Neuropathy, Claw Toes, Intrinsic Muscle Volume, and Plantar Aponeurosis Thickness in Diabetic Feet

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Abstract
Background: The objective of this study was to explore the relationship between claw toe deformity, peripheral neuropathy, intrinsic muscle volume, and plantar aponeurosis thickness using computed tomography (CT) images of diabetic feet.

Methods: Forty randomly-selected subjects with type 2 diabetes were selected for each of the following four groups (n = 10 per group): 1) peripheral neuropathy with claw toes, 2) peripheral neuropathy without claw toes, 3) non-neuropathic with claw toes, and 4) non-neuropathic without claw toes. The intrinsic muscles of the foot were segmented from processed CT images. Plantar aponeurosis thickness was measured in the reformatted sagittal plane at 20% of the distance from the most inferior point of calcaneus to the most inferior point of the second metatarsal. Five measurement sites in the medial-lateral direction were utilized to fully characterize the plantar aponeurosis thickness. A linear mixed effects analysis on the effect of peripheral neuropathy and claw toe deformity on plantar aponeurosis thickness and intrinsic muscle volume was performed.

Results: Presence of claw toe deformity (p = 0.008) and presence of neuropathy (p = 0.039) were both associated with decreased intrinsic muscle volume. Subjects with both neuropathy and claw toe deformity had significantly thicker plantar aponeurosis tissue compared with the other three permutation subgroups (p < 0.001). A negative correlation was observed between plantar aponeurosis thickness and intrinsic muscle volume (R² = -0.3233, p < 0.001).

Conclusions: In subjects with claw toe deformity, there were strong relationships between smaller intrinsic foot muscle volumes and thicker plantar aponeurosis tissue. Intrinsic muscle atrophy and plantar aponeurosis thickening may be related to the development of claw toes.

Background
Diabetes currently affects more than 425 million people worldwide and is expected to surpass 629 million individuals by 2045¹. Rate of non-traumatic amputation has trended downward, and is likely a result of improved preventive care, increases in revascularization interventions, and evolving orthopedic management². However, there are still a significant number of diabetic amputations each year (108,000 in the United States in 2014³) and it has been estimated that up to 80% of those are
preceded by diabetic foot ulcers. The development of diabetic foot ulcers is a multi-factorial process that has been associated with, among other factors, diabetic neuropathy, minor foot trauma, and foot deformities. The most common deformity is at the metatarsophalangeal joints (MTPJ), which has been shown to have a prevalence as high as 85% in persons with a history of ulcers and amputation.

Characteristically, this forefoot deformity is commonly called a “claw toe” or a “hammer toe”. A claw toe is defined as extended MTPJ, flexed proximal interphalangeal joint (PIPJ), and flexed distal interphalangeal joint (DIPJ), while a hammer toe is defined as extended MTPJ, flexed PIPJ, and extended DIPJ. For this study, we will refer to both as “claw toes”. Understanding the etiology of claw toes is important in the management of diabetic foot complications via conservative treatment options and/or surgical reduction of this deformity.

The literature is equivocal regarding the relationship between claw toes and diabetes. Initially, it was hypothesized that this deformity is caused by an imbalance between the extrinsic and intrinsic foot muscles. When the intrinsic muscles are weakened, theoretically they are overpowered by the extrinsic muscles. This is exacerbated by dorsiflexion of the MTPJ, which causes the moment arm of the interosseous tendons to decrease, further reducing the ability of the intrinsic muscles to maintain plantarflexion of the proximal phalanx. However, some studies using magnetic resonance imaging (MRI) to quantify intrinsic muscle atrophy in diabetic neuropathic subjects have raised important questions on this issue, warranting further investigation. Conversely, in addition to intrinsic muscle atrophy, there is also some evidence that the plantar aponeurosis (PA), claw toe deformity, and diabetes are closely linked. The PA contributes to MTPJ stability by providing plantarflexion at this joint during weight bearing. Several researchers have reported a relationship between claw toe and PA dysfunction. Others have found that subjects with diabetic feet have thicker PA than controls. On the basis of these prior studies, the etiology of the claw toe deformity as it relates to diabetic foot complications is not well-understood. Many studies have evaluated the links between single factors, but the links between multiple factors remain unclear. The
The purpose of this study was to explore the relationship between claw toes, neuropathy, intrinsic muscle volume, and plantar aponeurosis thickness using computed tomography (CT) images.

Materials And Methods

Subjects

This retrospective study was performed on a subset of subjects taken from a larger study of over 220 subjects with diabetes recruited from clinics at the Department of Veterans Affairs Puget Sound Health Care System, with approval from the Institutional Review Board. Subjects were excluded for a variety of reasons including: foot ulceration, bilateral foot amputation, non-ambulatory, inability to perform the protocol due to medical or psychiatric reasons, or inability to provide informed consent. The presence of claw toe deformity was determined via clinical examination and confirmed with a partial weight-bearing CT scan. Peripheral neuropathy was defined as insensitivity to a 10-gram Semmes-Weinstein monofilament at one of eight plantar locations (hallux, fifth toe, first metatarsal head, third metatarsal head, fifth metatarsal head, medial midfoot, lateral midfoot and heel) (Fig. 1E).

From this initial cohort, ten subjects with type 2 diabetes were randomly chosen in each of the following four groups: 1) peripheral neuropathy with claw toes (N + C+), 2) peripheral neuropathy without claw toes (N + C−), 3) non-neuropathic with claw toes (N − C+), and 4) non-neuropathic without claw toes (N − C−). Subjects were matched for sex, age, body mass index (BMI), duration of diabetes, and glycated hemoglobin (HbA1c). Out of a possible 8 monofilament testing sites, neuropathic subjects had insensitivity in 5 ± 2.5 locations (mean ± standard deviation).

CT images

Subjects underwent bilateral foot and ankle CT scanning (MX8000 IDT 16; Philips, the Netherlands; 140 kVp, 70 mA, 0.976 × 0.976 × 1.00 mm slices) in a custom-designed partial weight-bearing loading apparatus (target load = 20% body weight) in a neutral foot position (Fig. 1A). CT volumes were imported into Mimics (version 21, Materialise, Leuven, Belgium). These CT acquisitions were optimized for a larger study focused on quantifying bone shape and position, and so the reconstruction kernel and imaging parameters were not intended for soft tissue visualization. To approximate a soft tissue reconstruction kernel, the CT image data were filtered in Mimics to reduce noise and enhance the contrast of the plantar tissues relative to the surrounding regions. The
following filter banks were used: one iteration of binomial blur, followed by 3 × 3 median filtering, followed by one iteration of binomial blur, followed by 5 × 5 median filtering. This sequence of filters was optimized via experimentation on a subset of our scan data and resulted in acceptable noise reduction in the image intensities without adversely compromising the delineation of the plantar tissue borders (Fig. 1B).

**Intrinsic Muscle Segmentation and Volume Measurement**

The intrinsic muscles of the foot were initially segmented from the filtered images in Mimics by an orthopedic surgeon who has specialized in foot and ankle surgery for ~10 years (TK) using the LiveWire semi-automatic segmentation tool. The resulting segmentation masks were eroded by three pixels uniformly, and the Smart Expand segmentation tool was then used to grow the segmentations back away from the center until the computer detected a boundary in the images. Given the reduced noise in the filtered (low-pass) images, the Smart Expand tool (based on the Level-set segmentation method) should expand to fill the regions of the intrinsic muscles and stop at the tissue boundaries. Final muscle segmentation masks (Fig. 1D) were rendered as three-dimensional (3D) surface models of segmented bones and visually inspected for errors. The intrinsic muscle volume was calculated in Mimics as the volume of the segmentation mask based on the size and number of voxels that constitute the muscle mask. Foot length, defined as the distance from the most inferior point of the calcaneus to the most inferior point of the second metatarsal, was included as a co-variate to account for foot size. All operations were performed in a similar manner irrespective of subject group, i.e., subject group was unknown during processing.

**Plantar Aponeurosis Thickness Measurement**

CT volumes were resliced by an orthopedic surgeon (TK) using Mimics’s multi-planar reconstruction tool to locate the most proximal point of the calcaneus and the most distal point of the head of the second metatarsal on axial images; the volume was then resliced in the sagittal plane containing these two points (Fig. 1C). PA thickness was measured in the resliced sagittal plane at 20% of the distance from the most inferior point of the calcaneus to the most inferior point of the second metatarsal as described by D’Ambrogi et al.\(^\text{18}\). Five measurement sites in the medial to lateral
direction were utilized to appropriately characterize the PA thickness and reduce measurement error (the mid-substance of the PA central component, 1 mm medially, 2 mm medially, 1 mm laterally, 2 mm laterally). The PA tissue near the heel on the filtered sagittal CT appeared as a brighter region (higher Hounsfield units from greater radio-attenuation) relative to the surrounding tissues. To measure the apparent thickness of the PA, Mimics’s intensity profile tool was used to define measurements across the thickness of the PA at the measurement sites in the sagittal plane (Fig. 1E). Operators utilized the sagittal image data in conjunction with the intensity profile plots to demarcate the superior and inferior borders of the PA for each of the five measurement sites. All operations were performed while blinded to foot group.

Statistical analysis
The chi-squared test was used to verify equal distributions of sex between each group. One-way analysis of variance (ANOVA) was used to verify differences in age, BMI, foot length which is the distance from the most proximal point of the calcaneus to the most distal point of the head of the second metatarsal on axial images, duration of diabetes and HbA1c levels. Repeatability and reliability of the muscle volume and PA thickness measurements were assessed using intraobserver and interobserver correlation coefficients (ICC). To assess the reliability of intrinsic muscle volume measurements, five subjects, including one from each group, were segmented a second time, two weeks later, by an orthopaedic surgeon (TK). The rater was blinded to the first segmentation and the presentation order was randomized to prevent memory bias. To assess the reliability of the PA thickness measurements, measurements were performed by an orthopaedic surgeon (TK) and two biomechanical engineers with at least five years of experience in processing medical images of the foot and ankle (MK and WR). PA thickness measurements were repeated three separate times on 12 randomly selected subjects after intervals of at least five days.

A linear mixed effects analysis\textsuperscript{19} of the relationship between the presence of neuropathy and claw toe deformity was performed using R statistical software\textsuperscript{20}. PA thickness measurements and intrinsic muscle volume were modeled as fixed effects. For the intrinsic muscle volume model, random effects included intercepts for subjects as well as by-subject random slopes for the effects of foot length and
muscle volume. For the PA model, intercepts for subjects were included as random effects. Upon finding significant interactions between neuropathic status and claw toe deformity status, post-hoc pair-wise comparisons between the four subgroups (presence of claw toe deformity (C+) and presence of neuropathy (N+), or N + C+, N + C−, N − C+, N − C−) were performed. For all analyses, \( \alpha = 0.05 \) was used to indicate statistical significance.

### Results

Subject demographic characteristics demonstrated that sex distribution (\( p = 0.5 \)), age (\( p = 0.54 \)), BMI (\( p = 0.46 \)), foot length (\( p = 0.26 \)), duration of diabetes (\( p = 0.21 \)), and HbA1c level (\( p = .39 \)) were not statistically different between each group (Table 1). As a result, these non-significant variables were excluded from the linear mixed-effects model.

| Patient characteristics | Peripheral neuropathy | Non-neuropathic |
|-------------------------|-----------------------|-----------------|
|                         | Claw toes (N+C+)       | No claw toes (N+C−) |
|                         | 10                     | 10              |
| Sex (male/female)       | 9/1                    | 9/1             |
| Age (years)             | 60.2 ± 6.0             | 57.2 ± 5.8      |
| Body mass index (kg/m²) | 37.6 ± 4.6             | 34.9 ± 8.3      |
| Foot length (mm)        | 162.2 ± 11.9           | 158.4 ± 8.1     |
| Diabetes duration (years)| 9.3 ± 3.8             | 7.2 ± 5.3       |
| HbA1C (%)               | 6.7 ± 0.7              | 7.7 ± 0.8       |

Intrinsic muscle volume segmentations were highly repeatable (ICC = 0.993, 95% confidence interval [CI] range: 0.946–0.999). The difference in total intrinsic muscle volume between the first and second segmentations ranged from \(-4.9\%\) to \(+4.2\%\). The inter-class correlation coefficient of all PA thickness measurements between the three raters was ICC(A,1) = 0.84 (95% CI range: 0.784–0.889), and the intra-class correlation coefficients of the three raters were ICC\(_{rater1}\) = 0.983, ICC\(_{rater2}\) = 0.924, and ICC\(_{rater3}\) = 0.765. Rater 1 (TK) exhibited the highest repeatability amongst raters and subsequently performed all the PA thickness measurements for the study data analysis (95% CI range: 0.974–0.989).

The mean intrinsic muscle volume across all subjects was 99,525 ± 31,133 mm\(^3\). The presence of claw toe deformity (C+) and presence of neuropathy (N+) were both associated with decreased
intrinsic muscle volume (Fig. 2, Table 2).

| Predictor                  | Estimate | Standard error | Lower 95% CI | Upper 95% CI | p-value |
|----------------------------|----------|----------------|--------------|--------------|---------|
| Intrinsic muscle volume    |          |                |              |              |         |
| (Intercept)                | 32117    | 66284          | -            | -            | -       |
| Foot length                | 571      | 431            | -274         | 1417         | 0.19    |
| Neuropathy status          | -19857   | 9257           | -38002       | -1713        | 0.039*  |
| Clawed-toe status          | -25104   | 8999           | -42744       | -7465        | 0.008*  |
| Neuropathy * Claw-toe      | -30742   | 17245          | -62541       | 3057         | 0.08    |
| interaction                |          |                |              |              |         |
| Plantar aponeurosis        |          |                |              |              |         |
| (Intercept)                | 3.11     | 0.32           | 2.48         | 3.73         | -       |
| Neuropathy status          | 0.21     | 0.45           | -0.68        | 1.10         | 0.65    |
| Clawed-toe status          | 0.06     | 0.45           | -0.83        | 0.94         | 0.90    |
| Neuropathy * Claw-toe      | 1.77     | 0.64           | 0.51         | 3.02         | 0.006*  |
| interaction                |          |                |              |              |         |

Neuropathy was associated with a mean 19,857 mm$^3$ lower (20.0%) intrinsic muscle volume ($p = 0.039$), while claw toe deformity was associated with a mean 25,104 mm$^3$ lower (25.2%) intrinsic muscle volume ($p = 0.008$). Subjects with both neuropathy and claw toe deformity (N + C+) had significantly smaller intrinsic muscle volume compared with N + C− ($p = 0.019$) and N − C− ($p = 0.015$). Although there was a trend toward smaller intrinsic muscle volume in N + C+ subgroup compared to N − C + subgroup, this difference did not reach statistical significance ($p = 0.069$). The interaction between neuropathy and claw toe deformity was not significant for intrinsic muscle volume ($p = 0.08$).

The mean PA thickness value across all subjects and measurement sites was 3.68 ± 1.34 mm. Neither the presence of neuropathy nor the presence of claw toe deformity by itself had any significant between-group differences for the numbers we had in this study (Fig. 3, Table 2). However, the interaction between neuropathy and claw toe deformity was significant ($p = 0.006$). Subjects with both neuropathy and claw toe deformity (N + C+) had significantly thicker PA compared with the other three subgroups, with relative mean differences of 1.82 mm (N-C+, $p = 0.0015$), 1.98 mm (N + C−, $p = 0.0006$), and 2.03 mm (N-C−, $p = 0.0004$) (Table 2). A negative correlation was seen between PA thickness and intrinsic muscle volume ($R^2 = 0.3233$, $p < 0.001$) (Fig. 4).

Discussion
Although amputation rates due to diabetes have decreased, a large number of amputations are still performed annually\(^3\). Toe deformity has been shown to have a prevalence of over 85% in patients with a history of ulcers and amputation\(^6\). Previous studies have shown that multiple factors have been associated with claw toe deformity, but the relationships between each of these factors remain unclear. In this study, explored the association between claw toes, peripheral neuropathy, intrinsic muscle volume, and PA thickness.

CT scans have sufficient resolution to distinguish bone and muscle\(^21\) and have been used in earlier studies to estimate muscle size\(^22, 23\). Robertson et al.\(^23\) performed CT scans to assess soft tissue density under the metatarsal shaft, as a proxy measure of intrinsic muscle size in a patient with diabetic neuropathy. However, they reported difficulty defining the borders of the individual intrinsic muscles, which may be related to the insufficient contrast resolution of CT scans. In our study, we reduced noise and enhanced the contrast of the plantar tissues relative to the surrounding regions. While systematic errors in the soft tissue appearance on the CT images may occur, we have no reason to believe the biases are correlated with the subject conditions of neuropathy or claw toe presence. All measurement errors in the study are assumed to be random and equally-distributed between subject groups.

This study quantified intrinsic muscle volume and PA thickness on the same cohort of patients. Our findings indicate that neuropathic feet have less intrinsic muscle volume than non-neuropathic feet. Reduction of intrinsic muscle volume in the diabetic neuropathic foot has been demonstrated previously\(^8, 9\). Our results also revealed that diabetic feet with claw toes have less intrinsic muscle volume than diabetic feet without claw toes. Cheuy et al.\(^10\) and Robertson et al.\(^23\) also found a relationship between intrinsic muscle volume and forefoot deformity. They reported that reduced lean muscle volume or muscle density was associated with increased hyperextension at the MTPJ in diabetic patients with neuropathy. However, conflicting results regarding the relationship between intrinsic muscle volume reduction and claw toes have been shown in other literature. Andersen et al.\(^8\)
and Bus et al.\textsuperscript{9, 11} reported no relationship between muscle volume and MTPJ deformity. Bus et al. found a 73% decrease in intrinsic muscle cross sectional area between patients with diabetic neuropathy and non-neuropathic controls, but only two of eight patients with neuropathy had toe deformities\textsuperscript{9}. Anderson et al. found that patients with diabetic neuropathy had an intrinsic muscle volume just over half that of either controls or patients with no diabetic neuropathy, but none of the diabetic patients with neuropathy had toe deformities\textsuperscript{8}. The reasons for these differences are likely due to variations in experimental design or technique. For example, Andersen et al. was studying diabetic neuropathic feet and retrospectively considered the presence of claw toes\textsuperscript{8}. Further, Bus et al. used a single CT slice to estimate intrinsic muscle volume\textsuperscript{9, 11}. In contrast, Cheuy et al. reported that less forefoot lean muscle tissue was associated with greater MTPJ deformity\textsuperscript{10}. This group, whose results agree with the current study, truly measured the 3D intrinsic muscle volume as we did. Even though image segmentation and 3D analysis of the muscle volume is time-consuming, thus far this methodology is showing relationships not elucidated by the two-dimensional methods.

Several studies have reported thicker PA in diabetic feet than in control feet\textsuperscript{14, 15, 16, 18}. Duffin et al. concluded that the pathogenesis of PA thickening may have been caused by non-enzymatic glycation and mechanical loading\textsuperscript{15}. Our results indicated that diabetic neuropathic feet with claw toes had thicker PA than other groups, but we are unaware of a similar study comparing PA thickness between feet with or without claw toe deformity and with or without neuropathy. In our study, the mean PA thickness without claw toes and neuropathy was 3.68 ± 1.34 mm, which is similar to the average value 4.2 ± 0.9 mm reported by the measurements of Boulton et al. using CT images\textsuperscript{14} as we did. However, using ultrasound Duffin et al., Giacomozzi et al. and D’Ambrogi et al. measured diabetic PA thickness that was less than our results: 1.6 ± 1.8 mm, interquartile range, 2.9 ± 1.2 mm, and 2.9 ± 1.2 mm, respectively\textsuperscript{15, 16, 18}. This difference is likely due to differences in imaging modality, i.e., CT vs. ultrasound.

There were several limitations to this study. First, the duration of neuropathy and claw toes was not
determined. Second, we did not account for the possibility that the deformity might have been caused by ill-fitting footwear and congenital anomalies, especially for patients with claw toes without neuropathy. Third, we did not consider or quantify variation in patient daily activity levels (e.g., step counts), which may be related to a variety of health factors. Fourth, the threshold for diagnosing neuropathy is controversial. Wang et al. concluded in a meta-analysis review that monofilament tests have limited sensitivity for screening diabetic peripheral neuropathy. Feng et al. suggests testing at three sites including the plantar aspects of the great toe, the third metatarsal, and the fifth metatarsal, to maximize the diagnostic value of Semmes Weinstein monofilament examination. In our current study, we performed monofilament testing at eight plantar locations, including the three recommended sites by Feng et al. As such, we are confident in our classifications of neuropathic patients, despite the limitations of monofilament assessment described by Wang. Lastly, the CT scanning and image analysis presented multiple challenges. We had seven subjects in which there was incomplete contact between the heel and the foot plate on CT images (i.e., the subjects were not weight-bearing on their heels). We defined the profile line for measuring PA thickness as the “vertical” in the image coordinate system (see Fig. 1E). This was considered a potential source of bias in measurements of PA thickness because some of the subjects’ feet were tilted with respect to this vertical axis. The maximum angle error was approximately 10 degrees. However, even in the worst-case scenario of no heel contact, our values were within two percent of the “true PA thickness”. This equates to about 0.07 mm of error for the average 3.68 mm-thick PA tissue. Additionally, we did not quantify the function and strength of the intrinsic muscles and PA. Muscle volume and PA thickness do not necessarily reflect these factors. A final limitation of using CT to assess intrinsic muscle size is that CT is generally not the modality of choice for these kinds of soft tissue measurements. However, this paper is a secondary analysis of an osseous foot structure study and the CT scans were never intended to image the soft tissue of the foot.

Conclusion
From our results, we suggest that intrinsic muscle atrophy and increased PA thickness are potentially related to the development of claw toe deformity. Certainly, patient education and adequate control
of blood glucose level are important, but considering our results, a strength training program for the intrinsic muscles of the foot\textsuperscript{26} may help to improve specific muscle strength and prevent muscle atrophy to minimize the risk of development of deformity that could lead to amputation. However, additional research is required to test such an intervention for patients with diabetes.

**Abbreviations**

3D three dimensional

ANOVA one-way analysis of variance

BMI body mass index

CI confidence interval

C+ claw toe deformity

CT computed tomography

DIPJ distal interphalangeal joint

HbA1c glycated hemoglobin

ICC intraobserver and interobserver correlation coefficients

MRI magnetic resonance imaging

MTPJ metatarsophalangeal joints

N+ presence of neuropathy

N+C+ peripheral neuropathy with claw toes

N+C− peripheral neuropathy without claw toes

N−C+ non-neuropathic with claw toes

N−C− non-neuropathic without claw toes

PA plantar aponeurosis

PIPJ proximal interphalangeal joint

**Declarations**

**Ethics approval and consent to participate**

This study was performed following approval of the Department of Veterans Affairs Puget Sound Health Care System Institutional Review Board. Informed consent was obtained from test subjects.
Consent for publication

All subject identities were blinded, not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors’ contributions

TK conducted the data analysis and wrote the first draft of the manuscript. ET developed analysis software, generated the figures, helped analyze the data, and participated in the writing of the manuscript. MK helped analyze the data and participated in the editing of the manuscript. BS was involved in the initial funding mechanism, in determining clinical significance, and helped finalize the manuscript. WL wrote the initial grant, developed the data collection protocols, assisted in data analysis, and participated in the writing of the manuscript.

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Figures
Figure 1

A) Partial weight-bearing computed tomography loading frame (CT). B) Filtered CT image to reduce noise and enhance the contrast of the plantar tissues relative to the surrounding regions. C) CT volumes were resliced using the multi-planar reconstruction tool to align the sagittal image plane with the most proximal point of calcaneus and the most distal point of second metatarsal head. D) Final segmentation mask of intrinsic muscle of the foot. E) Eight monofilament probe sites (cyan regions) were used to determine peripheral neuropathy and five measurement sites (yellow lines) in the medial-lateral direction were utilized to fully characterize the plantar aponeurosis (PA) thickness. Measuring the apparent thickness of the PA by using intensity profile measurements defined across the thickness of the PA at the measurement sites in the sagittal plane. Distance between the superior (pink)/inferior (blue) marks was taken as the PA thickness.
Figure 2

Mean intrinsic muscle volume (IMV) by subgroup.
Figure 3

Mean plantar aponeurosis (PA) thickness by subgroup.
Correlation between plantar aponeurosis thickness and normalized intrinsic muscle volume.