Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

# A new application of the Rotterdam Diabetic Foot Study Test Battery: grading pedal sensory loss to predict the risk of foot ulceration

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

[a] Department of Plastic-, Reconstructive- and Hand Surgery, University Medical Center Utrecht, University of Utrecht, Utrecht, the Netherlands

[b] Department of Plastic-, Reconstructive- and Hand Surgery, Franciscus Gasthuis & Vlietland Hospital, Rotterdam, the Netherlands

[c] Department of Internal Medicine/Centre for Diabetes, Endocrinology and Vascular Medicine, Franciscus Gasthuis & Vlietland Hospital, Rotterdam, the Netherlands

ARTICLE INFO

*Article history:*
Received 15 March 2021
Received in revised form
13 April 2021
Accepted 21 April 2021
Available online 24 April 2021

*Keywords:*
Diabetic neuropathies
Diabetic foot
Foot ulcer
Risk factors
Regression analysis

ABSTRACT

*Aims:* To assess the relationship between the degree of loss of foot sensation at baseline and incidence of foot ulceration (DFU).

*Methods:* Diabetic patients (n = 416) participating in the observational Rotterdam Diabetic Foot (RDF) Study were followed prospectively (median 955.5 days (IQR, 841.5–1121)). Subjects underwent sensory testing of the feet (39-item RDF Study Test Battery) at baseline and were assessed regarding incident DFU. Seven groups of incremental degree of sensory loss were distinguished, according to the RDF-39 sum score. Kaplan-Meier and regression analyses were used to determine the independent hazard of baseline variables for new DFU.

*Results:* 40 participants developed DFUs. The mean incident rate of new-onset ulceration from study start was 4.5 (95%CI: 3.3 to 6.1) per 100 person-years, which increased significantly from 0 to 67.70 in the seven groups ($p < 0.0005$). Predictors for DFUs were higher RDF-39 score (aHR: 1.173, $p < 0.0005$) and kidney function (aHR: 1.022, $p = 0.016$). Prior DFU suggests increased mortality risk.

*Conclusions:* The degree of sensory loss at baseline was associated with progression to DFU during follow-up. Grading the loss of sensation using the RDF Study Test Battery may result in a more precise risk stratification compared to the use of the 10 g monofilament according to current guidelines.



## 1. Introduction

The prospect of a required amputation is feared more than death, foot infection or end-stage renal disease by patients with diabetic foot ulcers (DFUs) [1]. Since diabetes mellitus accounts for eight out of ten non-traumatic lower extremity amputations, of which 85% are preceded by

* 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).

https://doi.org/10.1016/j.diabres.2021.108836
0168-8227/

DFUs, it is reasonable to focus on risk factors for ulceration in order to prevent amputations [2,3].

Sensory deafferation due to neuropathy is considered to be one of the most important risk factors in the cascade of diabetic foot ulceration [4]. The International Working Group on the Diabetic Foot (IWGDF) risk stratification system designates patients with neuropathy and without other risk factors in the low ulcer risk category, defining loss of protective sensation when insensate to the 10 g monofilament at $\geq$ 2 test sites [5]. However, an extensive *meta*-analysis of prognostic factors for foot ulceration concluded that the predictive power of this particular test does not seem to be influenced by the number of test sites on the foot [3]. Yet, it has been concluded from more recent studies that the place of sensory testing on the foot has prognostic properties regarding diabetic foot ulceration, necessitating fewer tests and allowing a more accurate risk stratification [6].

The loss of protective sensation (i.e., a cutaneous threshold of > 10 g) is indicative of advanced nerve damage [7]. Recently developed grading scales of sensory loss at the feet show that other measures of somatosensory testing, for example vibratory testing, becomes abnormal before the loss of protective sensation [8]. Moreover, the location of sensory testing at the feet predicts the overall degree of sensory loss. In this way, combining both test and test site will make it possible to grade lower extremity sensory deafferation more precisely compared to random monofilament or vibratory testing [9].

The aim of this study was to investigate how degree of sensory loss relates to the risk of future diabetic foot ulceration. We explored new dimensions of somatosensory testing by comparing several categories of sensory loss to the risk categories of the IWGDF risk classification.

## 2. Methods

### 2.1. Study design and subjects

The RDF-study is a prospective cohort study of unselected patients with diabetes followed at the outpatient Diabetes Clinic of Franciscus Gasthuis & Vlietland hospital, 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 insulin and/or oral blood glucose lowering drugs), 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 [8,10]. Baseline measurements were carried out between January 2014 to June 2015, for which patients were subjected to an interview and 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 disease-related (e.g., weight, length, blood pressure, diabetes type, duration, lower extremity complications (i.e., DFU/amputation) and treatment) and laboratory results were retrieved from the patients' files. No patients with prior major amputations (i.e., above ankle) were included. The Medical Research Ethics Research Committee of the Erasmus Medical Center, Rotterdam, the Netherlands approved the study (MEC-2009–148).

### 2.2. Physical examination: The Rotterdam Diabetic Foot Study Test Battery

Both feet were examined. The 39-item RDF-39 includes both instruments and test sites to measure overall foot sensation [8]. This scoring system contains 39 dichotomized items on static- and moving two-point discrimination (S2PD and M2PD), static one-point discrimination (S1PD), vibration sense, cold stimulus tests, Romberg's test, experienced numbness, prior diabetic foot ulcer and prior amputation (Supplemental Table S1). The RDF-39 is unidimensional and valid in the assessment of sensation at the feet [8]. S2PD and M2PD were tested with a Disk-Criminator™ (US Neurologicals LLC, Poulsbo, Washington, USA), with the threshold set at 8 mm, based on previously published normative values [7]. S1PD was tested with a 10 g Semmes-Weinstein monofilament (Baseline® Tactile™, Minneapolis, Minnesota, USA), based on current international standards of medical care in diabetes [11]. S2PD, M2PD and S1PD test sites were chosen in concordance with the nerve territories of the foot: I, 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, 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 (Martin, Tuttlingen, Germany) at the medial malleolus and dorsal interphalangeal joint of the hallux and compared to normative threshold data [12]. Cold sensation was tested by applying a cold piece of metal to the arch of the foot. Information on numbness was derived from the Michigan Neuropathy Symptom Instrument (MNSI), which was administered before the physical examination. Information on prior ulceration and/or minor amputation, as indicators of severe sensory loss, was derived from the patient interviews. Sensory test items constituted of both a sensory test and test location (e.g., S1PD at the lateral foot (S1PD IV), S2PD at the fifth toe (S2PD V)). For each RDF-39 item, a score 1 was noted when a patient scored above the threshold. The maximum score is 39 points (including both ankles and feet), with higher scores indicative of more severe sensory loss. Shorter versions of the RDF-39 are the 31-item RDF-31 and 13-item RDF-13 (Supplemental Table S1) [8]. Lower extremity artery pulsations were palpated for each foot separately.

### 2.3. 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 at these visits and half-yearly telephone call follow-up and included the circumstances of each ulcer (e.g., 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 were followed [13].

### 2.4. Data and statistical analysis

Baseline characteristics were presented as mean (SD) for variables with normal distributions, median (interquartile (IQR)) for variables with skewed distributions, and n (%) for categorical variables. The Shapiro-Wilk test was used to assess normality. Differences between patients without ulceration and with incident ulceration were assessed using a Mann-Whitney *U* test and Pearson chi-square test, as were people with and without a history of DFU. Differences between patients available for follow-up and lost to follow-up were compared with the same tests. Differences between patients that were available for follow-up, withdrew from study participation, were lost to follow-up or dead were compared with Kruskal-Wallis and Pearson chi-square tests (Supplemental Table S2). A sub-score on nerve related neuropathic MNSI items is reported [10].

Kaplan-Meier survival analysis was conducted to compare the time to first DFU development for seven categories of sensory loss. Incident ulceration was considered an event. The categories were determined using the RDF-39 sum scores: Group 1, no sensory loss (RDF-39 = 0); Group 2, loss of S2PD (RDF-39: 0 and $\leq$ 10); Group 3, loss of M2PD (RDF-39: 11 and $\leq$ 18); Group 4, loss of vibration sense (RDF-39: 19 and $\leq$ 22); Group 5, loss of protective sensation [plantar] (RDF-39: 23 $\leq$ 29); Group 6, aberrant Romberg test or insensate to cold stimulus (RDF-39: 30 $\leq$ 34); Group 7, prior ulcer or amputation (RDF-39: 35 $\leq$ 39) [8]. A log rank test was conducted to determine if there were differences in the survival distributions for the different groups. Moreover, survival curves were plotted separately for patients with and without prior DFU at RDF-study baseline. The Kaplan-Meier curves were not adjusted for covariables. Patients were also categorized according to the IWGDF 2019 Risk Stratification System (Category 0 to 3) to be compared to the RDF-39 risk categories [5]. Current monofilament and/or vibratory testing were thereby directly compared to the RDF-39 and the shorter versions (RDF-31 and RDF-13) [8]. The three versions take 10, 8 and 4 min to carry out, respectively. Crude estimates of ulcer incidence rates were calculated as the total number of cases with DFUs, divided by the total number of subjects in the respective groups, using standard person-time methods. Confidence intervals (CIs) were obtained as 95% binomial confidence intervals.

Receiver operating characteristic (ROC) analysis and area under the curves (AUCs) were used to determine the optimal cut-off points (Youden's J statistic) of the RDF-39, (and short-form RDF-31 and −13) to differentiate individuals with and without DFU development [8]. Prognostic accuracy at the optimal cut-off was expressed as sensitivity (i.e. the true positive rate (probability of detection) and specificity (i.e. the true negative rate), together with likelihood ratios [14]. ROCs were plotted in which the IWGDF 2019 Risk Stratification System was compared to the RDF-39 in predicting new onset ulceration.

#### 2.4.1. Prediction modelling

Cox proportional hazard models were fit to identify independent predictors of DFU development, in which RDF-study subjects with incident DFU during RDF-study follow-up were compared with subjects without incident DFU. Potential predictor variables were chosen on the basis of 1) current literature; 2) expert opinion and 3) availability in the RDF-study dataset. When two or more covariables were highly correlated, only one was selected for the analysis to avoid multicollinearity. A univariable model was fitted that included the baseline measurement variables only. A multivariable adjusted model included all exposure variables, the final adjusted model was determined using backward stepwise (likelihood ratio) reduction, maintaining all univariable exposure variables with $p < 0.10$, in 20 iterations. Differences were expressed in unadjusted and adjusted hazard ratios (HR) with 95% CIs. To assess the fit of the multivariable model, a logistic regression model was fitted with adjusted predictors, together with ROC analysis. A model was also fitted for patients without prior DFU, using ulcer-free survival as outcome of interest [6]. 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.

### 2.5. Data availability

The full data(set) is available upon request.

## 3. Results

### 3.1. Included subjects

Baseline characteristics of the 416 RDF-study consecutive participants are shown in Table 1. Patients with a history of DFU at baseline (n = 52) were more frequently male (p = 0.039), were taller (p = 0.001), had a higher systolic blood pressure (p = 0.022), reported more symptoms of neuropathy (p < 0.0005), had worse kidney function (P = 0.06) and more often micro albuminuria (p = 0.13), had a lower proportion of palpable lower extremity arteries (p < 0.007) and more often had a history of lower extremity amputations compared with patients without a history of DFU (n = 364, see Supplemental Table S3). During RDF-study follow-up, 32 patients withdrew from study participation, 66 patients were lost to follow-up and 22 patients died (5.3% (95%CI: 3.1 to 7.4)). Patients who were lost to follow-up were significantly older compared to the remaining patients (p < 0.001), had worse renal function (p < 0.001) and a lower percentage of palpable dorsal pedis arteries (left: p = 0.013, right: p = 0.080). Patients who died were older; more often had peripheral artery disease, worse renal function, more frequently a history of DFU and a higher RDF-39 score (see Supplemental Table S2). Five out of 22 (22.7%) patients who died had a prior DFU. At study baseline 39.2% (145/370) of patients were classified in IWGDF Risk Category 0 (Very low), 16.8% (62/370) in Category 1 (Low),

**Table 1 – Baseline and outcome data.**

| | No DFUs during follow-up (n=376) | DFUs during follow-up (n=40) | P-value |
|---|---|---|---|
| Gender (M/F) | 210/166 | 31/9 | 0.008* |
| Age (median (y), IQR) | 63.6 (55.0–69.8) | 65.7 (54.5–75.4) | 0.473# |
| Ethnicity (n (%)) | | | 0.180* |
| - Caucasian | 305 (81.8%) | 36 (90.0%) | |
| - Indo-Surinamese | 34 (9.0%) | 1 (2.5%) | |
| - African | 13 (3.5%) | 1 (2.5%) | |
| - Asian | 7 (1.9%) | – | |
| - Other | 17 (4.5%) | 2 (5.0%) | |
| Height (median (m), IQR) | 172.0 (165.0–180.0) | 179.5 (173.0–184.8) | 0.094# |
| Weight (median (kg), IQR) | 88.0 (77.0–102.9) | 87.3 (76.3–111.5) | 0.019# |
| BMI (median (kg/m$^2$), IQR) | 29.5 (26.4–33.8) | 28.5 (24.7–32.8) | 0.400# |
| Duration of diabetes (median (y), IQR) | 16.0 (9.0–24.8) | 17.5 (11.0–29.0) | 0.544# |
| Type of diabetes (n (%)) | | | 0.707* |
| - Type 1 | 85 (22.6%) | 8 (20.0%) | |
| - Type 2 | 291 (77.4%) | 32 (80.0%) | |
| Insulin use (n (%)) | 319 (84.8%) | 32 (80.0%) | 0.423* |
| Systolic blood pressure (median mmHg, IQR) | 136.0 (125.3–148.0) | 139.5 (125.0–147.8) | 0.402# |
| Retinopathy (n (%)) | 54 (22.7%) | 12 (54.5%) | 0.001* |
| Lifetime smoking history (n (%)) | 95 (36.8%) | 10 (30.3%) | 0.464* |
| Lower limb sensory status | | | |
| Neuropathic symptoms° (median score (IQR)) | 1.0 (0–2.0) | 2.0 (1.0–3.0) | 0.002# |
| RDF-39 (median score (IQR)) | 16.0 (8.0–21.0) | 28.5 (19.3–34.0) | < 0.0005# |
| Vascular limb status | | | |
| History of DFUs (n (%)) | 28 (7.4%) | 24 (60.0%) | < 0.0005* |
| Previous amputations (n (%)) | | | |
| - Left extremity | 3 (0.8%) | 3 (7.5%) | < 0.001* |
| - Right extremity | 4 (1.1%) | 4 (10.0%) | < 0.0005* |
| Palpable lower extremity arteries (%) | | | |
| - Left posterior tibial artery | 75.1% | 40.0% | < 0.0005* |
| - Left dorsalis pedis artery | 77.5% | 58.3% | 0.011* |
| - Right posterior tibial artery | 73.2% | 39.5% | < 0.0005* |
| - Right dorsalis pedis artery | 79.7% | 52.9% | 0.023* |
| Laboratory measurements | | | |
| HbA1c (median (mmol/L), IQR) | 60.0 (53.0–70.0) | 59.0 (52.8–71.5) | 0.488# |
| MDRD (median ml/min/1.73m$^2$, IQR) | 79.4 (61.1–96.5) | 62.4 (45.4–102.3) | 0.477# |
| Total cholesterol (median (mmol/L), IQR) | 4.0 (3.5–4.8) | 4.3 (3.8–5.0) | 0.468# |
| LDL-C (median (mmol/L), IQR) | 1.8 (1.4–2.5) | 2.2 (1.2–2.7) | 0.181# |
| HDL-C (median (mmol/L), IQR) | 1.3 (1.1–1.6) | 1.4 (1.1–1.9) | 0.261# |
| TG (median (mmol/L), IQR) | 1.6 (1.0–2.4) | 1.8 (1.0–3.0) | 0.170# |
| ApoB (median (g/L), IQR) | 0.9 (0.8–1.1) | 0.9 (0.6–1.2) | 0.127# |
| Microalbumin (median (mg/L), IQR) | 16.0 (8.0–52.0) | 31.0 (10.0–85.5) | 0.135# |

Legend: M, male; F, female; *, Pearson chi-square test; #, Mann-Whitney *U* test; statistically significant results appear in boldface type (p<0.05); 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; °, a subscore on nerve-related neuropathic MNSI items is reported.

10.0% (37/370) in Category 2 (Moderate) and 34.1% (126/370) in Category 3 (High).

#### 3.1.1. *The incidence of diabetic foot ulceration*

Forty patients with diabetes developed DFUs during RDF-study follow-up (median 955.5 days (IQR, 841.5–1121)). Compared to patients in whom no DFUs were observed during follow-up, patients who developed DFU during follow-up were more frequently male (p = 0.008), had a lower body weight (p = 0.019), had frequently retinopathy (p = 0.001), had more neuropathic symptoms (p = 0.002), a more severe degree of sensory loss (p < 0.0005), more frequently a history of DFUs (p < 0.0005) and amputations (p < 0.001) and fewer palpable lower extremity arteries (p < 0.05) at study baseline. In the 40 participants who developed DFUs, 48 episodes of ulceration were registered. The incident rate of new-onset ulceration from study start was 4.5 (95%CI: 3.3 to 6.1) per 100 person-years. Seven patients developed multiple DFU episodes in the period of observation. In total, 65 ulcers were observed with an average number of 1.3 DFUs 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%), plantar-side of the midfoot (1.5%) and in 3 patients (4.6%) these data were not available.

#### 3.1.2. *Impact of sensory loss on ulcer-related outcomes*

Fig. 1 shows the survival distribution (i.e., time to the event of interest: DFU) for the seven groups, according to degree of

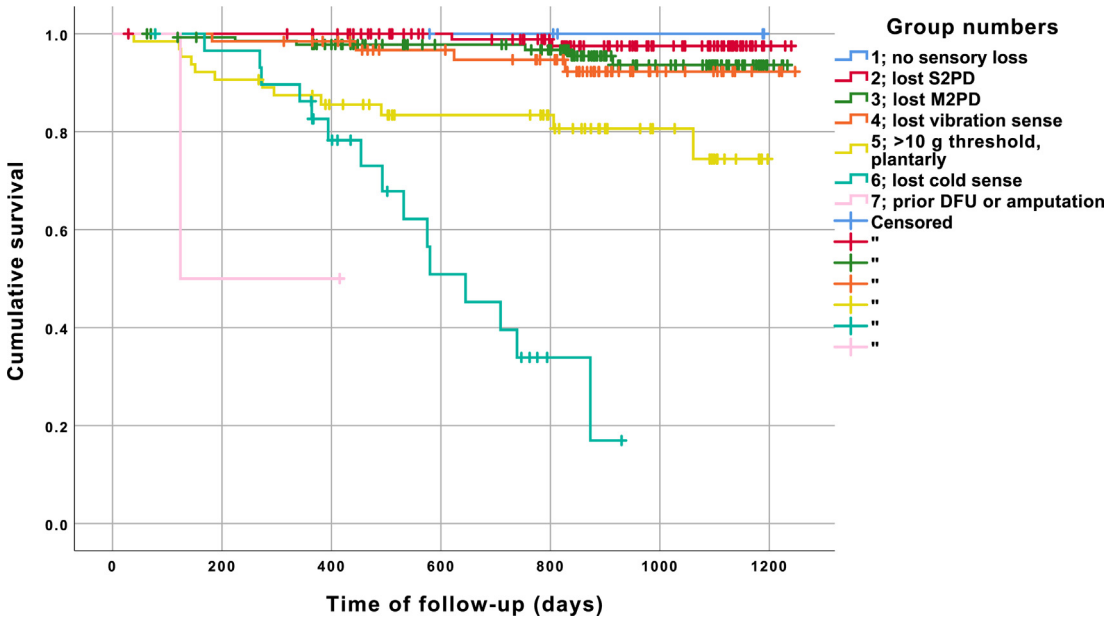


**Fig. 1 – Kaplan-Meier curves of groups with variable degrees of sensory loss. Legend: Median time (days (IQR)) to new DFU is given per group, alongside the number of patients with DFUs in the total period of observation (median 836.5 days (IQR, 459–1078)). Group 1, n = 0 DFUs; Group 2, n = 2 DFUs (median 711 days (IQR, 620-)); Group 3, n = 6 DFUs (median 545 days (IQR, 197.8–857); Group 4, n = 4 DFUs (median 534.5 days (IQR, 247.8–776.3)); Group 5, n = 12 DFUs (median 230.5 days (IQR, 129.8–463.5)); Group 6, n = 15 DFUs (median 493 days (IQR, 342–645)); Group 7, n = 1 DFU (median 124 days).**

| Days (n) | 0 | 183 | 365 | 548 | 730 | 913 | 1095 | 1278 |
|---|---|---|---|---|---|---|---|---|
| **No. at risk** | | | | | | | | |
| Group 1 | 6 | 6 | 5 | 5 | 4 | 1 | 1 | |
| Group 2 | 110 | 109 | 103 | 88 | 84 | 54 | 35 | 0 |
| Group 3 | 139 | 133 | 112 | 94 | 90 | 51 | 32 | 0 |
| Group 4 | 65 | 63 | 57 | 49 | 47 | 20 | 11 | 0 |
| Group 5 | 64 | 58 | 45 | 34 | 34 | 16 | 8 | 0 |
| Group 6 | 30 | 28 | 20 | 10 | 6 | 0 | | |
| Group 7 | 2 | 1 | 1 | 0 | | | | |

sensory loss using the RDF-39 sum score. A log rank test showed statistically significant different survival distributions, $X^2(6) = 129.704$, $p < 0.0005$. Patients without sensory loss (Group 1, n = 6) did not develop DFUs. Patients with loss of S2PD (Group 2, n = 110) had an ulcer incidence rate of 0.76 (95%CI: 0.13 to 2.50) per 100 person-years. In patients with loss of M2PD (Group 3, n = 139) this was 2.00 (95%CI: 0.81 to 4.17) per 100 person-years, in those with lost vibration sense (Group 4, n = 65) 2.78 (95%CI: 0.88 to 6.70). In patients who lost protective sensation at the plantar side of the foot (Group 5, n = 64) the incidence was 10.0 (95%CI: 5.43 to 17.04) per 100 person-years, in patients with an aberrant Romberg test or being insensate to a cold stimulus (Group 6) the incidence was 36.33 (95%CI: 21.11 to 58.58). The highest incidence per 100 person-years was seen in patients with prior DFU or amputation (Group 7, n = 2): 67.70 (95%CI: 3.40 to 334.0).

Fig. 2 shows the survival distributions plotted separately for patients with and without prior DFU at study baseline ($X^2(1) = 134.966$, $p < 0.0005$). Since group allocation was based on RDF-39 sum scores, not every patient with DFU before study entry (n = 52) was allotted to Group 7. In patients without prior foot ulceration, the incidence was 2.00 (95%CI: 1.20 to 3.17) per 100 person-years versus 31.20 (95%CI: 20.45 to 45.73) in patients with prior DFU.

#### 3.1.3. *Accuracy of the RDF-39, −31 and −13 in predicting incident ulceration*

The ability of the RDF-39 to differentiate participants with and without a high risk of DFU development was (AUC (CI) = 0.805 (0.725 to 0.884)) (Supplemental Figure 1). At the optimal probability cut-off point of 24 points, the RDF-39 yielded a sensitivity of 67.5% and specificity of 84.8%. The effect on posttest probability of disease was 4.44 (positive likelihood ratio (LR + )). Comparable values were seen for the RDF-31 (AUC (CI) = 0.799 (0.720 to 0.878)) and RDF-13 (AUC (CI) = 0.825 (0.751 to 0.898). At a cut-off of 18 points, the RDF-31 yielded a sensitivity of 70.0% and specificity of 81.6% (LR+: 3.80). The short-form RDF-13 had an optimal probability cut-off point at 7 points (sensitivity: 77,5%, specificity: 72,9%, LR+: 2.86) to differentiate the risk of ulcer development. The ulcer risk categories of the IWGDF guidelines had lower ability to differentiate patients at risk for future DFU development

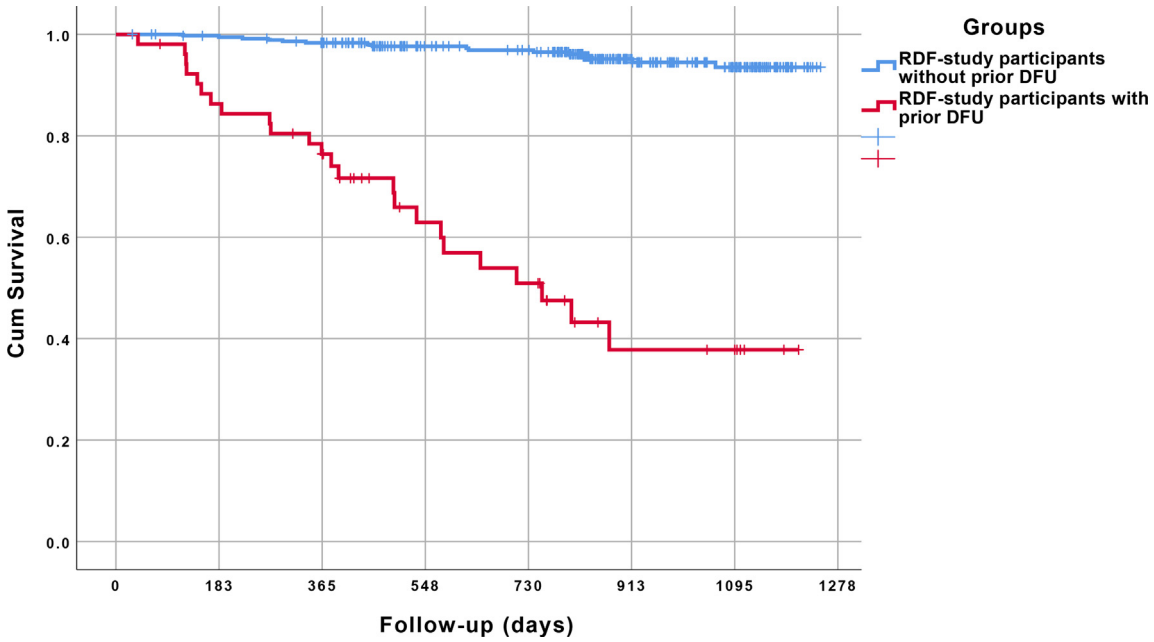


**Fig. 2 – Kaplan-Meier curves for the time until the first occurrence of new DFU of groups with and without prior DFU. Legend: Median time (days (IQR)) to new DFU is given per group, alongside the number of patients with DFUs in the total period of observation. No prior DFU, n = 16 DFUs (median 537 days (IQR, 275.5–820.8)); Prior DFU, n = 24 (median 372.5 (IQR, 155.3–578.8).**

| Days (n) | 0 | 183 | 365 | 548 | 730 | 913 | 1095 | 1278 |
|---|---|---|---|---|---|---|---|---|
| **No. at risk** | | | | | | | | |
| No prior DFU | 364 | 356 | 314 | 263 | 252 | 140 | 86 | 0 |
| Prior DFU | 52 | 43 | 33 | 20 | 16 | 6 | 4 | 0 |

(AUC (CI) = 0.623 (0.534 to 0.712)), as was observed by a composite score of 10 g monofilament tests (at 10 locations): AUC (CI) = 0.757 (0.668 to 0.845).

#### 3.1.4. *Cox-regression analysis*

Table 2 shows the results of the univariable and multivariable Cox proportional hazards models, comparing the risk of ulceration to controls. In unadjusted analyses, the baseline RDF-39 score was significantly associated with ulcer risk (HR: 1.178 (95%CI: 1.061 to 1.308). In adjusted analysis, the RDF-39 score (HR: 1.173 (95%CI: 1.086 to 1.267) and MDRD (HR: 1.022 (95%CI: 1.004 to 1.040) were associated with an increased risk of ulceration. Based on these results, the estimated logistic regression equation including those parameters showed a sensitivity and specificity for the prediction of DFU of 67.5% and 84,8%, respectively (LR+: 4.44, AUC (CI) = 0.801 (0.722 to 0.880)).

Supplemental Table S4 shows the results of Cox proportional hazards models, comparing ulcer-free survival in patients without prior DFU to controls. In unadjusted analyses, the baseline RDF-39 score was significantly associated with disease-free survival (HR: 1.039 (95%CI: 1.007 to 1.071). In adjusted analysis, the RDF-39 score (HR: 1.023 (95%CI: 1.000 to 1.047) and a palpable dorsalis pedis artery (HR: 0.520 (95%CI: 0.293 to 0.921) were associated with ulcer-free survival. The resultant logistic regression showed an ability to predict ulcer-free survival with an AUC of (CI) = 0.794 (0.671 to 0.917), sensitivity: 76.5%, specificity: 79.7%, LR+: 3.77.

## 4. Discussion

This study showed that the degree of sensory loss at the feet of patients with diabetes predicts the development of DFU. Moreover, the degree of sensory loss was the most important driver in the development of DFU. Close follow-up of patients with moderate to severe sensory loss may ultimately help to reduce the incidence of those feared amputations. To our knowledge, this prospective cohort study in patients with diabetes is the first and only to evaluate the risk of incident DFU in relation to the degree of pedal sensory loss, as assessed with a psychometrically validated grading scale [15,16]. This in contrast to the dichotomous monofilament test. The gloomy fact that DFU is associated with death was also confirmed in our study [17].

The incidence of ulcer occurrence was 4.5 (95%CI: 3.3 to 6.1) per 100 person-years in this regional teaching hospital was in line with previous reports from the literature (2.2 to 6.8 per 100 person-years) [18–20]. As the current study underlines, neuropathy is the most important risk factor for DFU development and therefore it is reasonable for clinicians to focus further on this entity in order to prevent progression to tissue breakdown. Especially in the patient without a his-

**Table 2 – 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 | 1.413 (0.303 to 6.596) | 0.660 | | |
| Age (years) | 1.043 (0.936 to 1.162) | 0.445 | | |
| Duration of diabetes (years) | 0.954 (0.874 to 1.041) | 0.290 | | |
| Diabetes type 2 | 1.178 (0.105 to 13.233) | 0.894 | | |
| Insulin use | 0.446 (0.066 to 3.019) | 0.408 | | |
| BMI (kg/m$^2$) | 0.925 (0.817 to 1.047) | 0.217 | | |
| Systolic blood pressure (mmHg) | 0.986 (0.955 to 1.019) | 0.409 | | |
| Lifetime smoking history | 1.398 (0.296 to 6.610) | 0.672 | | |
| Retinopathy | 3.590 (0.610 to 21.139) | 0.158 | | |
| RDF-39 (points) | **1.178 (1.061 to 1.308)** | **0.002** | **1.173 (1.086 to 1.267)** | **<0.0005** |
| Palpable lower extremity arteries | | | | |
| - Left posterior tibial artery | 1.310 (0.166 to 10.320) 1.377 (0.203 to 9.357) | 0.798 | | |
| - Left dorsalis pedis artery | 1.673 (0.174 to 16.100) | 0.743 | | |
| - Right posterior tibial artery | 1.386 (0.141 to 13.606) | 0.656 | | |
| - Right dorsalis pedis artery | | 0.780 | | |
| HbA1c (mmol/L) | 1.053 (1.000 to 1.109) | 0.050 | | |
| MDRD (ml/min/1.73 m$^2$) | 1.012 (0.987 to 1.038) | 0.341 | **1.022 (1.004 to 1.040)** | **0.016** |
| Total cholesterol (mmol/L) | 1.225 (0.628 to 2.387) | 0.552 | | |
| TG (mmol/L) | 0.988 (0.639 to 1.527) | 0.957 | | |

Legend: HR, hazard ratio; statistically significant results appear in boldface type ($p < 0.05$); BMI, body mass index; RDF-39, 39-item Rotterdam Diabetic Foot Study Test Battery; HbA1c, glycated hemoglobin; MDRD, Modification of Diet in Renal Disease; TG, triglycerides.

tory of prior ulceration it is judicious to focus on peripheral nerve function, because patients with prior DFU fall in another risk category with consequent screening recommendations [5]. This study also adds that patients with poor renal function should be subjected to lower extremity risk analysis.

Previous studies have shown that symptoms of neuropathy do not necessarily correlate with peripheral nerve function [8]. For example, numbness at the feet is reported when S2PD, M2PD and vibration sense have already become absent in the natural history of loss of sensation, whereas hyperesthesia, hyperalgesia, allodynia and 'wind-up' may occur without overt nerve damage. Patients often report having excellent sensation because they still can feel pain, however, this is not the same as touch and intact protective sensation. Risk groups 1 to 4 in our study had a gradually increasing ulcer incidence rate of 0.76 to 2.78 per 100 person-years. Although the survival curves are close to each other, this still means an almost 4 times higher risk between risk groups 1 and 4. We therefore recommend the use of objective measures of somatosensory function, as such presented in the RDF scales, in order to equitably estimate the associated hazards of sensory loss.

The RDF grading scales provide an overall estimation of pedal sensory status, from ankle level to hallux, including both extremities. Early to advanced stages of (large fiber) sensory loss are assessed, now also resembling ulcer risk. The RDF-39 has been shown to correlate with postural stability and predicts recurrent falls [21]. The primary outcome of the current study was incident DFU occurring in either foot. Albeit extremity-specific item scores have not been formerly evaluated to be validly summed in a total score, the relative symmetric distribution of sensory loss in both extremities allows making judgments on the contralateral extremity when one side is tested [9]. In regard to monitoring the feet, assessing sensory status is a sensible first step in estimating the chance of DFU occurrence, with consequent recommendations on further risk factor analysis [22]. The screening frequency may then be more patient tailored. The presented median time to ulcer occurrence may aid this debate since there is no published evidence to support the suggested intervals [5]. Because it is very difficult to predict where the DFU will occur, in the absence of overt risk factors such as Charcot deformities, the general sensory status provided by the RDF sum score will be sufficient in estimating the overall risk of ulceration. A recent study developed the concept of 'ulcer metastasis', showing that 48% of wounds recurred to the contralateral foot and that only 17% of ulcers relapsed at the same anatomical location [23]. Adding the RDF scales as measure of neuropathy to current prediction models of first onset ulceration will likely improve accuracy of detecting the patient at risk, as well in estimating disease-free survival [24].

Several caveats of our study are important to highlight. First, the RDF-cohort is a hospital-based cohort, with patients at an increased annual risk of foot ulceration compared to the general population (mean: 2.1% (95%CI: 1.52 to 2.29) per year) [25]. The baseline prevalence of previous DFU was considerable (12.5% (95%CI: 9.3–15.7)) and 24 out of 40 patients (60%) suffered from reulceration during follow-up. However, we do think that the conclusions from our study may be validly extrapolated to different populations, since the majority of the RDF-cohort (n = 364) was ulcer free at baseline (IWGDF Risk Categories 0 to 2), as is generally the case for the annually checked primary care population. A recently developed shorter and quicker version of the RDF-39 can estimate the RDF-39 sum score in as few as three tests, from which balance impairment, risk of falls and now risk for ulceration can be estimated. This is especially of use in primary care or the outpatient clinic, yet external validity has to be determined in future studies.

Second, no direct comparisons to other screenings tools in regard to ulcer risk were possible since these were not assessed in the RDF cohort. Other assessment scales for

polyneuropathy include the Toronto Clinical Scoring System and Diabetic Neuropathy Symptom Score, which are validated with the Mayo criteria, nerve conduction studies and biopsies. The downside of these scores are the extensiveness of the examination and varying contents (e.g., both upper and lower extremity, subjective and objective measures). We are confident that the objective sensory tests of the RDF scales can overcome this and have additional value in predicting future DFU events, since neuropathy can cloud patient' statements on sensory status of the feet.

Third, no (invasive) testing on peripheral artery disease (PAD), other than palpation of arteries, was conducted in RDF-Study participants. As concluded previously from a study that developed a foot ulcer risk model in the primary care setting, the lack of significant contribution of pedal pulses to the likelihood of foot ulceration was also found in our study. PAD is probably only relevant for healing processes, since the limb has to be end-stage ischemic to compromise soft tissue integrity leading to ulceration [26]. Future studies should at least assess peripheral artery status with Doppler waveforms, although no definite answer is given on which test is superior [5].

Fourth, information on foot deformity was only available in a subset of patients. In order not to jeopardize the power of the prediction model, it was decided to exclude those parameters, although they are considered risk factors for foot ulceration [27]. Finally, the observation that kidney function is negatively associated with diabetic foot disease is confirmed in our population. This is especially illustrated by the fact that patients undergoing intermittent dialysis are at very high risk of developing limb complications as has been reported by others [28].

In summary, we have demonstrated that in patients with diabetes degree of sensory loss at baseline relates to the risk of ulceration at follow-up. Patients with more severe stages of sensory loss and worse kidney function are at higher risk of DFU development. This new information may serve as an extension of the currently advised instruments to predict ulceration. Moreover, grading the loss of sensation in patients allows for a closer follow-up by risk stratification and early interventions. Increased surveillance may prevent lower extremity complications from occurring, adding ulcer-free days together with prolongation of life.

## Author contributions

W.D.R. researched data, wrote the manuscript. M.C.C/J.H.C. contributed to the discussion and reviewed/edited the manuscript. All authors approved the final version of the manuscript and take responsibility for the integrity of the data and analysis.

## 6. Guarantor's statement

Dr. Willem D. Rinkel is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

## Funding

Support for the RDF-study was partially provided by Nuts Ohra Fund, the Netherlands, a nonprofit organization providing financial aid for medical research [grant no. 1002–042]. Nuts Ohra did not have any influence on the design, analysis or interpretation of this study.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2021.108836.

## REFERENCES

[1] Wukich DK, Raspovic KM, Suder NC. Patients With Diabetic Foot Disease Fear Major Lower-Extremity Amputation More Than Death. Foot Ankle Spec 2018;11(1):17–21.
[2] Singh N, Armstrong DG, Lipsky BA. Preventing foot ulcers in patients with diabetes. JAMA 2005;293(2):217–28.
[3] Crawford F, Cezard G, Chappell FM, et al. A systematic review and individual patient data meta-analysis of prognostic factors for foot ulceration in people with diabetes: the international research collaboration for the prediction of diabetic foot ulcerations (PODUS). Health Technol Assess 2015;19(57):1–210.
[4] McNeely MJ, Boyko EJ, Ahroni JH, et al. The independent contributions of diabetic neuropathy and vasculopathy in foot ulceration. How great are the risks?. Diabetes Care 1995;18(2):216–9.
[5] http://www.iwgdfguidelines.org.
[6] 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/metabolism Res Rev 2019;35(3) e3119.
[7] Rinkel WD, Aziz MH, Van Deelen MJM, et al. Normative data for cutaneous threshold and spatial discrimination in the feet. Muscle Nerve 2017;56(3):399–407.
[8] Rinkel WD, Aziz MH, Van Neck JW, Cabezas MC, van der Ark LA, Coert JH. Development of grading scales of pedal sensory loss using Mokken scale analysis on the Rotterdam Diabetic Foot Study Test Battery data. Muscle Nerve 2019;60(5):520–7.
[9] Rinkel WD, van der Oest MJW, Coert JH. Item reduction of the 39-item Rotterdam Diabetic Foot Study Test Battery using decision tree modelling. Diabetes Metabolism Research and Reviews 2020;36(4). https://doi.org/10.1002/dmrr.3291.
[10] Rinkel WD, Castro Cabezas M, van Neck JW, Birnie E, Hovius SER, Coert JH. 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(5):1258–66.
[11] American Diabetes Association. Standards of medical care in diabetes – 2014. Diabetes Care 2014;37(Suppl 1):S14–80.
[12] Martina IS, van Koningsveld R, Schmitz PI, van der Meche FG, van Doorn PA. Measuring vibration threshold with a

graduated tuning fork in normal aging and in patients with polyneuropathy. European Inflammatory Neuropathy Cause and Treatment (INCAT) group. J Neurol Neurosurg Psychiatry 1998;65(5):743–7.
[13] 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.
[14] Hayden SR, Brown MD. Likelihood ratio: A powerful tool for incorporating the results of a diagnostic test into clinical decisionmaking. Ann Emerg Med 1999;33(5):575–80.
[15] Young MJ, Breddy JL, Veves A, Boulton AJ. The prediction of diabetic neuropathic foot ulceration using vibration perception thresholds A prospective study. Diabetes Care 1994;17(6):557–60.
[16] Abbott CA, Vileikyte L, Williamson S, Carrington AL, Boulton AJ. Multicenter study of the incidence of and predictive risk factors for diabetic neuropathic foot ulceration. Diabetes Care 1998;21(7):1071–5.
[17] Armstrong DG, Swerdlow MA, Armstrong AA, Conte MS, Padula WV, Bus SA. Five year mortality and direct costs of care for people with diabetic foot complications are comparable to cancer. J Foot Ankle Res 2020;13(1):16.
[18] 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. Diabetic Med J British Diabet Assoc 2002;19(5):377–84.
[19] Boyko EJ, Ahroni JH, Cohen V, Nelson KM, Heagerty PJ. Prediction of diabetic foot ulcer occurrence using commonly available clinical information: the Seattle Diabetic Foot Study. Diabetes Care 2006;29(6):1202–7.
[20] Lavery LA, Armstrong DG, Wunderlich RP, Tredwell J, Boulton AJ. Diabetic foot syndrome: evaluating the prevalence and incidence of foot pathology in Mexican Americans and non-Hispanic whites from a diabetes disease management cohort. Diabetes Care 2003;26(5):1435–8.
[21] Rinkel WD, van Nieuwkasteele S, Castro Cabezas M, van Neck JW, Birnie E, Coert JH. Balance, risk of falls, risk factors and fall-related costs in individuals with diabetes. Diabetes Res Clin Pract 2019;158 107930.
[22] Arad Y, Fonseca V, Peters A, Vinik A. Beyond the monofilament for the insensate diabetic foot: a systematic review of randomized trials to prevent the occurrence of plantar foot ulcers in patients with diabetes. Diabetes Care 2011;34(4):1041–6.
[23] Petersen BJ, Rothenberg GM, Lakhani PJ, et al. Ulcer metastasis? Anatomical locations of recurrence for patients in diabetic foot remission. J Foot Ankle Res 2020;13:1.
[24] Monteiro-Soares M, Dinis-Ribeiro M. External validation and optimisation of a model for predicting foot ulcers in patients with diabetes. Diabetologia 2010;53(7):1525–33.
[25] Muller IS, de Grauw WJ, van Gerwen WH, Bartelink ML, van Den Hoogen HJ, Rutten GE. Foot ulceration and lower limb amputation in type 2 diabetic patients in dutch primary health care. Diabetes Care 2002;25(3):570–4.
[26] Heald A, Lunt M, Rutter MK, et al. Developing a foot ulcer risk model: what is needed to do this in a real-world primary care setting?. Diabetic Med J British Diabet Assoc 2018.
[27] Ledoux WR, Shofer JB, Smith DG, et al. Relationship between foot type, foot deformity, and ulcer occurrence in the high-risk diabetic foot. J Rehabil Res Dev 2005;42(5):665–72.
[28] Ndip A, Lavery LA, Lafontaine J, et al. High levels of foot ulceration and amputation risk in a multiracial cohort of diabetic patients on dialysis therapy. Diabetes Care 2010;33 (4):878–80.