickness beneath the metatarsal heads (mean, 10 mm) between the individuals with diabetes and the controls, but the soft-tissue thickness decreased with age. The individuals with diabetes had greater extension deformity of the first, second, and third metatarsophalangeal joints and greater arthropathy of the second, third, and fourth metatarsophalangeal joints. There were no significant differences in metatarsal bone density between the groups.

**Conclusions:** There were significant differences between the forefeet of individuals with diabetes and a previous plantar ulcer and those of controls: plantar muscle density was decreased, and metatarsophalangeal joint extension and arthropathy were increased. Interestingly, the soft-tissue thickness under the metatarsal heads in the controls was not greater than that in the diabetic patients.

**Clinical Relevance:** This study demonstrated structural differences between the forefeet of patients with diabetes and a previous ulcer and those of normal age-matched controls. The information can serve to guide new interventions to prevent or treat foot ulcerations in this patient population.

As a result of medical advances, patients with diabetes now lead healthier and longer lives<sup>1,2</sup>. However, foot ulceration, a common complication of diabetes, is a devastating and costly event that frequently recurs<sup>1,3-10</sup>. Foot ulcers are the most frequent cause of hospitalization of patients with diabetes and the most common reason for lower-extremity amputation in the United States<sup>1,4,5,11-13</sup>. Worse, the rates of diabetes-related amputation are increasing<sup>1</sup>.

Diabetes-associated neuropathy, peripheral vascular disease, and infection all contribute to the process that produces ulceration and diabetic foot disease<sup>12,14-20</sup>. Altered mechanical forces, especially high plantar pressures, are also an important

factor<sup>15-17,21-25</sup>. Although a specific ulcer-producing pressure threshold has not been identified and appears to vary according to patient-related characteristics, reduction of high plantar pressure in feet that have lost protective sensation is the cornerstone of current prevention and treatment<sup>15,17,19,20,22,26,27</sup>. While current accommodative or protective treatments are useful, their success is limited, as evidenced by rates of ulcer recurrence of approximately 35% at one year and 70% at five years<sup>7-9</sup>. A reduction in the rate of plantar ulceration and its sequelae would improve the quality of many lives and provide considerable medical cost savings.

Peak plantar pressures occur in the forefoot, at the site of

TABLE I Demographics and Attributes

	Age* (yr)	Gender	Race	Foot
Individuals with diabetes	56 ± 10 (40-80)	5F, 11M	2B, 14W	9R, 7L
Controls	57 ± 11 (40-73)	6F, 10M	2B, 14W	7R, 9L
P value	0.78#	0.71**	1.00**	0.48**

\*The values are given as the mean and standard deviation, with the range in parentheses. †Overweight has been defined as a body-mass index of  $\geq 25$  kg/m<sup>2</sup> and obesity, as an index of  $\geq 30$  kg/m<sup>2</sup> or more<sup>72</sup>. ‡NA = not applicable. §The duration of diabetes indicates the number of years following the original diagnosis of diabetes. #Two-tailed independent-samples t test. \*\*Chi-square test.

skin breakdown, in individuals in whom ulcers develop<sup>16,22-24</sup>. However, few studies have detailed the structural changes in the forefoot that produce high pressures and result in ulceration in feet with reduced sensation<sup>22,28</sup>. Architectural changes such as hammer toe are a frequent finding and have been postulated to increase the risk of ulceration<sup>23,29,30</sup>. Changes in material properties produced by tissue glycosylation and reparative new tissue have also been postulated to increase the likelihood of ulceration<sup>23,31-33</sup>. However, little is actually known about how these factors are related to the production of foot ulcers.

Improved knowledge of the structure of feet at risk should assist in both prevention and treatment. Most investigators have used radiography to study the structure of the foot in diabetic patients; ultrasound has been used only recently<sup>29,30,34-38</sup>. The limitations of planar studies (radiography and ultrasound) are that they do not allow a unified structural assessment.

Computed tomography, an accurate and reproducible imaging method, displays three-dimensional musculoskeletal structure<sup>39-42</sup>. Internal and external soft tissue, osseous geometry, material properties (tissue density), and arthropathy can be evaluated and quantified<sup>39-47</sup>. In addition, computed tomography reveals interrelationships between different structures and tissue types<sup>39-42,46</sup>. Also, computed tomography structural analyses can be coupled with mechanical analyses, such as measurements of plantar pressure<sup>42,48</sup>. Thus, computed tomography is useful for exploring the relationship between foot structure and function and elucidating methods to improve the prevention and treatment of foot disease.

The purpose of this study was to use computed tomography to identify, quantify, and elucidate relationships among structural changes of the forefoot in diabetic individuals with a prior plantar ulcer and in matched controls. We expected diabetes-related muscle-wasting and tissue-stiffening to produce changes in plantar muscle density and soft-tissue thickness, metatarsophalangeal joint extension, metatarsophalangeal arthropathy, and metatarsal bone density.

### Materials and Methods

Thirty-two subjects were studied. Each gave informed consent and was studied according to a protocol approved by an institutional review board. Sixteen subjects who had been diagnosed as having diabetes with peripheral neuropathy (loss of protective sensation [5.07 on the Semmes-Weinstein mono-

filament test]) and a prior neuropathic plantar ulcer were recruited from a multidisciplinary tertiary-care diabetes clinic. At the time of the study, thirteen of these patients were receiving insulin therapy, and three were receiving oral hypoglycemic medications. The types of diabetes, duration of the diabetes since the diagnosis, and hemoglobin A1c values are summarized in Table I. The anatomical distribution of the prior ulcers, which had all healed (grade 0, according to Wagner's system<sup>49</sup>), is illustrated in Figure 1. Ten patients had had a single ulcer, five had had ulcers at two sites, and one had had ulcers at three sites. The foot with the prior ulcer or ulcers was studied. When both

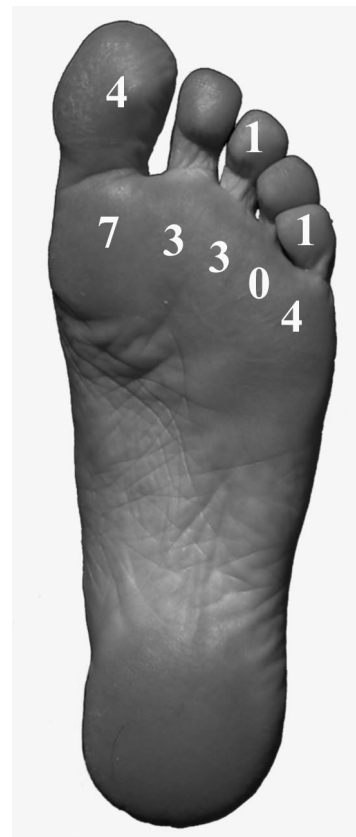


Fig. 1  
Location and frequency of prior plantar ulcers in the individuals with diabetes. Ten patients had a single ulcer, five had ulcers at two sites, and one had ulcers at three sites.

TABLE I (continued)

Height* (cm)	Weight* (kg)	Body-Mass Index*† (kg/m <sup>2</sup> )	Type of Diabetes†	Duration of Diabetes*‡§ (yr)	Hemoglobin A1c*‡ (%)
179 ± 10 (155-201)	104 ± 25 (72-161)	33 ± 8 (24-47)	5 I, 11 II	20 ± 11 (2-40)	7.6 ± 1 (5-10)
175 ± 12 (156-194)	100 ± 36 (72-199)	32 ± 9 (23-55)	NA	NA	NA
0.33#	0.74#	0.89#			

feet had had one or more prior ulcers, the foot that the subject judged to have caused the most problems was studied, except when the subject had had a partial foot resection. Sixteen healthy control subjects were matched to the diabetic group by age, gender, race, foot studied (right or left), height, weight, and body-mass index (the individual's weight [in kilograms] divided by the square of his or her height [in square meters]). Individuals were excluded if they were unable to walk independently, were women of childbearing age, or had inflammatory arthritis.

Computed tomography scanning was performed with the subject sitting, on a specially constructed chair on top of the scanner table, with the leg extended and the foot pressed flat against a fixed vertical force-plate<sup>42,48</sup>. Subjects were asked to relax and to not push against the force-plate. A digital read-out, visible to the subjects, assisted them in maintaining the "no-load" condition (defined as <4.5 kg). The spiral computed tomography scanning (Somatom Plus 4; Siemens, Iselin, New Jersey) was performed with 3-mm collimation, 3-mm table increment, 120-kVp, and 220 mÅ. The foot was imaged from the plantar surface to the ankle with scan times of approximately thirty seconds.

Image slices, 1-mm thick, were reconstructed and were transferred to an image-processing workstation. The original volumetric computed tomography data set was resized to isotropic voxels with use of trilinear interpolation (AnalyzePC; Biomedical Imaging Resource, Rochester, Minnesota). All analyses used the resized volumetric data set. Isotropic voxel dimensions ranged from 0.4 to 0.6 mm per side. All image reformations and image analyses were performed with use of AnalyzePC.

#### *Plantar Soft-Tissue (Muscle) Density at the Midparts of the Metatarsal Shafts*

Measurements of plantar soft-tissue (muscle) density (a material property) quantified the structural change produced by diabetes-related atrophy of the intrinsic plantar muscles. In some diabetic individuals, it was difficult to delineate the outlines of the intrinsic muscles because of atrophy and infiltration. For this reason, we outlined the plantar soft tissue superficial to the metatarsals and deep to the dermis as a surrogate measurement of the plantar muscles. Although this soft-tissue region consisted mostly of plantar muscle, it also

contained fat and tendon. Axial computed tomography images (perpendicular to the long axis of the metatarsal) through the midpart of each metatarsal shaft were produced by reformatting the volumetric computed-tomography data set. The soft tissue (excluding dermis) plantar to each metatarsal was manually outlined on the computed tomography image. The mean number (and standard deviation) of Hounsfield units (HU) was calculated from the pixels within the outlined region on the computed tomography scan. Hounsfield units, which are directly related to mass density<sup>43-45</sup>, range from -1000 (air) to 3095 (metal), with water being 0. Typical values for fat, muscle, cancellous bone, and cortical bone are -40, 20, 200, and 1000 HU, respectively<sup>50,51</sup>.

#### *Soft-Tissue Thickness*

##### *Beneath the Metatarsal Heads*

The thickness of the plantar soft tissue at the level of each metatarsal head was measured on lateral-view maximum-intensity projections of each ray. The distance (perpendicular to the sole of the foot and the force-plate) from the most plantar bone at the head (or sesamoid) to the inner surface of the skin defined the plantar soft-tissue thickness. This measurement quantified architectural change at the most common site of plantar ulcers.

##### *Metatarsophalangeal Joint Angle*

Three-dimensional maximum-intensity projections of lateral views of each ray were constructed for each foot, and the midpoints of the metatarsophalangeal joint, tarsometatarsal joint, and proximal interphalangeal joint were identified on each of these projections. Joining the midpoints of the appropriate joints created metatarsal and proximal phalangeal lines. For each ray, the metatarsophalangeal joint angle was defined by subtracting from 180 the angle formed by the intersection of the metatarsal and proximal phalangeal lines. Positive angles represented extension of the joint. The angle of the proximal interphalangeal joint was not measured; thus, extension deformities may represent hammer or claw toes. The metatarsophalangeal joint angle also does not differentiate static from dynamic toe deformities.

##### *Bone Density of the Metatarsal Heads*

Sagittal computed-tomography images of each metatarsal

were reformatted from the volumetric computed-tomography data set. These images bisected the metatarsal along its long axis and were used to measure the bone density of the metatarsal head. The periosteal contour around each metatarsal head was outlined manually, and the mean number of Hounsfield units (and standard deviation) was calculated from the pixel values within the outlined region of the metatarsal head on the scan<sup>52,53</sup>.

#### *Bone Density of the Midparts of the Metatarsal Shafts*

Axial computed-tomography sections of the midpart of each metatarsal shaft were used to measure bone density. The periosteal and endosteal contours of each metatarsal cross-section were manually outlined, and the mean number of Hounsfield units (and standard deviation) of the metatarsal cortical bone was calculated from the pixel values within the outlined region on the scan<sup>52,53</sup>.

#### *Metatarsophalangeal Arthropathy*

To better describe the condition of the metatarsophalangeal joint, we developed an arthropathy rating based on joint subluxation, loss of cartilage space, the presence of osteophytes, and lysis of the metatarsal head. Three-dimensional maximum-intensity projections of the foot and multiple multiplanar images (sagittal, coronal, and axial) of the metatarsophalangeal joints were reformatted from the volumetric computed tomography volume. Subluxation was graded on a 3-point scale, with 3 points given for 67% to 100% coverage, 2 points for 34% to 66% coverage, and 1 point for 0 to 33% coverage. Three-point scales were also used to grade loss of cartilage space (3 points when  $\geq 50\%$  of the normal space was present, 2 points when 1% to 49% was present, and 1 point when no space was present), to grade osteophytes (3 points for no or small osteophytes, 2 points for moderate osteophytes, and 1 point for large osteophytes), and to grade lysis of the metatarsal head (3 points when  $\geq 75\%$  of the head circumference was present, 2 points when 50% to 74% was present, and 1 point when 0% to 49% was present) (Fig. 2). The maximum score for each joint was 12 points, which indicated that it was generally normal. The maximum score for the sum of all five joints was 60 points. All feet were rated by a consensus score of two observers who were blinded to the subject group from which the images were derived.

#### *Statistical Analysis*

Two-tailed independent-samples t tests were used to test for differences, between individuals with diabetes and controls, with respect to age, height, weight, body-mass index, soft-tissue density, soft-tissue thickness, bone density of the midparts of the metatarsal shafts, and bone density of the metatarsal heads. Chi-square tests of independence were used to test for differences, between individuals with diabetes and controls, with respect to gender, race, and foot studied (right or left). The Wilcoxon signed-rank test was used to evaluate differences, between individuals with diabetes and controls, with respect to metatarsophalangeal arthropathy ratings and metatarsophalangeal joint angles. In addition, associations between variables were analyzed with correlation analysis. Pearson correlation was used for data derived from measurements, and Spearman rank-order correlation was used for ranked data. All statistical testing was performed with use of JMP software (SAS Institute, Cary, North Carolina), with the level of significance set at  $p \leq 0.05$ .

#### *Reliability, Repeatability, and Interobserver Variation of Measurements*

To test reliability and repeatability, original and repeat measurements of plantar soft-tissue density, soft-tissue thickness beneath the metatarsal heads, bone density of the midparts of the metatarsal shafts, and bone density of the metatarsal heads were made by one observer for the first sixteen feet. Reliability (precision) was defined as the mean difference between repeated measurements of the same feet. Repeatability was the measure of reliability relative to the variation among specimens.

Since the metatarsophalangeal arthropathy rating was semiquantitative, it was based on the measurements made by two observers. In addition to assigning a consensus rating to each foot, both observers independently reevaluated each foot at least eight weeks after assigning the first rating. The independent ratings were compared with each other and with the consensus rating. The scores for the arthropathy characteristics (subluxation, loss of cartilage space, osteophytes, and lysis) were summed for each metatarsophalangeal joint, producing 80 data points for analysis (sixteen subjects, with five joints per subject). Calculation of the percentage of identical scores and Spearman rank-order correlation were used to

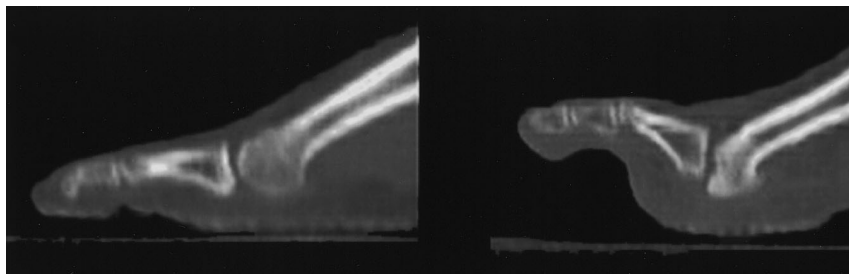


Fig. 2

Metatarsophalangeal joint arthropathy. Sagittal computed tomography reformations through the second metatarsal of a control subject with no arthropathy (left) and an individual with diabetes (right). Note the extended and subluxated metatarsophalangeal joint and lysis of the metatarsal head in the diabetic foot.

**TABLE II Correlation Coefficients (R) and P Values\* Derived from Linear Regression Analyses of Selected Parameters for the Control Subjects**

Subjects	Metatarsophalangeal Joint Angle	Plantar Soft-Tissue (Muscle) Density	Soft-Tissue Thickness Beneath Metatarsal Heads	Bone Density of Metatarsal Heads	Age	Body-Mass Index
Metatarsophalangeal arthropathy rating	-0.41 0.11	0.16 0.54	-0.35 0.19	-0.11 0.69	-0.29 0.27	-0.26 0.33
Metatarsophalangeal joint angle		-0.15 0.59	-0.24 0.37	0.22 0.42	0.64 0.01	-0.02 0.95
Plantar soft-tissue (muscle) density			-0.12 0.67	0.49 0.06	-0.09 0.74	-0.67 0.004
Soft-tissue thickness beneath metatarsal heads				0.26 0.33	-0.53 0.04	0.06 0.83
Bone density of metatarsal heads					0.02 0.95	-0.37 0.16
Age						-0.07 0.81

\*The correlation coefficients (r) are on top, and the p values are underneath.

evaluate reliability of the arthropathy ratings.

## Results

### *Plantar Soft-Tissue (Muscle) Density Beneath the Midparts of the Metatarsal Shafts*

The mean density (and standard deviation) of the plantar soft tissue (muscle) under the midpoint of the metatarsals was  $18 \pm 18$  HU (range, -30 to 43 HU) in the control subjects and  $1 \pm 12$  HU (range, -22 to 18 HU) in the individuals with diabetes (Fig. 3). The densities of the two groups were significantly different (two-tailed independent-samples t test,  $p = 0.004$ ).

The plantar soft-tissue (muscle) density was inversely related to the body-mass index in the control group ( $r = -0.67$ ,  $p = 0.004$ ) and the pooled subject group ( $r = -0.40$ ,  $p = 0.03$ ) (Tables II and III). The plantar soft-tissue (muscle) density was directly related to the bone density of the metatarsal heads in the group with diabetes ( $r = 0.60$ ,  $p = 0.01$ ) and the pooled subject group ( $r = 0.55$ ,  $p = 0.001$ ) (Tables III and IV).

### *Soft-Tissue Thickness Beneath the Metatarsal Heads*

The mean thickness (and standard deviation) of the plantar soft tissues under the metatarsal heads was  $10 \pm 2$  mm (range, 7 to 13 mm) in the control subjects and  $10 \pm 1$  mm (range, 7 to 12 mm) in the individuals with diabetes. There was no difference between the two groups (two-tailed independent-samples t test,  $p = 0.62$ ). The soft-tissue thickness was inversely related to age in the control group ( $r = -0.53$ ,  $p = 0.04$ ) and in the pooled data ( $r = -0.47$ ,  $p = 0.006$ ) (Tables II and III).

### *Metatarsophalangeal Joint Angle*

The metatarsophalangeal joint angles were all positive (i.e., in

extension). The angles of the first, second, and third toes of the individuals with diabetes were greater than those of the control subjects; the differences ranged from 32% to 170% (Table V). These differences were significant for the first and third toes but not for the second toe.

In the control subjects, the metatarsophalangeal joint angle was directly related to age ( $r = 0.64$ ,  $p = 0.01$ ) (Table II). In the individuals with diabetes, the metatarsophalangeal joint angle was directly related to the body-mass index ( $r = 0.56$ ,  $p = 0.03$ ) and inversely related to the plantar soft-tissue density ( $r = -0.46$ , which



Fig. 3

Plantar soft-tissue density beneath the midparts of the metatarsal shafts. A control foot is at the top, and a diabetic foot is on the bottom. Note the lower attenuation within the plantar tissues and the indistinctness of the plantar muscles of the diabetic foot.

**TABLE III Correlation Coefficients (R) and P Values\* Derived from Linear Regression Analyses of Selected Parameters for the Pooled Data on the Control Subjects and the Individuals with Diabetes**

	Metatarso- phalangeal Joint Angle	Plantar Soft-Tissue (Muscle) Density	Soft-Tissue Thickness Beneath Metatarsal Heads	Bone Density of Metatarsal Heads	Age	Body-Mass Index
Metatarsophalangeal arthropathy rating	-0.72 <0.001	0.51 0.003	-0.11 0.53	0.32 0.08	-0.20 0.28	-0.16 0.37
Metatarsophalangeal joint angle		-0.41 0.02	0.05 0.79	-0.08 0.66	0.33 0.06	0.31 0.09
Plantar soft-tissue (muscle) density			-0.09 0.62	0.55 0.001	-0.05 0.77	-0.40 0.03
Soft-tissue thickness beneath metatarsal heads				0.11 0.55	-0.47 0.006	-0.01 0.96
Bone density of metatarsal heads					-0.26 0.16	-0.17 0.34
Age						0.03 0.89

\*The correlation coefficients (r) are on top, and the p values are underneath.

approached significance with  $p = 0.07$ ) (Table IV). For the pooled data, the metatarsophalangeal joint angle was inversely related to the plantar soft-tissue density ( $r = -0.41$ ,  $p = 0.02$ ) (Table III).

#### *Bone Density of the Metatarsal Heads*

The mean bone density (and standard deviation) of the metatarsal heads was  $301 \pm 51$  HU (range, 204 to 419 HU) in the control subjects and  $272 \pm 64$  HU (range, 163 to 365 HU) in the individuals with diabetes. There was no difference between the two groups (two-tailed independent-samples t test,  $p = 0.16$ ).

The bone density of the metatarsal heads was inversely

related to the age of the individuals with diabetes ( $r = -0.54$ ,  $p = 0.03$ ) but not to that of the control subjects or in the pooled data (Tables II, III, and IV). As noted, the plantar soft-tissue (muscle) density was directly related to the bone density of the metatarsal heads in the individuals with diabetes and in the pooled data (Tables III and IV). In the control subjects, this relationship approached significance (Table II).

#### *Bone Density of the Midparts of the Metatarsal Shafts*

The mean bone density (and standard deviation) of the mid-

**TABLE IV Correlation Coefficients (R) and P Values\* Derived from Linear Regression Analyses of Selected Parameters for the Pooled Data on the Control Subjects and the Individuals with Diabetes**

	Metatarso- phalangeal Joint Angle	Plantar Soft-Tissue (Muscle) Density	Soft-Tissue Thickness Beneath Metatarsal Heads	Bone Density of Metatarsal Heads	Age	Body-Mass Index
Metatarsophalangeal arthropathy rating	-0.72 <0.001	0.51 0.003	-0.11 0.53	0.32 0.08	-0.20 0.28	-0.16 0.37
Metatarsophalangeal joint angle		-0.41 0.02	0.05 0.79	-0.08 0.66	0.33 0.06	0.31 0.09
Plantar soft-tissue (muscle) density			-0.09 0.62	0.55 0.001	-0.05 0.77	-0.40 0.03
Soft-tissue thickness beneath metatarsal heads				0.11 0.55	-0.47 0.006	-0.01 0.96
Bone density of metatarsal heads					-0.26 0.16	-0.17 0.34
Age						0.03 0.089

\*The correlation coefficients (r) are on top, and the p values are underneath.



TABLE V Metatarsophalangeal Joint Angles

Metatarsophalangeal Joint	Control Subjects*	Individuals with Diabetes*	P Value†
1st	10 ± 5 (4-19)	27 ± 21 (6-71)	<b>0.004</b>
2nd	38 ± 12 (15-57)	50 ± 21 (20-88)	0.064
3rd	33 ± 12 (16-55)	45 ± 16 (22-83)	<b>0.029</b>
4th	28 ± 12 (8-52)	35 ± 16 (12-77)	0.179
5th	24 ± 10 (9-44)	28 ± 14 (9-62)	0.368

\*The values are given, in degrees, as the mean and standard deviation, with the range in parentheses. Positive values indicate extension.

†Significant differences according to the Wilcoxon signed-rank test are in bold.

parts of the metatarsal shafts was  $754 \pm 138$  HU (range, 509 to 966 HU) in the control subjects and  $716 \pm 148$  HU (range, 506 to 997 HU) in the individuals with diabetes. There was no difference between the two groups (two-tailed independent-samples t test,  $p = 0.46$ ).

#### Metatarsophalangeal Arthropathy

Significant differences between the individuals with diabetes and the control subjects were found for the ratings of the second, third, and fourth joints (Table VI).

The individuals with diabetes had greater variability among the ratings for the metatarsophalangeal joints, with standard deviations ranging from 2.0 to 2.7 for the first through fourth toes, than did the control subjects, who had standard deviations ranging from 0.3 to 0.6 for the second, third, and fourth toes (Table VI). In the control group, the variability (standard deviation) among the ratings for the first toe was 1.0 compared with 2.7 in the group with diabetes. The ratings for the fifth toe had low variability in both groups (Table VI).

In the group with diabetes (Table IV), the metatarsophalangeal arthropathy rating was inversely related to the metatarsophalangeal joint angle ( $r = -0.73$ ,  $p = 0.001$ ) and directly related to the soft-tissue density ( $r = 0.58$ ,  $p = 0.02$ ).

These relationships were found in the pooled subject data (Table III), but not in the control subjects when that group was analyzed alone (Table II).

#### Reliability, Repeatability, and Interobserver Variation of Measurements

All objective measurements were highly reliable. The original and repeat measurements averaged  $33^\circ \pm 18^\circ$  and  $33^\circ \pm 18^\circ$  for the metatarsophalangeal joint angles,  $12 \pm 18$  and  $12 \pm 18$  HU for the plantar soft-tissue (muscle) density,  $10 \pm 2$  and  $10 \pm 2$  mm for the soft-tissue thickness, and  $292 \pm 96$  and  $291 \pm 72$  HU for the bone density of the metatarsal heads. The repeatability of the measurements was high, with the variation between the original and repeat measurements representing  $<1.0\%$  (range,  $<0.1$  to  $0.6\%$ ) of the measurement variation among the feet.

The mean difference (and standard deviation) between the two observers with regard to their rating of the metatarsophalangeal arthropathy was  $1.3 \pm 1.8$  of a possible 60 points per subject. The independent ratings of the two observers agreed with each other 66% of the time, and they agreed with the initial consensus rating 61% and 54% of the time. The Spearman rank-order correlation coefficients were 0.91 for the repeat ratings of the two observers, 0.80 for the original

TABLE VI Metatarsophalangeal Arthropathy Ratings

Metatarsophalangeal Joint	Control Subjects*	Individuals with Diabetes*	P Value†
1st	11.5 ± 1.0 (8-12)	10.0 ± 2.7 (5-12)	0.179
2nd	11.8 ± 0.5 (10-12)	9.7 ± 2.6 (5-12)	<b>0.011</b>
3rd	11.9 ± 0.3 (11-12)	10.5 ± 2.0 (7-12)	<b>0.013</b>
4th	11.8 ± 0.6 (10-12)	10.1 ± 2.1 (5-12)	<b>0.003</b>
5th	11.7 ± 0.5 (11-12)	11.25 ± 0.9 (10-12)	0.212
All	58.6 ± 2.5 (51-60)	51.5 ± 7.8 (35-60)	<b>&lt;0.001</b>

\*The values are given, in points, as the mean and standard deviation, with the range in parentheses. The maximum score for each joint was 12 points, which indicates an essentially normal joint. The maximum score for all five joints was 60 points. †Significant differences according to the Wilcoxon signed-rank test are in bold.

consensus ratings and the first observer's repeat ratings, and 0.74 for the original consensus ratings and the second observer's repeat ratings.

### Discussion

Computed tomography is an accurate, reliable, and reproducible tool for studying the musculoskeletal system<sup>39-42,46</sup>. It has been used to aid in the diagnosis of infection in diabetic patients<sup>6,54-56</sup>, but it has not been used to quantify and understand the structure of the diabetic forefoot. We utilized computed tomography instead of magnetic resonance imaging because computed tomography provides more accurate measurements of bone morphology and density, creates higher-spatial-resolution volumetric information, allows subjects to sit during scanning, and permits use of the force-plate and electronics without special adaptation.

While the cause of diabetic ulceration is multifactorial, soft-tissue change (secondary to neuropathy and tissue glycosylation) is a key factor in the process. We found that plantar soft-tissue (muscle) density was significantly lower in the individuals with diabetes. Although edematous changes could have played a role, the reduction in density was most likely due to fatty infiltration and replacement of the muscle. This hypothesis is supported by recent work demonstrating fatty infiltration and replacement in diabetic and denervated muscle<sup>57-59</sup>.

The plantar soft-tissue (muscle) density in the control subjects was inversely related to the body-mass index. Thus, obese control subjects had less dense plantar soft tissue (muscle). We again postulated that this was due to fatty infiltration and replacement of the muscle<sup>60-62</sup>. This relationship between plantar soft-tissue (muscle) density and body-mass index was not found in the individuals with diabetes, probably because of the overriding influence of diabetes-associated peripheral neuropathy. In other words, while obesity results in morbid changes in the forefoot, the influence of diabetes is greater. Interestingly, the plantar soft-tissue (muscle) density was related to the bone density of the metatarsal heads. This probably was a reflection of the general status of the foot—that is, healthy feet had good muscle and bone densities and diseased feet did not.

Despite widely held opinion, we found no difference between the individuals with diabetes and the control subjects with regard to the thickness (an architectural property) of the soft tissue under the metatarsal heads. The soft-tissue thickness was inversely related to age—i.e., older subjects had thinner tissue. Thinning of soft tissue may have a role in the development of metatarsalgia or discomfort beneath the metatarsal heads in older individuals. It may also contribute to production of ulcers in elderly individuals with diabetes.

The magnitudes of our thickness measurements were similar to those in a recent study in which ultrasound was used to measure plantar tissue thickness in four individuals with diabetes (mean age, sixty-three years; mean duration of the diabetes, twelve years)<sup>37</sup>. In that study, the feet of four young healthy individuals (mean age, twenty-two years) were studied for comparison. The tissue thickness in the controls

was approximately twice that in the individuals with diabetes. This finding could be explained by our observation that plantar soft-tissue thickness under the metatarsal heads decreases with age.

Osseous changes are also key factors in the multifactorial process of ulceration. Extension of the metatarsophalangeal joint (an architectural property) unloads the toe and increases weight-bearing pressure on the metatarsal heads<sup>28,63</sup>. Intrinsic muscle atrophy can produce extension of the metatarsophalangeal joint<sup>64,65</sup>. In this study, extension of the metatarsophalangeal joint was more prevalent among the individuals with diabetes, probably as a result of muscle-wasting produced by diabetes-associated neuropathy. This finding corroborates those of previous studies in which hammer toe was found to be a risk factor for ulceration<sup>23,29,30</sup>.

To complete the analysis of forefoot structure, we studied the bone density of the metatarsal heads and metatarsophalangeal arthropathy. Interestingly, we found no difference in the bone density of the metatarsal heads between the individuals with diabetes and the control subjects. However, as noted previously, the bone density of the metatarsal heads was directly related to plantar soft-tissue (muscle) density. To provide an internal control, we also measured the bone (cortical) density of the midparts of the metatarsal shafts. No difference was found between the individuals with diabetes and the control subjects. Our bone density values were in agreement with the measurements of metatarsal density reported by others<sup>66-68</sup>.

In order to better describe the metatarsophalangeal joint, we developed an arthropathy rating based on subluxation, loss of cartilage space, lysis of the metatarsal heads, and osteophytes. While there are other characteristics of arthropathy<sup>30,35</sup>, we wanted to keep the system simple, reliable, and capable of distinguishing individuals with diabetes from control subjects. As tested, the rating system was reliable and reproducible. With use of the arthropathy rating system, we were able to detect differences, between the metatarsophalangeal joints of individuals with diabetes and those of the control subjects, not accounted for by joint extension angles alone.

Individuals with diabetes had more arthropathy than controls, especially in the second, third, and fourth toes. As with other measurements in this study, variability among the individuals with diabetes was higher than that among the control subjects. The first toe was an exception: the measurements at this site varied moderately among the control subjects, which contributed to the lack of a significant difference between the groups with regard to these measurements. The variability of the ratings for the first toes of the control subjects was due to the prevalence of osteoarthritis, which is not surprising since the first toe is the primary site of osteoarthritis in the forefoot<sup>69-71</sup>.

In the individuals with diabetes, an increase in metatarsophalangeal arthropathy was related to an increase in the metatarsophalangeal joint angle and a decrease in the plantar soft-tissue (muscle) density. This patterned data influ-

enced the pooled data but was not present in the control group. We postulated that increased diabetic effects (worse hammer-toe deformity and plantar muscle density) directly or indirectly cause (through altered weight-bearing) worse arthropathy.

Two general concepts stood out in this study. One was that there was more variability among individuals with diabetes than there was among control subjects. The other was that diabetes-associated morbidities were dominant. Aging and obesity caused forefoot comorbidities, but their effects were overridden by those of the diabetes. Both of these concepts demonstrate the complexity of understanding, modeling, and treating the diabetic foot.

In conclusion, computed tomography was an effective tool for demonstrating variations between the forefeet of individuals with diabetes and a previous plantar ulcer and those of normal age-matched controls. By linking architectural and material properties (density) of both soft and osseous tissue, our study provided information that can guide new interventions for prevention or treatment of foot ulcers in individuals with diabetes. ■

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