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The natural history of tarsal tunnel syndrome in diabetic subjects

Willem D. Rinkel[a,b,*], **Manuel Castro Cabezas**[c], **Erwin Birnie**[d,e], **J. Henk Coert**[a,b]

[a] *Department of Plastic-, Reconstructive- and Hand Surgery, Franciscus Gasthuis & Vlietland, Rotterdam, the Netherlands*
[b] *Department of Plastic-, Reconstructive- and Hand Surgery, Utrecht University Medical Center, Utrecht, the Netherlands*
[c] *Department of Internal Medicine/Centre for Diabetes, Endocrinology and Vascular Medicine, Franciscus Gasthuis & Vlietland, Rotterdam, the Netherlands*
[d] *Department of Statistics and Education, Franciscus Gasthuis & Vlietland, Rotterdam, the Netherlands*
[e] *Department of Genetics, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands*

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KEYWORDS
Tarsal tunnel syndrome;
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Summary *Introduction:* Tibial nerve entrapment is highly prevalent in diabetic subjects, resulting in significantly more neuropathic complaints and concomitant sensory disturbances. The study aim was to assess the impact of tarsal tunnel syndrome (TTS) and sensory loss at baseline on incident diabetic foot ulceration (DFU) in diabetic patients, since decompressing the tibial nerve might change the natural history of the disease.
Methods: In this study, 113 subjects with TTS (69 bilateral, 23 left-sided and 21 right-sided) participating in the prospective Rotterdam Diabetic Foot Study were compared to 303 diabetic controls without TTS, regarding incident DFU. Kaplan–Meier analysis and Cox's regression analysis were used to determine the independent hazard of baseline variables for new DFU.
Results: The median observation period was 836.5 days (IQR, 459–1077.8). In bilateral TTS, 17.4% (95% CI: 8.4–26.3%) of subjects experienced DFU versus 8.3% (95% CI: 5.1–11.6%) in controls (left or right) during follow-up ($p = 0.0036$). In left-sided TTS, no subjects versus 6.2% (95% CI: 3.4–9.0%) in controls had DFUs ($p = 0.243$). Incident ulceration was seen in 14.3% (95% CI: −0.7% to −29.3%) of right-sided TTS subjects versus 4.1% (95% CI: 1.5–6.3%) in controls ($p = 0.034$). Besides HbA1c, diminished sensation at the hallux independently increased the

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* Corresponding author at: UMCU – University Medical Center Utrecht, Department of Plastic-, Reconstructive- and Hand Surgery, Room G.04-122, Box 85500, 3508 GA Utrecht, the Netherlands.
E-mail address: w.d.rinkel@umcutrecht.nl (W.D. Rinkel).

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risk of ulceration, in patients with (HR: 4.692, $p=0.003$) and without (HR: 2.307, $p=0.002$) prior DFU.
Discussion: Elevated sensory thresholds in TTS render diabetic patients at a higher risk for DFU. With effective surgery, TTS is likely to be an amenable factor to potentially prevent diabetic foot disease and thereby reduce amputation risk.
Level of evidence: II.

Introduction

Tibial nerve entrapment at the tarsal tunnel was first reported in 1962, when Keck described a patient with anesthesia over the sensory distribution of the tibial nerve with localized tenderness and paresthesias of the foot sole when tapping the nerve posterior to the medial malleolus.[1] Since then multiple reports have been published on diagnostic criteria, including the physical examination, electrodiagnostic studies, and imaging, together with studies on treatment modalities, which are mainly surgical.[2-4] In the 1980s, diabetic patients were identified for having higher rates of tarsal tunnel syndrome (TTS), as diabetes predisposes the peripheral nerve to chronic compression (i.e. the double crush syndrome).[5,6] Only a few studies have been published related to the beneficial effects of a tibial nerve release, these effects include relief of complaints, gain of sensory function, and prevention of lower extremity ulcers and amputations.[7-14]

TTS is a more common condition of the foot and ankle than has been historically appreciated in the literature, but no studies exist on its natural history. Therefore, the prospective and observational Rotterdam Diabetic Foot (RDF) Study was initiated to investigate the natural course of tibial nerve entrapment in diabetic subjects. A previous cross-sectional analysis of baseline RDF study measurements has shown that TTS in diabetic subjects is prevalent and accompanied by significantly higher plantar cutaneous thresholds and significantly more neuropathic symptoms.[4] The aim of the current study was to investigate the degree to which sensory deficits observed in uni- and bilateral TTS in diabetic subjects result in an increased risk of diabetic foot ulceration (DFU) compared to those without signs of tibial nerve entrapment.

Methods

Study design and subjects

The RDF study is a prospective cohort study of unselected diabetic patients followed at the outpatient Diabetes Clinic of Franciscus Gasthuis and Vlietland, Rotterdam, the Netherlands. The aim of the RDF study was to investigate the natural history of neuropathy, including deterioration of sensation of the feet. The RDF study participants were recruited from patients visiting the specialized outpatient diabetes clinic. RDF study inclusion criteria were: type 1 or type 2 diabetes mellitus (treated by oral blood glucose-lowering drugs and/or insulin), age over 18 years, no significant cognitive impairment, speaking Dutch, and signed informed consent. Exclusion criteria were: active radicular syndrome and neurological disease interfering with sensibility of the feet, as reported in the interview and screening questionnaire. The RDF study design and methods have been described in detail.[4,15] Baseline measurements were carried out between January 2014 and June 2015, for which patients were subjected to an interview, to a physical examination and were requested to fill in a questionnaire (on smoking history, neuropathic symptoms, and history of foot or leg ulcer and amputation), which was repeated during the follow-up visits with 1–1.5 years' intervals. Demographic, anthropometric, and care data (e.g., weight, length, blood pressure, diabetes type, duration, and treatment), and laboratory results were retrieved from the patient file. The Medical Research Ethics Research Committee of Erasmus MC Medical University Center, Rotterdam, the Netherlands, approved the study (MEC-2009-148).

Physical examination: the Rotterdam Diabetic Foot Study Test Battery

Both feet were examined. Static- and moving two-point discrimination (S2PD and M2PD) were tested with a Disk-Criminator™ (from 2 to 15 mm) (US Neurologicals, LLC, Poulsbo, WA, USA). Static one-point discrimination (S1PD) was tested with a set of Semmes-Weinstein monofilaments (from 0.008 to 300 g) (Baseline® Tactile™, Minneapolis, MN, USA). S2PD, M2PD and S1PD test sites were chosen in agreement with the nerve territories of the foot: I, plantar hallux (medial plantar nerve [tibial nerve]); II, medial heel (calcaneal nerve [tibial nerve]); III, first dorsal web (deep peroneal nerve); IV, lateral foot (sural nerve); and V, plantar fifth toe (lateral planter nerve [tibial nerve]). M2PD was not tested at the fifth toe due to its small surface area. Vibration sense was tested with a Rydel-Seiffer tuning fork (scored from 0 to 8) (Martin, Tuttlingen, Germany) at the medial malleolus and dorsal interphalangeal joint of the hallux. Neuropathy symptoms were assessed using the Michigan Neuropathy Screening Instrument (MNSI), which was administered before the physical examination. Sensory test items consisted of both a sensory test and test location (e.g., S1PD at the lateral foot [S1PD IV], S2PD at the plantar fifth toe [S2PD V]). Lower extremity artery pulsations were palpated for each foot separately. TTS was diagnosed at study baseline when both a positive Tinel sign at the tarsal tunnel and neuropathic complaints were present, according to a

previous study.[4] Patients were categorized in 1) bilateral TTS, 2) unilateral TTS (right), 3) unilateral TTS (left), and 4) diabetic patients without TTS.

Data collection

Demographic (age, sex, medical history), anthropometric (height, weight, body mass index), and lower limb sensory status information (full RDF Study Test Battery) was collected at RDF study baseline and follow-up visit one (January 2015 to October 2016) and two (March 2017 to July 2017). Data on incident DFU was collected half-yearly using telephone call follow-up and included the circumstances of each ulcer (e.g. side, date), usage of medical resources and the need for hospitalization. The reporting standards of studies on the prevention and management of foot ulcers in diabetes are followed.[16]

Statistical analysis

Shapiro-Wilk tests were used to assess the normality of continuous data. Differences between groups were assessed using Kruskal-Wallis tests. A subscore on nerve-related neuropathic MNSI items is reported for the three groups[4]. Crude estimates of ulcer incidence rates in the different groups were calculated as the total number of cases with DFUs, divided by the total number of subjects in the respective groups. Confidence intervals (CIs) were obtained as 95% binomial confidence intervals. The Kaplan-Meier analysis was conducted to compare the time to DFU of bilateral and unilateral (left and right) TTS in diabetic patients to those without TTS, in terms of DFU development. Incidence of ulceration was considered an event. A log rank test was conducted to determine whether there were differences in the distributions for the different groups. The Kaplan-Meier curves were not adjusted for covariates. Cox proportional hazards models were fit to identify independent predictors of DFU development, in which RDF study subjects with TTS were compared with subjects without TTS. Potential predictor variables were chosen on the basis of 1) current literature; 2) expert opinion, and 3) availability in the RDF study dataset. Since sensory measurements correlated highly, only monofilament (S1PD) measurements of both halluces were included in the models. A univariate model was fitted that included the baseline measurement variables only. A multivariable adjusted model included all exposure variables, and the final adjusted model was determined using backward stepwise (likelihood ratio) reduction, maintaining all univariate exposure variables with $p < 0.10$, in 20 iterations. Differences were expressed in unadjusted and adjusted hazard ratios (HR) with 95% CIs. Since previous DFU was an interaction variable, Kaplan-Meier curves are depicted that show the differences in occurrence according to the degree of sensory loss (S1PD). Two curves were plotted separately for patients with and without a previous DFU. Statistical analysis was carried out using IBM SPSS Statistics version 24.0 (IBM Corp., Armonk, New York, USA). We considered p values below 0.05 (two-sided) to be statistically significant.

Results

Patient characteristics

At baseline, 69 diabetic patients with a median age of 62.7 years (interquartile range (IQR), 52.6-69.6) had bilateral TTS and 44 patients (65.2 years (IQR, 55.1-71.3)) had unilateral TTS (prevalence: 17.7% (95% CI: 13.9-21.5) vs. 29.9% (25.2-34.5%)).[4] The remaining RDF study participants without TTS served as controls ($n = 303$). Groups were comparable regarding the majority of demographic data, but patients with bilateral TTS had a higher body weight ($p = 0.005$), had more often retinopathy ($p = 0.032$), and on average higher HbA1c levels ($p = 0.016$) at study entry compared to the other groups (Table 1, Baseline data). During RDF study follow-up, 32 patients withdrew from study participation, 66 patients were lost to follow-up and 22 patients died.

Limb-level characteristics

Table 2 shows that more severe sensory deficit was observed in TTS patients compared to controls, in the form of higher cutaneous thresholds (S1PD, all parameters: $p < 0.001$), impaired spatial discrimination (S2PD, all parameters: $p \leq 0.004$ and M2PD, all parameters: $p \leq 0.009$), and a more frequent history of ulceration ($p = 0.021$). The cutaneous threshold (S1PD) frequently surpassed the critical limit of 10 g in the majority of tibial nerve innervated test locations in both bilateral and left-sided TTS patients, but generally not in right-sided patients, compared to controls. Left-sided TTS patients had fewer palpable lower extremity arteries compared to the other groups, but this did not reach statistical significance. Bilateral and unilateral TTS patients had significantly more neuropathic symptoms compared to controls ($p < 0.0005$). Fifty-two participants had a history of ulceration and 14 participants a prior amputation due to previous DFU disease (before study entry).

Incidence of ulceration

During follow-up, 48 episodes of ulceration were registered, in 40 participants. The rate of new-onset ulceration from study start was 9.6% (95% CI: 7.0-12.9%) in a median observation period of 836.5 days (IQR, 459-1077.8). A total of 65 ulcers occurred, with nine patients developing multiple DFU episodes in the period of observation. An average number of 1.3 DFUs were observed per episode. The majority of patients presented with ulcer(s) at toes two to five (43.1%), followed by DFUs at the hallux (38.5%). A minority suffered from ulcers at the heel (9.2%), plantar-side of the metatarsophalangeal joints (3.1%), and plantar-side of the midfoot (1.5%), and in 3 patients (4.6%), these data were not available.

Ulcer-related outcomes in tarsal tunnel syndrome

In bilateral affected TTS patients ($n = 69$), 12 ulcers (17.4%, 95% CI: 9.3-28.4%) occurred (left or right), compared to 23 ulcers (8.7%, 95% CI: 5.6-12.7%) in control subjects ($n = 265$) during a median follow-up of 824 days (IQR, 487-1098.5). Figure 1 shows the distributions for the bilateral, unilateral (left), and unilateral (right) TTS groups compared to controls. A log rank test showed statistically significantly

Table 1 Baseline data.

	Bilateral TTS	Unilateral TTS	Other RDF-study participants	*P*-value
Subjects (n)	69	44	303	
Gender (M/F)	25/44	20/24	130/173	0.097*
Age (median (y), IQR)	62.7 (52.6-69.6)	65.2 (55.1-71.3)	64.0 (55.2-69.9)	0.645#
Ethnicity (n (%))				0.669*
- Caucasian	58 (84.1)	40 (90.9)	243 (80.2)	
- Indo-Surinamese	5 (7.2)	1 (2.3)	29 (9.6)	
- African	1 (1.4)	2 (4.5)	11 (3.6)	
- Asian	1 (1.4)	-	6 (2.0)	
- Other	4 (5.8)	1 (2.3)	14 (4.6)	
Height (median (m), IQR)	178.0 (167.5-183.0)	175.0 (164.3-180.8)	172.0 (165.0-180.0)	0.272#
Weight (median (kg), IQR)	94.6 (82.5-112.2)	86.1 (75.3-99.9)	86.8 (76.0-102.0)	0.005#
BMI (median (kg/m^2), IQR)	31.4 (26.9-35.3)	29.1 (25.7-32.6)	29.0 (25.8-33.4)	0.053#
Duration of diabetes (median (y), IQR)	18.0 (8.5-27.5)	17.0 (9.3-26.0)	16.0 (9.0-24.0)	0.688#
Type of diabetes (n (%))				0.980*
- Type 1	16 (23.2)	10 (22.7)	67 (22.1)	
- Type 2	53 (76.8)	34 (77.3)	236 (77.9)	
Insulin use (n (%))	59 (85.5)	37 (84.1)	255 (63.1)	0.961*
Systolic blood pressure (median mmHg, IQR)	140.0 (126.5-150.0)	135.5 (124.8-144.5)	136.0 (125.0-147.0)	0.518#
Diastolic blood pressure (median mmHg, IQR)	80.0 (69.5-85.0)	75.5 (69.0-80.0)	77.0 (70.0-82.0)	0.587#
Retinopathy (n (%))	19 (40.4)	5 (22.7)	42 (22.0)	0.032*
Lifetime smoking history (n (%))	42 (73.7)	23 (67.6)	121 (60.5)	0.167*
Laboratory measurements				
HbA1c (median (mmol/L), IQR)	63.0 (55.0-74.5)	61.0 (54.0-75.0)	59.0 (51.0-68.0)	0.016#
MDRD (median ml/min/1.73 m^2, IQR)	77.1 (57.7-100.8)	77.0 (51.6-100.6)	79.1 (61.1-95.7)	0.948#
Total cholesterol (median (mmol/L), IQR)	4.2 (3.6-5.0)	4.3 (3.5-4.6)	4.0 (3.5-4.8)	0.931#
LDL-C (median (mmol/L), IQR)	1.9 (1.4-2.7)	1.7 (1.3-2.4)	1.8 (1.4-2.5)	0.631#
HDL-C (median (mmol/L), IQR)	1.3 (1.1-1.6)	1.3 (1.1-1.6)	1.3 (1.1-1.7)	0.363#
TG (median (mmol/L), IQR)	1.5 (1.0-2.5)	1.8 (1.1-2.7)	1.5 (1.0-2.3)	0.272#
ApoB (median (g/L), IQR)	0.9 (0.8-1.1)	0.9 (0.8-1.2)	0.9 (0.8-1.1)	0.659#
Microalbumin (median (mg/L), IQR)	21.0 (8.0-72.0)	15.5 (8.0-41.0)	16.5 (8.0-54.3)	0.672#

*, Pearson-Chi Square statistic; #, Kruskal-Wallis test; TTS, tarsal tunnel syndrome; M, male; F, female; IQR, interquartile range; BMI, body mass index; HbA1c, glycated hemoglobin; MDRD, Modification of Diet in Renal Disease; LDL, low density lipoprotein; HDL, high density lipoprotein; TG, triglycerides; ApoB, apolipoprotein B; RDF, Rotterdam Diabetic Foot.

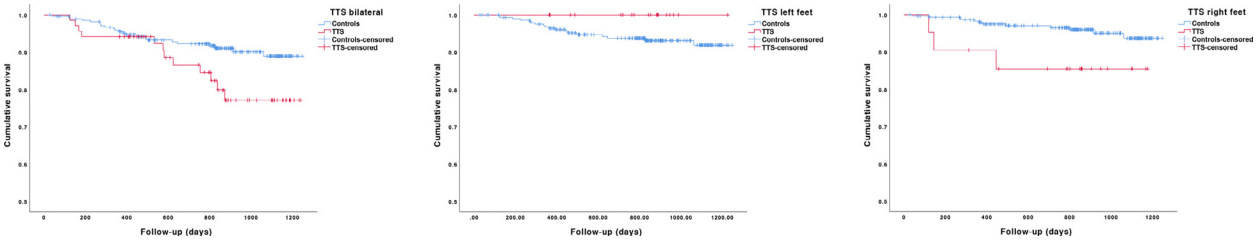

Figure 1 Kaplan-Meier curves of tarsal tunnel syndrome in diabetic subjects.
TTS, tarsal tunnel syndrome.

different distributions, $X^2(1) = 4.418$, $p = 0.036$. Unilateral affected patients had a median follow-up of 839 days (IQR, 454-1077). In left-sided affected patients ($n = 23$), no ulcers occurred in the left foot, compared to 18 ulcers (6.2%, 95% CI: 3.7-9.6%) in controls ($n = 290$). The distributions were not statistically significantly different ($X^2(1) = 1.366$, $p = 0.243$). In right-sided affected patients ($n = 21$), three ulcers (14.3%, 95% CI: 3.0-36.3%) occurred in the right foot, compared to 12 ulcers (4.1%, 95% CI: 2.1-7.0%) in controls ($n = 294$). A log rank test showed statistically significantly different distributions ($X^2(1) = 4.479$, $p = 0.034$).

Cox-regression analysis

Table 3 shows the results of the univariate and multivariable Cox proportional hazards models, comparing the risk of

Table 2 Limb-level measurements.

	Bilateral tarsal tunnel syndrome ($n=69$)	Left-sided tarsal tunnel syndrome ($n=23$)	Right-sided tarsal tunnel syndrome ($n=21$)	Other RDF-study participants ($n=303$)	*P*-value
Limb sensory status					
Static one-point discrimination♦ (median g (IQR))					
- Left hallux	4.0 (1.4-100.0)	6.0 (2.0-180.0)	2.0 (0.6-10.0)	2.0 (0.6-6.0)	$< 0.0005^{\#}$
- Left medial heel	4.0 (1.4-15.0)	15.0 (1.4-60.0)	2.0 (0.6-8.0)	2.0 (0.6-8.0)	$< 0.0005^{\#}$
- Left fifth toe	4.0 (1.4-26.0)	2.0 (1.0-60.0)	2.0 (1.2-4.9)	1.4 (0.6-4.0)	$< 0.0005^{\#}$
- Right hallux	4.9 (1.4-88.0)	6.0 (2.0-180.0)	2.0 (1.0-10.0)	1.4 (0.6-8.0)	$< 0.0005^{\#}$
- Right medial heel	6.0 (1.4-26.0)	8.0 (1.4-60.0)	2.0 (0.8-11.0)	2.0 (0.6-8.0)	$0.001^{\#}$
- Right fifth toe	4.0 (1.0-26.0)	2.0 (1.0-60.0)	2.0 (0.8-4.0)	1.4 (0.6-4.0)	$< 0.0005^{\#}$
Static two-point discrimination♦ (median mm (IQR))					
- Left hallux	16.0 (11.3-16.0)	16.0 (11.0-16.0)	13.0 (8.0-16.0)	11.0 (8.0-16.0)	$< 0.0005^{\#}$
- Left medial heel	16.0 (12.0-16.0)	16.0 (10.0-16.0)	16.0 (12.0-16.0)	14.0 (8.0-16.0)	$0.004^{\#}$
- Left fifth toe	16.0 (15.0-16.0)	15.0 (10.0-16.0)	16.0 (9.5-16.0)	12.0 (7.0-16.0)	$< 0.0005^{\#}$
- Right hallux	16.0 (12.0-16.0)	15.0 (9.0-16.0)	11.0 (6.5-16.0)	11.0 (7.0-16.0)	$0.001^{\#}$
- Right medial heel	16.0 (12.3-16.0)	16.0 (7.0-16.0)	16.0 (11.5-16.0)	13.0 (8.0-16.0)	$0.001^{\#}$
- Right fifth toe	16.0 (11.5-16.0)	16.0 (9.0-16.0)	16.0 (11.5-16.0)	12.0 (7.0-16.0)	$< 0.0005^{\#}$
Moving two-point discrimination♦ (median mm (IQR))					
- Left hallux	12.5 (8.0-16.0)	11.5 (8.0-16.0)	12.0 (8.0-16.0)	8.0 (5.0-14.0)	$< 0.0005^{\#}$
- Left medial heel	12.0 (7.0-16.0)	14.0 (8.0-16.0)	15.0 (10.5-16.0)	9.0 (6.0-15.0)	$0.009^{\#}$
- Right hallux	12.0 (9.0-16.0)	10.5 (6.5-16.0)	10.0 (6.0-16.0)	8.0 (5.0-14.8)	$< 0.0005^{\#}$
- Right medial heel	13.0 (7.8-16.0)	14.0 (8.0-16.0)	13.0 (7.5-16.0)	9.0 (5.0-15.0)	$0.004^{\#}$
Vibration sense (median (IQR))					
- Left interphalangeal joint	4.0 (1.0-5.5)	3.0 (0.0-6.0)	4.0 (3.0-6.5)	4.0 (2.0-6.0)	$0.157^{\#}$
- Right interphalangeal joint	4.0 (0.0-5.0)	4.0 (0.0-4.0)	4.0 (2.5-6.0)	4.0 (2.0-6.0)	$0.049^{\#}$
Michigan Neuropathy Screening Instrument					
Neuropathic symptoms (median score (IQR))	2.0 (1.0-3.0)	1.0 (1.0-3.0)	2.0 (1.0-2.0)	0.0 (0.0-2.0)	$<0.0005^{\#}$
Vascular limb status					
Previous diabetic foot ulceration (n%))	16 (23.2)	4 (17.4)	2 (9.5)	30 (9.9)	0.021^{*}
Previous amputations (n (%))					
- Left extremity	0	1 (4.3)	0	5 (1.7)	0.428^{*}
- Right extremity	2 (2.9)	0	0	6 (2.0)	0.749^{*}
Palpable lower extremity arteries (%)					
- Left posterior tibial artery	74.2	60.0	73.7	71.7	0.661^{*}
- Left dorsalis pedis artery	73.8	70.0	84.2	75.8	0.749^{*}
- Right posterior tibial artery	66.7	60.0	65.0	71.5	0.888^{*}
- Right dorsalis pedis artery	69.7	65.0	80.0	71.7	0.948^{*}

♦, S1PD, S2PD and M2PD are censored data. Only on tibial nerve innervated areas is reported. *, Pearson-Chi Square statistic #, Kruskal-Wallis test.

ulceration in combined bilateral and unilateral TTS patients to controls. In unadjusted analyses, baseline measurements of the following characteristics were significantly associated with ulcer risk: male sex, retinopathy, diminished one-point discrimination (i.e. monofilaments), non-palpable lower extremity arteries, prior foot ulcer, prior amputation, and HbA1c. In adjusted analyses, diminished one-point discrimination at the right hallux, prior ulcer, and HbA1c were associated with an increased risk of ulceration, while a lower risk of ulceration was seen with a lower systolic blood pressure.

The hazard ratio of prior ulceration in the whole group was 2.40 (CI: 1.11-5.19), $p=0.026$. In the group of patients with prior ulceration, this was 4.69 (CI: 1.69-13.01), $p=0.003$, in the group without prior ulceration this was 2.31 (CI: 1.36-3.90), $p=0.002$. Figure 2 shows the resultant Kaplan-Meier curves.

Discussion

This study showed that the natural history of TTS in a diabetic patient has a positive predictive value for the development of DFU. In a large prospective cohort of adults with diabetes, a higher risk for DFU development was found in patients with TTS, in both bilateral and right-sided affected patients. Diagnosis-specific multivariable analysis showed a more important role for prior DFU, the level of HbA1C at inclusion, and increased sensory thresholds. With regard to abnormal sensory thresholds, multivariable analysis showed

Table 3 Unadjusted and adjusted hazard ratios for incident diabetic foot ulceration among diabetic patients.

	HR (95%CI), unadjusted	*P-value*	*HR (95%CI), adjusted*	*P-value*
Male sex	**2.614 (1.191-5.737)**	**0.017**		
Age (years)	1.015 (0.986-1.044)	0.326		
Duration of diabetes (years)	1.012 (0.987-1.038)	0.333		
Diabetes type 2	1.287 (0.564-2.939)	0.549		
Insulin use	0.850 (0.354-2.042)	0.716		
BMI (kg/m^2)	0.992 (0.938-1.048)	0.768		
Systolic blood pressure (mmHg)	1.001 (0.984-1.018)	0.909	0.967 (0.928-1.007)	0.108
Lifetime smoking history	0.817 (0.383-1.746)	0.603		
Retinopathy	**3.400 (1.381-8.368)**	**0.008**		
Tarsal tunnel syndrome	1.711 (0.876-3.344)	0.116		
Static one-point discrimination				
- Left hallux	**3.390 (2.378-4.832)**	**< 0.0005**		
- Right hallux	**4.137 (2.810-6.092)**	**< 0.0005**	**2.401 (1.111-5.189)**	**0.026**
Palpable lower extremity arteries				
- Left posterior tibial artery	**0.235 (0.119-0.463)**	**< 0.0005**		
- Left dorsalis pedis artery	**0.392 (0.202-0.761)**	**0.006**		
- Right posterior tibial artery	**0.274 (0.141-0.531)**	**< 0.0005**		
- Right dorsalis pedis artery	**0.455 (0.236-0.879)**	**0.019**		
Previous diabetic foot ulceration	**17.005 (8.679-33.316)**	**< 0.0005**	**9.786 (2.387-40.127)**	**0.002**
Previous diabetes-related amputation	**9.852 (3.766-25.774)**	**< 0.0005**		
HbA1c (mmol/L)	**1.024 (1.002-1.046)**	**0.032**	**1.038 (1.002-1.076)**	**0.037**
MDRD (ml/min/1.73 m^2)	0.994 (0.982-1.007)	0.381		

HR, hazard ratio; statistically significant results appear in boldface type ($p < 0.05$); BMI, body mass index; HbA1c, glycated hemoglobin; MDRD, Modification of Diet in Renal Disease.

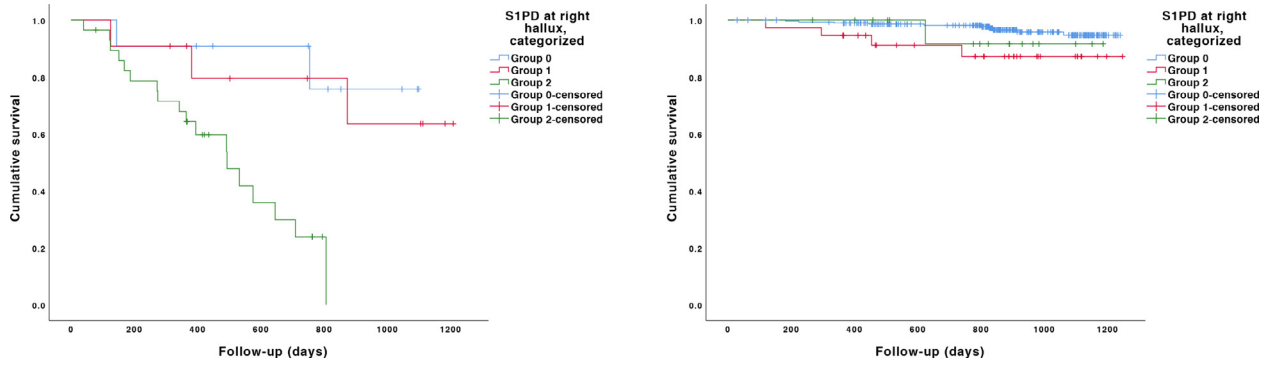

Figure 2 Kaplan–Meier curves of diabetic subjects with (left panel) and without (right panel) prior ulceration, according to the degree of sensory loss.
S1PD measurements are categorized according to hallux measurements (Group 0: $0 \leq 10$ g, Group 1: $>10 \leq 100$ g and Group 2: >100 g).

that the degree of sensory loss was significantly associated with the risk of ulceration, independent of the signs of tibial nerve entrapment at baseline. In our opinion, these findings may have important consequences for patient selection for tarsal tunnel decompression.

The results from our data support a complex etiology of DFU that includes both person- and limb-level factors.[17] As proposed earlier from baseline RDF study measurements, the increased sensory thresholds observed in tibial nerve compression relates to the risk of ulceration.[4] In fact, neuropathy, in the form of sensory deafferation, is arguably the most important risk factor in the cascade to ulcer development in persons with and without prior DFU. The associated hazard ratio was of the highest magnitude in the adjusted Cox proportional hazards analysis, with symptoms of TTS being surpassed by this hazard. Prior ulceration was associated with re-ulceration, and therefore, the foot in which wound closure is achieved should be regarded as in remission, rather than being healed.[17,18] Since the diagnostic limitation of self-reported symptoms is acknowledged, we conclude that the more objective somatosensory examination is key in accessing the risk of ulceration and may also serve in the decision when to decompress the tarsal tunnel in the natural history of tibial nerve entrapment. Current literature suggests a dramatic improvement in spatial acuity and cutaneous pressure thresholds after tarsal tunnel release in diabetic subjects, with studies reporting postoperative sensory thresholds of 0.5–0.8 g, coming from 32.9

to 65.6 g pre-operatively.[7,8,10,12] This type of surgery may therefore change the natural history of neuropathy in diabetes, since re-innervation of the foot sole may reverse the associated hazards of the insensate foot.[11,19] If surgical decompression is to be performed, the timing of the surgery is an important factor for optimizing the operative result.[20]

Patients are generally operated when having positive (hyperalgesia, allodynia) or negative (hypoesthesia, hypoalgesia) symptoms of neuropathy, together with a positive Tinel sign or positive provocative testing at the site of compression.[2] The decision to decompress the tarsal tunnel depends on the physical examination, since electrodiagnostic testing does not aid to the diagnosis of TTS due to the high percentage of asymptomatic people who have abnormal sensory and motor results.[21,22] In all stages of neuropathy the Tinel sign may be present, of which processes of de- and remyelinization lie at root.[23,24] Relief of pressure sufficiently soon restores nerve function, with blood flowing in the altered neurovascular structures, after decompression.[25] An optimal timing of surgery has not yet been established, but should include consideration of complaints, quality of life, and the increased sensory thresholds at the plantar side of the foot.[10,26] Somatosensory function presumably correlates with the likelihood of nerve regeneration.[20] Since a cutaneous threshold of $\geq$10 g is a significant predictor of future ulceration and surpasses the normative cutaneous threshold of the feet exceedingly, lower values should probably be availed, supplemented with other sensory measurements, when surgery is specifically planned to prevent lower extremity complications.[27] A recent grading scale of somatosensory function of the feet may aid this debate.[15,20,23] Interestingly, recent reports on lower extremity nerve decompression (LEND) showed that nerve outgrowth could also be expected from patients with end-stage neuropathy, reversing the chance of ulcer recurrence.[12,28,29]

To date, the RDF study is the only observational cohort study to determine the prognostic value of tibial nerve compression in diabetic subjects in light of risk of ulcer development. An additional important finding is that the associated degree of sensory loss is the most important hazard in both patients with and without prior ulceration. However, our study had a number of limitations. First, the RDF cohort is a hospital-based cohort, with patients at higher risk of lower extremity complications compared to the general diabetes population. The incidence rate of DFUs for the whole cohort was comparable with the literature and slightly higher compared to the numbers seen in primary care, as expected.[30] However, only relatively low absolute numbers of new DFUs were seen in the TTS groups, due to sample size limitations, but still with significant differences. In fact, no new ulcers were observed in the 23 unilateral left-sided affected limbs, resulting in a non-significant trend in this time frame, compared to controls. Our hypothesis was nonetheless confirmed in the 69 bilateral and 21 right-sided affected patients and may also be confirmed in left-sided patients when a longer follow-up is available. The generalizability of our findings remains to be determined. Second, no complete data were available on the type or severity of foot deformations, which is considered a risk factor for foot ulceration.[17,31] Third, in the adjusted analysis, palpable pulses in the lower limbs were not selected, although previous studies found associations between these measurements and new DFU and/or amputation.[32,33] A combination of tests is recommended to more reliably exclude peripheral artery disease.[34] Finally, potential confounders of this multivariable analysis cannot be ignored, with new ulcers being influenced by risk factors not measured at baseline. Examples include compliance with foot care, healthcare provision, and patient-factors such as kidney disease. Also we do not know if the condition spontaneously resolves or inexorably progresses to foot ulceration. Our cohort of 416 diabetic subjects represents the most detailed assessment of plantar sensory function in the light of tibial nerve pathology, together with a unique 3.5-year follow-up assessment of DFU development in non-operated patients with TTS. Our data seem representative; since the baseline demographic characteristics of our population and reports on TTS characteristics are comparable with other teaching hospitals and with data from the literature.[12,35]

In conclusion, we have demonstrated that patients with TTS are at higher risk of foot ulceration due to the observed increased cutaneous thresholds at study baseline. Bilateral affected patients do worse compared to unilateral patients and controls, and are at higher risk of DFU development than unilateral patients. Furthermore, we have now elucidated the natural history of TTS in diabetic subjects, for which surgical interventions may help change its course into DFU development.[12,36,37] High expediency is anticipated from re-innervating the insensate foot, making this type of surgery a promising therapy to battle the increasingly burdensome and expensive DFU pandemic.[38,39] Although controversy towards LEND surgery continues to exist, our study provides the necessary evidence to progress to high-quality data.[40]

Declaration of Competing Interest

None of the authors has a financial interest in any of the products, devices, or drugs mentioned in this manuscript.

CRediT authorship contribution statement

Willem D. Rinkel: Conceptualization, Data curation, Writing - original draft, Formal analysis. **Manuel Castro Cabezas:** Writing - review & editing. **Erwin Birnie:** Conceptualization, Writing - review & editing, Formal analysis. **J. Henk Coert:** Writing - review & editing, Formal analysis.

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References

1. Keck C. The tarsal tunnel syndrome. *J Bone Jt Surg Am* 1962;44:180–2.

2. Kinoshita M, Okuda R, Morikawa J, Jotoku T, Abe M. The dorsiflexion-eversion test for diagnosis of tarsal tunnel syndrome. *J Bone Jt Surg Am* 2001;**83-A**:1835–9.
3. Patel AT, Gaines K, Malamut R, et al. Usefulness of electrodiagnostic techniques in the evaluation of suspected tarsal tunnel syndrome: An evidence-based review. *Muscle Nerve* 2005;**32**:236–40.
4. Rinkel WD, Castro Cabezas M, van Neck JW, et al. Validity of the Tinel sign and prevalence of tibial nerve entrapment at the tarsal tunnel in both diabetic and nondiabetic subjects: A cross-sectional study. *Plast Reconstr Surg* 2018;**142**:1258–66.
5. Dellon AL, Mackinnon SE, Seiler WAt. Susceptibility of the diabetic nerve to chronic compression. *Ann Plast Surg* 1988;**20**:117–19.
6. Dellon AL. Treatment of symptomatic diabetic neuropathy by surgical decompression of multiple peripheral nerves. *Plast Reconstr Surg* 1992;**89**:689–97 discussion 98-9.
7. Wieman TJ, Patel VG. Treatment of hyperesthetic neuropathic pain in diabetics. Decompression of the tarsal tunnel. *Ann Surg* 1995;**221**:660–4 discussion 64-5.
8. Aszmann OC, Kress KM, Dellon AL. Results of decompression of peripheral nerves in diabetics: a prospective, blinded study. *Plast Reconstr Surg* 2000;**106**:816–22.
9. Tambwekar DS. Extended neurolysis of the posterior tibial nerve to improve sensation in diabetic neuropathic feet. *Plast Reconstr Surg* 2001;**108**:1452–3.
10. Wood WA, Wood MA. Decompression of peripheral nerves for diabetic neuropathy in the lower extremity. *J Foot Ankle Surg* 2003;**42**:268–75.
11. Aszmann O, Tassler PL, Dellon AL. Changing the natural history of diabetic neuropathy: Incidence of ulcer/amputation in the contralateral limb of patients with a unilateral nerve decompression procedure. *Ann Plast Surg* 2004;**53**:517–22.
12. Gondring WH, Tarun PK, Trepman E. Touch pressure and sensory density after tarsal tunnel release in diabetic neuropathy. *Foot Ankle Surg* 2012;**18**:241–6.
13. Dellon AL, Muse VL, Nickerson DS, et al. Prevention of ulceration, amputation, and reduction of hospitalization: Outcomes of a prospective multicenter trial of tibial neurolysis in patients with diabetic neuropathy. *J Reconstr Microsurg* 2012;**28**:241–6.
14. van Maurik JF, van Hal M, van Eijk RP, Kon M, Peters EJ. Value of surgical decompression of compressed nerves in the lower extremity in patients with painful diabetic neuropathy: A randomized controlled trial. *Plast Reconstr Surg* 2014;**134**:325–32.
15. Rinkel WD, Rizopoulos D, Aziz MH, et al. Grading the loss of sensation in diabetic patients: A psychometric evaluation of the Rotterdam Diabetic Foot Study Test Battery. *Muscle Nerve* 2018;**58**:559–65.
16. Jeffcoate WJ, Bus SA, Game FL, et al. Reporting standards of studies and papers on the prevention and management of foot ulcers in diabetes: Required details and markers of good quality. *Lancet Diabetes Endocrinol* 2016.
17. Armstrong DG, Boulton AJM, Bus SA. Diabetic foot ulcers and their recurrence. *N Engl J Med* 2017;**376**:2367–75.
18. Rinkel WD, van der Oest MJW, Dijkstra DA, Castro Cabezas M, Coert JH. Predicting ulcer-free survival using the discriminative value of screening test locations. *Diabetes Metab Res Rev* 2019;**35**:e3119.
19. Rinkel WD, van Nieuwkasteele S, Castro Cabezas M, et al. Balance, risk of falls, risk factors and fall-related costs in individuals with diabetes [submitted] 2019.
20. Rinkel WD, de Kleijn JL, Macare van Maurik JFM, Coert JH. Optimization of surgical outcome in lower extremity nerve decompression surgery. *Plast Reconstr Surg* 2018;**141**:482–96.
21. Dellon AL, Muse VL, Scott ND, et al. A positive Tinel sign as predictor of pain relief or sensory recovery after decompression of chronic tibial nerve compression in patients with diabetic neuropathy. *J Reconstr Microsurg* 2012;**28**:235–40.
22. Lee CH, Dellon AL. Prognostic ability of tinel sign in determining outcome for decompression surgery in diabetic and nondiabetic neuropathy. *Ann Plast Surg* 2004;**53**:523–7.
23. Rinkel WD, Aziz MH, Van Neck JW, et al. Development of grading scales of pedal sensory loss using Mokken scale analysis on the Rotterdam Diabetic Foot Study Test Battery data. *Muscle Nerve* 2019.
24. Gupta R, Rowshan K, Chao T, Mozaffar T, Steward O. Chronic nerve compression induces local demyelination and remyelination in a rat model of carpal tunnel syndrome. *Exp Neurol* 2004;**187**:500–8.
25. Jung J, Hahn P, Choi B, Mozaffar T, Gupta R. Early surgical decompression restores neurovascular blood flow and ischemic parameters in an in vivo animal model of nerve compression injury. *J Bone Jt Surg Am* 2014;**96**:897–906.
26. Yang W, Guo Z, Yu Y, Xu J, Zhang L. Pain relief and health-related quality-of-life improvement after microsurgical decompression of entrapped peripheral nerves in patients with painful diabetic peripheral neuropathy. *J Foot Ankle Surg* 2016;**55**:1185–9.
27. Rinkel WD, Aziz MH, Van Deelen MJM, et al. Normative data for cutaneous threshold and spatial discrimination in the feet. *Muscle Nerve* 2017;**56**:399–407.
28. Nickerson DS. Low recurrence rate of diabetic foot ulcer after nerve decompression. *J Am Podiatr Med Assoc* 2010;**100**:111–15.
29. Nickerson DS, Rader AJ. Nerve decompression after diabetic foot ulceration may protect against recurrence: A 3-year controlled, prospective analysis. *J Am Podiatr Med Assoc* 2014;**104**:66–70.
30. Muller IS, de Grauw WJ, van Gerwen WH, et al. Foot ulceration and lower limb amputation in type 2 diabetic patients in Dutch primary health care. *Diabetes Care* 2002;**25**:570–4.
31. Martins-Mendes D, Monteiro-Soares M, Boyko EJ, et al. The independent contribution of diabetic foot ulcer on lower extremity amputation and mortality risk. *J Diabetes Complications* 2014;**28**:632–8.
32. Leese GP, Feng Z, Leese RM, Dibben C, Emslie-Smith A. Impact of health-care accessibility and social deprivation on diabetes related foot disease. *Diabet Med* 2013;**30**:484–90.
33. Abbott CA, Carrington AL, Ashe H, et al. The north-west diabetes foot care study: Incidence of, and risk factors for, new diabetic foot ulceration in a community-based patient cohort. *Diabet Med* 2002;**19**:377–84.
34. See https://iwgdfguidelines.org.
35. Hashemi S S, Cheikh I, Dellon AL. Prevalence of upper and lower extremity Tinel signs in diabetics: Cross-sectional study from a United States, urban hospital-based population. *J Diabetes Metab* 2013;**4**.
36. Best TJ, Best CA, Best AA, Fera LA. Surgical peripheral nerve decompression for the treatment of painful diabetic neuropathy of the foot: A level 1 pragmatic randomized controlled trial. *Diabetes Res Clin Pract* 2019;**147**:149–56.
37. Baltodano PA, Basdag B, Bailey CR, et al. The positive effect of neurolysis on diabetic patients with compressed nerves of the lower extremities: A systematic review and meta-analysis. *Plast Reconstr Surg Glob Open* 2013;**1**:e24.
38. Zhang P, Lu J, Jing Y, et al. Global epidemiology of diabetic foot ulceration: A systematic review and meta-analysis (dagger). *Ann Med* 2017;**49**:106–16.
39. Collaboration NCDRF Worldwide trends in diabetes since 1980: A pooled analysis of 751 population-based studies with 4.4 million participants. *Lancet* 2016;**387**:1513–30.
40. Albers JW, Jacobson R. Decompression nerve surgery for diabetic neuropathy: A structured review of published clinical trials. *Diabetes Metab Syndr Obes* 2018;**11**:493–514.