

# Ultrasound Findings After Surgical Decompression of the Tarsal Tunnel in Patients With Painful Diabetic Polyneuropathy: A Prospective Randomized Study

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## OBJECTIVE

It has been hypothesized that the development of diabetic polyneuropathy (DPN) is due to swelling of the nerve, as well as thickening and stiffening of the surrounding ligaments, causing chronic compression of nerves. We aimed to examine the effect of surgical decompression of the tibial nerve on the mean cross-sectional area (CSA).

## RESEARCH DESIGN AND METHODS

We performed a randomized controlled trial of 42 subjects with painful DPN diagnosed using the Diabetic Neuropathy Score. A computer randomized for the surgery arm of the study. A control group consisting of 38 healthy subjects was included. An experienced sonographer measured the CSA and thickness-to-width (T/W) ratio of the tibial nerve, as well as the thickness of the flexor retinaculum.

## RESULTS

CSA is significantly larger in patients with painful DPN ( $8.4 \pm 3.9 \text{ mm}^2$ ) than in control subjects ( $6.4 \pm 1.3 \text{ mm}^2$ ),  $P = 0.007$ . The T/W ratio in patients with painful DPN is 0.64 and in control subjects 0.59,  $P = 0.03$ . Patients with DPN have a significantly thicker retinaculum (1.07 mm) than control subjects (0.84 mm),  $P < 0.001$ . Mean follow-up was 28.2 weeks (range 23–45). Difference between baseline and follow-up in the operated leg was  $1.49 \text{ mm}^2$  and in the control leg  $1.81 \text{ mm}^2$ ,  $P = 0.674$ .

## CONCLUSIONS

Decompression of the tibial nerve does not result in a significant difference between baseline and follow-up in CSA using ultrasound between the operated and control leg. Ultrasound measurements show a significantly increased CSA, a significantly thicker retinaculum, and a significantly increased T/W ratio in patients with painful DPN compared with healthy control subjects.

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Polyneuropathy is a common complication in diabetes. The prevalence of neuropathy in patients with diabetes is ~30%. During the course of the disease, up to 50% of the patients will eventually develop neuropathy (1). Its clinical features are characterized by numbness, tingling, or burning sensations and typically extend in a distinct stocking and glove pattern. Prevention plays a key role since poor glucose control is a major risk factor in the development of diabetic polyneuropathy (DPN) (1,2).

There is no clear definition for the onset of painful diabetic neuropathy. Different hypotheses have been formulated.

Hyperglycemia in diabetes can lead to osmotic swelling of the nerves, related to increased glucose conversion into sorbitol by the enzyme aldose reductase (2,3). High sorbitol concentrations might also directly cause axonal degeneration and demyelination (2). Furthermore, stiffening and thickening of ligament structures and the plantar fascia make underlying structures more prone to biomechanical compression (4–6). A thicker and stiffer retinaculum might restrict movements and lead to alterations of the nerve in the tarsal tunnel.

Both swelling of the nerve and changes in the tarsal tunnel might lead to nerve damage through compression.

Furthermore, vascular changes may diminish endoneural blood flow and oxygen distribution. Decreased blood supply in the (compressed) nerve might lead to ischemic damage as well as impaired nerve regeneration.

Several studies suggest that surgical decompression of nerves at narrow anatomic sites, e.g., the tarsal tunnel, is beneficial and has a positive effect on pain, sensitivity, balance, long-term risk of ulcers and amputations, and quality of life (3,7–10). Since the effect of decompression of the tibial nerve in patients with DPN has not been proven with a randomized clinical trial, its contribution as treatment for patients with painful DPN is still controversial.

Lee and Dauphinée (11) observed that nerves in patients with diabetic neuropathy are swollen and their cross-sectional area (CSA) is significantly

greater than in patients with diabetes but without neuropathy. Watanabe et al. (12) found that the CSA of both the tibial and median nerve in patients with diabetes is significantly increased compared with healthy control subjects.

In this study, we compare the mean CSA and any changes in shape of the tibial nerve before and after decompression of the tarsal tunnel using ultrasound in order to test the hypothesis that the tarsal tunnel leads to compression of the tibial nerve in patients with DPN.

## RESEARCH DESIGN AND METHODS

### Design

This single-center, randomized, controlled trial was performed at the University Medical Center Utrecht between 2011 and 2013. This study is part of the Lower Extremity Nerve Entrapment Study (LENS).

### Subjects

Forty-two patients with type 1 or type 2 diabetes between 18 and 85 years of age were enrolled in the study. All subjects suffered from painful bilateral DPN, diagnosed using the Diabetic Neuropathy Score (13), with a pain score on the visual analog scale (>2) (14). All patients had a positive Tinel sign of the tibial nerve at the malleoli and an Ankle Brachial Index between 0.8 and 1.15 with palpable peripheral pulsations in the posterior tibial artery and dorsal pedal artery, the toe-brachial blood pressure  $\geq 0.7$  (15).

To compare the results with the normal population, a control group consisting of 38 healthy subjects aged 18–90 years with no anamnestic medical history of a poor vascular state was enrolled. Subjects with previous ankle fractures were excluded as well as subjects with a BMI  $> 35 \text{ kg/m}^2$ , or with other causes for neuropathy (e.g., HIV infection or chemotherapy). Demographic information of age, height, weight, BMI, and sex was recorded for all subjects, as well as type and duration of diabetes for patients.

### Randomization

Randomization was performed by the computer, using a web-based randomization system. Subjects were matched for visual analog scale, age, and sex.

### Protocol

The protocol of the LENS was approved by the Committee of Medical Research Ethics of the University Medical Center Utrecht. The study was conducted according to the principles of the Declaration of Helsinki (version 22–10–2008) in accordance with the Dutch Medical Research Involving Human Subjects Act (WMO).

### Surgery

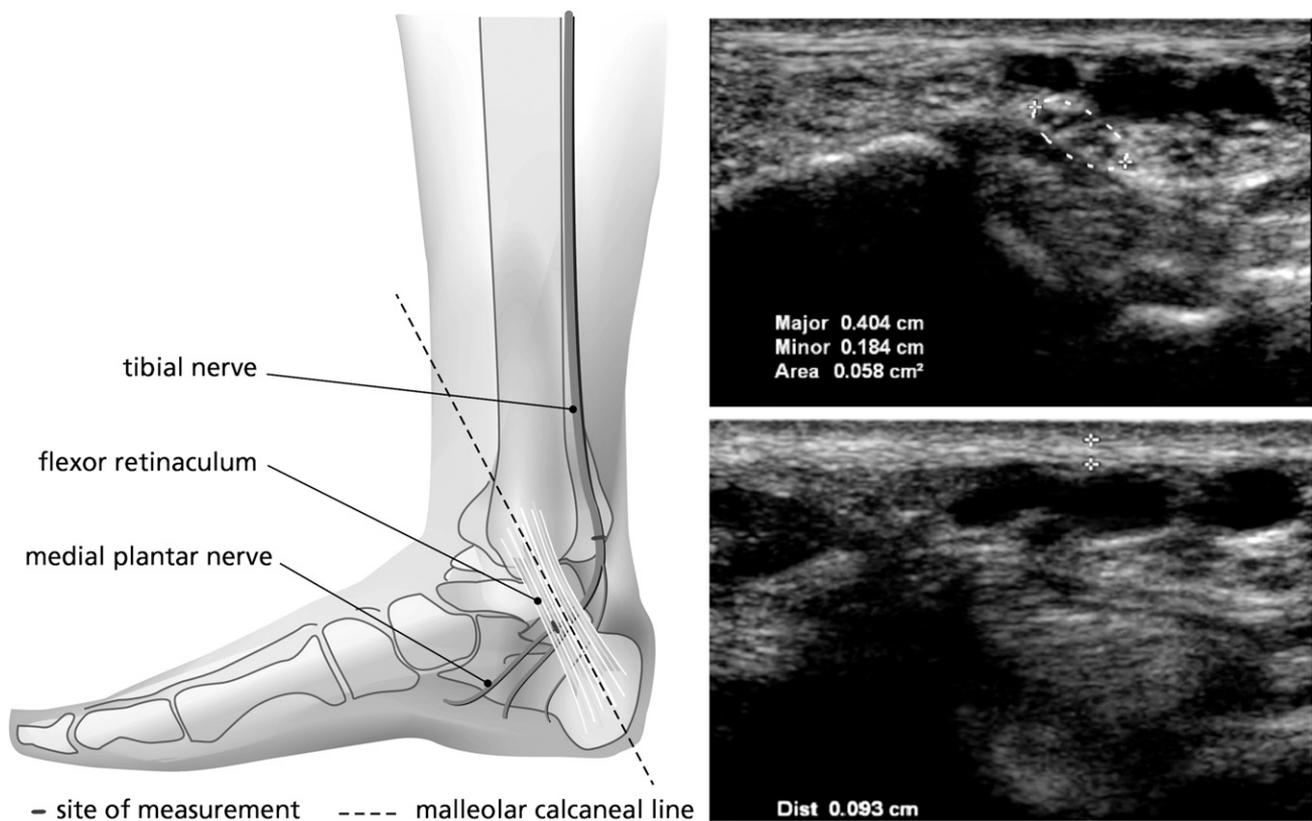
All patients underwent decompression of the nerves of the lower limbs by the same surgeon (J.F.M.M.v.M.). Decompression of the lower limb nerves included the following: the tibial nerve and its calcaneal, medial, and lateral plantar branches at the ankle; the deep peroneal nerve over the dorsum of the foot; the common peroneal nerve near the head of the fibula; and the superficial peroneal nerve at the calf.

### Ultrasound

One single radiologist (I.t.K.) performed an ultrasound in both legs of the tibial nerve at the medial ankle, with the patient in supine position and the hip in exorotation, using a Philips iU22 with a 15–7-MHz transducer. The short axis and long axis of the tibial nerve were measured at two specific locations: the medial plantar branch of the tibial nerve under the flexor retinaculum and the tibial nerve cranial to flexor retinaculum, 3 cm proximal to the malleolar calcaneal line. Measurements were performed by drawing an ellipse around the nerve, after which the program calculated the minor and major axis and the CSA (Fig. 1). The thickness of the flexor retinaculum itself was measured as well. All measurements were performed twice. All subjects underwent ultrasonography at baseline, and patients at follow-up as well. At baseline, the radiologist randomly examined healthy control subjects and patients with DPN. At follow-up, the radiologist was not blinded for the groups. CSA was calculated by major axis  $\times$  minor axis  $\times \pi \times 1/4$ . The thickness-to-width (T/W) ratio was determined by dividing the shortest axis by the longest axis.

### Statistical Analysis

Analyses were performed in IBM SPSS statistics version 20.0. All measured



**Figure 1**—Left panel: Ultrasound probe placement. Upper right: in the ellipse, the tibial nerve is shown with corresponding measurements. Lower right: The thickness of the flexor retinaculum with corresponding measurement is shown between the marks.

values were compared between the patients with DPN and the control subjects. The mean and SDs for the CSA, T/W ratio, and thickness of the retinaculum were assessed. To determine whether there were significant differences between the patients and control subjects, an independent samples Student *t* test was applied for continuous variables and the  $\chi^2$  test for categorical variables. For comparison of values within patients, a paired Student *t* test was applied. To identify potential confounding effects, multivariate analysis was performed using MANOVA. To test the reliability of the ultrasound measurements, intraclass correlation coefficients (ICCs) were calculated using a two-way mixed model and consistency measures. Statistical significance was assessed as  $P < 0.05$ . The current study was performed as a substudy from a randomized controlled trial. The sample size of the study was therefore not tailored to the current research question. Using 38 control subjects and

42 patients, we have 80% power to detect differences between the groups of 0.65 SDs (=Cohen's D) per variable, which is a medium size difference.

## RESULTS

### Patient Characteristics

Thirty-eight control subjects and 42 patients with painful DPN were enrolled in this study. The painful DPN patient characteristics are summarized in Table 1. Patients with painful DPN were significantly taller and heavier, had a higher BMI, and were more likely to be male.

### Nerve Appearance

Nerve size was significantly different between the painful DPN group and control subjects (Table 2). Baseline data from one patient were missing, and data from nine subjects were not obtained due to difficulties identifying the nerve.

The nerve size was significantly larger in the painful DPN group than in the control group in the tarsal tunnel, but different between the groups cranial to the tarsal tunnel. The thickness of the flexor

retinaculum was significantly larger in subjects with painful DPN compared with control subjects (Table 2).

No significant differences in CSA in the tarsal tunnel at baseline and at follow-up after tarsal tunnel release were observed between the painful DPN group and the control group (Table 3). Follow-up measurements were obtained 23–45 weeks after surgery (mean 28.2 weeks). Data at baseline from one patient were missing. Follow-up data of four patients at follow-up were not obtained due to death (not study related), loss to follow-up, disturbed architecture, and Charcot foot.

The T/W ratio of the nerve in the tarsal tunnel was significantly larger in patients with painful DPN compared with control subjects. The T/W ratio cranial to the tarsal tunnel was not significantly different between patients with painful DPN and control subjects (Table 2). Baseline data from one patient were missing, and data from eight patients were not obtained due to

**Table 1—Patient characteristics**

	Painful DPN group (n = 42)	Control group (n = 38)	P value
Age (years)	60.36 ± 11.34	61.29 ± 14.62	0.75
Height (cm)	175.74 ± 9.10	170.21 ± 8.05	0.002
Weight (kg)	89.76 ± 17.22	70.84 ± 11.71	<0.001
BMI (kg/m <sup>2</sup> )	28.98 ± 4.70	24.40 ± 3.21	<0.001
Male [n (%)]	26 (61.90)	11 (28.95)	0.003
Diabetes duration (years)	18.53 ± 11.96	—	—
Type 1 diabetes [n (%)]	10 (23.81)	—	—

Data are mean ± SD unless otherwise indicated.

difficulties with nerve identification. The difference at baseline and at follow-up in the operated leg was not significantly different from the difference in the control leg (Table 3).

### Multivariate Analysis

Possible confounders that were taken into account were height, weight, BMI, and sex. After correction for these factors with MANOVA, differences between patients and control subjects remain significant ( $P = 0.006$ ). When also correcting for age, the  $P$  value is 0.007.

### ICCs

Ultrasound measurements of the patients were performed at baseline and follow-up, and the control subjects were measured once. All measurements were performed by one single radiologist. The ICC for all the measurements in the right leg was 0.66. In the group of the first 59 recorded measurements, the ICC was 0.62 (good), and the ICC in the last 59 measurements was 0.76 (very good), suggesting an improvement of reliability of ultrasound in time.

### CONCLUSIONS

Polyneuropathy is a common complication in diabetes. Because of diabetes and changes in glucose levels, nerves will swell due to osmosis and

ligament structures will be stiffer and thicker (1,2,4,6,11). In this study, we aimed to demonstrate the changes in these structures and the influence of decompression of the tarsal tunnel on the tibial nerve at the ankle using ultrasound.

First our study demonstrates that the CSA in the tarsal tunnel is significantly larger in patients with painful DPN ( $8.4 \pm 3.9$  mm<sup>2</sup>) than in healthy control subjects ( $6.4 \pm 1.3$  mm<sup>2</sup>),  $P = 0.007$ . Variations in methods in the current literature give a variation in results and make the studies difficult to compare (11,12,16–21). For example, Lee and Dauphinée (11) found an increased CSA using ultrasound in patients with DPN (24 mm<sup>2</sup>) compared with healthy control subjects (12 mm<sup>2</sup>). Four studies evaluated healthy individuals and describe CSAs between 7.9 and 13.7 mm<sup>2</sup>. All the CSAs were measured at different locations in the ankle (16–18,20). Riazi et al. (18) compared people with diabetes with and without polyneuropathy and found a significant increase in CSA in patients with DPN. Watanabe et al. (12) found a significant increase in CSA in people with diabetes with a low conduction velocity compared with people with a high conduction velocity and also in people with diabetes with a low conduction velocity compared with healthy control

subjects. The CSAs found in patients with polyneuropathy vary between 15.0 and 23.0 mm<sup>2</sup> (12,21).

Interestingly, in our study, decompression of the tibial nerve did not lead to a significant difference in CSA between baseline and follow-up between the operated leg and the control leg. At follow-up, a decrease was found in both the operated leg and the control leg. Since the effect was found in both legs, it is unlikely to be due to the decompression. It might be explained by improved accuracy of measurements due to increasing experience of the radiologist. The reliability improved from “good” in the measurements performed in the first half of the study to “very good” in the measurements in the second half. The changes in CSA might be too small to be measurable with ultrasound. Also, there were follow-up data missing from some subjects, which might have led to nonsignificant outcomes.

Only one recent study by Zhang et al. (22) evaluates the CSA in patients with DPN before and after decompressive surgery and compares this with people with diabetes. A significant swelling and increase of CSA in patients with DPN compared with patients with diabetes is noted, and a significant improved CSA after decompression is described. Exact numbers are not given, and it is unclear what results are used for the comparison. Baseline characteristics of the patients are concise, and the baseline characteristics of the control subjects are missing. Therefore, possible confounders are not taken into account, which may lead to inaccurate and misleading results.

Current study results in literature suggest that the CSA also differs at other locations than the tarsal tunnel. Liu et al. (23) found a significantly increased CSA

**Table 2—Results of patients with painful DPN compared with controls**

	Location	Painful DPN group	Control subjects	Δ (95%CI)	P value
Mean CSA	Tarsal tunnel (mm <sup>2</sup> ) ± SD	8.45 ± 3.99	6.43 ± 1.32	2.02 (0.69 to 3.34)	0.004
	Cranial to tarsal tunnel (mm <sup>2</sup> ) ± SD	8.08 ± 3.48	9.20 ± 1.96	1.11 (−2.44 to 0.22)	0.10
T/W ratio	Tarsal tunnel (mm <sup>2</sup> ) ± SD	0.64 ± 0.12	0.59 ± 0.12	0.06 (0.004 to 0.11)	0.03
	Cranial to tarsal tunnel (mm <sup>2</sup> ) ± SD	0.69 ± 0.10	0.65 ± 0.12	0.04 (−0.01 to 0.09)	0.13
Flexor retinaculum		1.07 ± 0.22	0.84 ± 0.11	0.23 (0.15 to 0.3)	<0.001

**Table 3—Difference at baseline and follow-up**

		Difference baseline and follow-up in operated leg	Difference baseline and follow-up in control leg	$\Delta$ (95%CI)	P value
CSA	Tarsal tunnel (mm <sup>2</sup> ) $\pm$ SD	1.49 $\pm$ 3.91	1.81 $\pm$ 4.10	0.32 (−1.88 to 1.23)	0.67
T/W ratio	Tarsal tunnel (mm <sup>2</sup> ) $\pm$ SD	−0.004 $\pm$ 0.16	0.018 $\pm$ 0.14	0.02 (−0.03 to 0.08)	0.42

and T/W ratio in the sural nerve in people with diabetes with neuropathy compared with people with diabetes without neuropathy and with healthy control subjects. The CSA of the median nerve in the carpal tunnel of patients with DPN was greater than without DPN and healthy control subjects (24). CSA in patients with idiopathic carpal tunnel syndrome is also greater than in control subjects (25). Besides the increased CSA in idiopathic carpal tunnel syndrome, the nerve is also significantly more flattened, determined using ultrasound and magnetic resonance imaging (MRI) (26). Based on these results, a flattened tibial nerve might be expected, although contrary to our findings. This might be explained by the larger amount of soft tissue and structures surrounding the tibial nerve, leading to more diffusely spread pressure. In patients with idiopathic carpal tunnel syndrome and without diabetes, release of the flexor retinaculum results in a decrease of CSA (27–29). One study showed an increase of CSA and T/W ratio (30). We found no studies evaluating the nerve with ultrasound after carpal tunnel release in patients with diabetes or DPN.

Cranial to the tarsal tunnel, the CSA is larger than in the tarsal tunnel. The measurement cranial to the tarsal tunnel was proximal to the bifurcation of the tibial nerve into the medial and lateral branch. No significant differences between patients with DPN and control subjects in CSA were found. This might be caused by a relatively large proportion of missing values (12.5%) due to difficulties identifying the nerve at this location using a 15–7-MHz transducer. The use of a 12-MHz transducer cranial of the tarsal tunnel might be helpful since the nerve is located deeper at that location than in the tarsal tunnel. Riazi et al. (18) measured the CSA of the tibial nerve at three locations, respectively 1, 2, and 3 cm proximal to the medial malleolus,

and found at 3 cm a sensitivity of 0.69 and a specificity 0.77 for determining DPN. Based on these findings, we suggest future studies to measure at this location.

Diabetes and changes in glucose levels have been suggested to lead to peripheral nerve swelling due to osmosis (2,3). Swelling would then lead to ischemia of the swollen nerve in the stiff tarsal tunnel, the so-called double crush theory (31,32). Our increased CSA and T/W ratio outcome supports this theory. Diabetes also leads to thickening and stiffening of ligamental structures. This is concordant with our findings as well. Based on these two findings, we might conclude that the tibial nerve at the ankle in patients with diabetes is more prone to compression due to nerve swelling and the thicker flexor retinaculum. Nevertheless, we did not see direct compression of the nerve using ultrasound. Recent reviews discussing the pathophysiology of painful diabetic neuropathy describe many potential mechanisms, e.g., changes in channel function, loss of spinal inhibitory control, and increased thalamic vascularity. Compression of peripheral nerves is not mentioned (33,34). A large randomized controlled trial using electromyography to evaluate the conduction velocity at the ankle site before and after decompressive surgery in patients with painful DPN will be necessary.

There are a few limitations to our study. Peripheral nerves consist of multiple nerve fascicles surrounded with epineurium. The number and size of the fascicles depend on the type of nerve (35). Fascicles that are oblique and not perpendicular to the ultrasound beam may remain undetected, and the epineurium might lead to artifacts (36). This might lead to a small underestimation of the CSA of the nerve using ultrasound and imaginably for all imaging devices using perpendicular beams, e.g., MRI.

Since the patient group contains only patients with painful diabetic neuropathy, our findings may not be generalizable to diabetic neuropathy in general.

This study, with a large sample size and standardized sonographic imaging procedure with a good reliability, is the first randomized controlled trial that evaluates the effect of decompression of the tibial nerve on the CSA. Although no effect on CSA after surgery was found, this study using ultrasound demonstrates a larger and swollen tibial nerve and thicker flexor retinaculum at the ankle in patients with DPN compared with healthy control subjects.

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