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Balance, risk of falls, risk factors and fall-related costs in individuals with diabetes

Willem D. Rinkel [a,b,*], Shelly van Nieuwkasteele [b,c], Manuel Castro Cabezas [d], Johan W. van Neck [c], Erwin Birnie [e,f], J. Henk Coert [a,b]

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

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ABSTRACT

Aims: Sensory loss and impaired balance are considered risk factors of incident falls. The aim of this study was to assess the relationship between degree of foot sensation and balance, risk of falls, incidence of fall-related injuries and costs in a cohort of patients with diabetes.

Methods: (Non)-neuropathic subjects participating in the Rotterdam Diabetic Foot Study were followed prospectively. Subjects underwent sensory testing of the feet (39 item Rotterdam Diabetic Foot Study Test Battery (RDF-39)); balance was assessed at the second follow-up (Brief-BESTest) as were data on incident falls. Medical records and financial data were abstracted to estimate fall-related morbidity and in-hospital costs.

Results: A higher RDF-39 score, cerebral artery disease, type 2 diabetes, height and age were predictors of the Brief-BESTest total score. 41/296 patients (13.9%) reported two or more falls during follow-up. Predictors for recurrent falls were a higher RDF-39 score (aOR: 1.124, $p < 0.0005$), male gender (aOR: 0.319, $p = 0.016$), age (aOR: 0.938, $p = 0.003$) and type 2 diabetes (aOR: 3.157, $p = 0.100$). Thirty-one patients used medical resources (median US $ 440.45 (IQR: 179–1162).

Conclusions: Degree of sensory loss correlates significantly with an increased imbalance and risk of falls. The RDF-39 may be used as stratification tool in medical decision-making and patient information.

* 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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1. Introduction

Balance is the ability to maintain the body's line of gravity over its base of support. A correctly functioning balance system allows a person to maintain a proper vision while moving, to determine the direction and speed of movement, to identify the body's position in its space and to make automatic postural adjustments to maintain posture and stability in varying circumstances [1].

Balance is achieved and maintained by a complex set of sensorimotor control systems that necessitates sensory input from vision (sight), proprioception (touch) and the vestibular system (motion, equilibrium, spatial orientation) [2]. This input information is integrated in the brain, together with motor output to the eye and body muscles as effector organs. Ageing, disease, injury and certain drugs can affect one or more of these components, resulting in an elevated risk of balance impairment and gait disorders [3,4]. Diabetes mellitus, for example, may affect sensory input from the feet, resulting in an increased risk of falls, fractures and death [5,6].

One of the sequelae of diabetes is diabetic sensorimotor polyneuropathy (DSP), which is prevalent in the diabetes population and associated with both neuropathic symptoms like burning, tingling and pain, and an insidious simultaneous process of loss of sensation at the feet [7–9]. Prevalence rates of DSP in type 2 diabetes increase to 50% after 10 years of disease duration and in type 1 diabetes this is 20% after 20 years [10]. Severe loss of sensation may also result in balance problems and falls [8,11]. Patients with reduced cutaneous sensation have different plantar pressure distributions compared to healthy individuals [12]. However, little is known about the influence of reduced sensation to balance impairment [12–15]. To further quantify the relationship between diabetes related sensory loss and balance impairment, we evaluated whether the 39-item Rotterdam Diabetic Foot Study Test Battery (RDF-39), a validated instrument to grade the loss of sensation, is capable of stratifying patients in high or low risk categories of accidental falls [8,11]. The RDF-39 contains dichotomized test items on incremental severity of sensibility loss at the feet, ranging from loss of static- and moving two-point discrimination to prior ulceration and amputation [8,9,16].

The aim of this study was to assess the relationship between degree of foot sensation and balance, risk of falls and its consequences in terms of incident fall-related injuries and fall-related costs in a cohort of individuals with diabetes.

2. Methods

2.1. Study design and subjects

The current study is part of the Rotterdam Diabetic Foot Study (RDF-study), a prospective cohort study of unselected diabetes type 1 and type 2 patients followed at the outpatient Diabetes Clinic of the Franciscus Gasthuis & Vlietland hospital, Rotterdam, the Netherlands. RDF-study design and methods have been reported in detail elsewhere[11,17]. In short, the aim of the RDF-study is to investigate the natural history of neuropathy, including deterioration of sensation of the feet. The RDF-study participants were recruited from patients visiting the outpatient diabetes clinic. RDF-study inclusion criteria were: 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 assessed at the baseline interview and with the screening questionnaire. The Medical Research Ethics Committee of Erasmus University Medical Center, Rotterdam, the Netherlands approved the study (MEC-2009-148).

2.2. Data collection and tests

Baseline measurements were conducted between January 2014 and June 2015, with patients first subjected to an interview (history taking (e.g. prior ulceration, amputation, comorbidities), Michigan Neuropathy Screening Instrument (MNSI)), then to a physical examination (full Rotterdam Diabetic Foot Study Test Battery) together with gathering of demographic (age, sex), anthropometric (height, weight) and laboratory (routine measurements) data, which was repeated in follow-up visits 1–1.5 years later. At the second follow-up visit, balance tests (The Brief-Balance Evaluation Systems Test (Brief-BESTest)) were performed in an unselected group of participants. Data on falls were collected at each follow-up visit and included the circumstances of each fall, usage of medical resources and whether hospitalization was required. Non-fallers and recurrent fallers were distinguished. Medical resource use and associated costs were retrieved from the hospital's financial systems or general practitioner. Costs were originally estimated in Euros and later converted in the US dollars 2016 exchange rate: one Euro equaled approximately 1.11 US dollars.

2.2.1. Brief-BESTest

The primary outcome of this study was patients balance status. The Brief-BESTest is a valid balance test that constitutes of 6 balance control system items from the original BESTest [18–20], referring to biomechanical constraints, stability limits, sensory orientation and stability in gait. The assessor scores each item from 0 (severe balance impairment) to 3 (no balance impairment). Two of the 6 items (transition-anticipatory postural adjustment, reactive postural response) are scored bilaterally, resulting in an 8-item balance test. The score range is 0–24 points, with higher scores indicative of a better balance performance [18,21]. The Brief-BESTest has a high interrater (ICC = 0.86 – 0.96) and test-retest (ICC = 0.90 – 0.98) reliability in subjects with and without neurological diagnosis. The Brief-BESTest is able to validly discriminate between patients with and without a history of falls (mean total score 12.5 and 15.5, respectively) [18,19]. The Brief-BESTest was only administered in RDF-study patients who entered the second follow-up visit.

2.2.2. Falls

The secondary outcome of this study was the risk of falls. A fall was defined as a person inadvertently ending up on the ground or at a lower level [22]. Because multiple falls are asso-

ciated with an increased risk of falling and isolated falls are not, a fall in this study was defined as multiple or recurrent falls [23,24]. Individual patients reported their history of falls using standardized questions and were provided with a clear definition of falls. Other secondary measures were the incidence of fall-related injuries and cumulative fall-related costs.

2.2.3. *The Rotterdam diabetic foot study test battery*

The 39-item RDF-39 includes both instruments and test sites to measure overall foot sensation [8,11]. 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 (Supplementary Table A). The RDF-39 is unidimensional and valid in the assessment of sensation at the feet [8,11]. 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 [16]. S1PD was tested with a 10 g Semmes-Weinstein monofilament (Baseline® Tactile™, USA), based on current international standards of medical care in diabetes [25,26]. 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 [27]. Cold sensation was tested by applying a cold piece of metal to the arch of the foot. Information on numbness was derived from the MNSI, which was administered by the physician before the physical examination. Information on prior ulceration and/or 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 [8,11].

2.3. *Statistical analysis*

Analyses were based on the 296 included patients who were assessed at the second follow-up. Baseline characteristics were presented as mean (SD) for variables with normal distributions, median (IQR) for variables with skewed distributions, and n (%) for categorical variables. The Shapiro-Wilk test was used to assess normality. Differences between categories were assessed using a Kruskal-Wallis test.

2.3.1. *Brief-BESTest predictors*

Relationships between the Brief-BESTest and baseline continuous predictor variables (RDF-39, MNSI total score, body mass index (BMI), age and diabetes duration) were explored using Spearman's correlation coefficients. Univariate linear regression analysis was used to explore the relationship between each potential predictor variable with the Brief-BESTest. Only baseline variables with a realistic potential contribution to the outcome variable and availability in the RDF-study dataset were included in the models (i.e. sex, age, weight, height, duration and type of diabetes, medical history and pedal sensory status (RDF-39). Significant factors, as determined by a $p < 0.10$, were included in the multivariable linear regression model with backward selection and considered significant with $p < 0.05$ (two-sided).

2.3.2. *Relationships between Brief-BESTest and falls and RDF-39 and falls*

Receiver operating characteristic analysis and area under the curves (AUCs) were used to determine the optimal cut-off points (Youden's J statistic) of both the RDF-39 and Brief-BESTest to differentiate individuals with and without a history of (recurrent) falls (Brief-BESTest) or future falls (RDF-39) [28]. Prognostic accuracy at the optimal cut-off was expressed as sensitivity and specificity.

2.3.3. *Predictors of falls*

A binary logistic regression analysis was used to explore the relationship between each potential predictor variable with incident future falls. Again, only variables with a realistic potential contribution to the outcome variable were included in the models. Significant factors with $p < 0.10$ were included in the multivariable logistic regression model with backward conditional selection and considered significant with $p < 0.05$. When two or more covariables were highly correlated, only one was selected for the analysis to avoid multicollinearity. As a result, weight and height were selected instead of BMI.

2.3.4. *Fall- and fracture incidence per person-time*

Fall- and fracture incidence was calculated using standard person-time methods.

All statistical analysis was carried out using IBM SPSS Statistics 24.0 (IBM Corp., Armonk, New York, USA). P-values <0.05 (two-sided) were considered statistically significant.

3. Results

3.1. *Included subjects*

Included were 416 subjects. During RDF-study follow-up, 32 patients withdrew from study participation, 66 patients were lost to follow-up and 22 patients died. The remaining 296 patients (71.2%) were assessed at the second follow-up (median follow-up: 885 days (IQR): 833-1000). Of these, 134 patients (65.5%) underwent the balance tests. 255 of 296 patients (86.1%) were non-fallers and the remaining 41 patients (13.9%) were recurrent fallers. Table 1 shows the baseline characteristics of the different groups. Demographic and anthropometric data were comparable between groups. Recurrent fallers had more often type 2 diabetes, neuropathy complaints (MNSI score), increased sensory loss (RDF-39 score) and impaired balance tests (Brief-BESTest).

Table 1 – Baseline and outcome data.

	Patients with Brief-BESTest at second follow-up (n = 134)	Patients without Brief-BESTest at second follow-up (n = 162)	Non-fallers (second follow-up) (n = 255)	Recurrent fallers (second follow-up) (n = 41)
Gender (M/F)	84/59	89/73	152/103	21/20
Age (median (y), IQR)	63.2 (55.2 – 68.6)	64.4 (55.8 – 72.3)	64.0 (55.2 – 69.9)	62.7 (56.6 – 72.2)
Ethnicity (n (%))				
- Caucasian	116 (86.6%)	130 (80.2%)	211 (82.7%)	35 (85.4%)
- Indo-Surinamese	8 (3.0%)	16 (9.9%)	21 (8.2%)	3 (7.3%)
- African	4 (3.0%)	5 (3.1%)	9 (3.5%)	-
- Asian	3 (2.2%)	3 (1.9%)	6 (2.4%)	-
- Other	3 (2.2%)	8 (4.9%)	8 (3.1%)	3 (7.3%)
Height (median (m), IQR)	176.0 (167.8 – 183.0)	172.0 (164.0 – 179.0)	175.0 (166.0 – 180.0)	172.0 (164.5 – 181.5)
Weight (median (kg), IQR)	90.0 (79.0 – 106.2)	85.5 (75.0 – 98.2)	87.0 (76.0 – 102.0)	94.3 (77.0 – 113.0)
BMI (median (kg/m^2), IQR)	29.7 (26.8 – 34.4)	29.1 (25.6 – 32.5)	29.1 (25.7 – 32.8)	30.9 (27.0 – 36.5)
Duration of diabetes (median (y), IQR)	16.0 (9.0 – 26.0)	16.0 (9.8 – 24.3)	16.0 (9.0 – 26.0)	16.0 (11.0 – 24.5)
Type of diabetes (n (%))				
- Type 1	32 (23.9%)	37 (22.8%)	64 (25.1%)	5 (12.2%)
- Type 2	102 (76.1%)	125 (77.2%)	191 (74.9%)	36 (87.8%)
Mean Arterial Pressure (median (mmHg), IQR)	97.2 (91.0 – 103.3)	96.7 (88.7 – 104.3)	96.7 (89.0 – 103.3)	97.3 (90.7 – 106.2)
Systolic blood pressure (median (mmHg), IQR)	136.0 (126.8 – 149.3)	136.0 (125.0 – 146.0)	136.0 (125.0 – 146.0)	140.0 (127.0 – 155.0)
Diastolic blood pressure (median (mmHg), IQR)	77.0 (70.0 – 82.0)	77.5 (69.0 – 82.0)	77.0 (125.0 – 146.0)	77.0 (70.0 – 84.0)
Drugs (n (%))				
- Lipid lowering drugs	80 (59.7%)	107 (66.0%)	166 (65.1%)	21 (51.2%)
- Oral blood glucose lowering drugs	76 (56.7%)	88 (54.3%)	143 (56.1%)	21 (51.2%)
- Insulin	109 (56.7%)	141 (87.0%)	216 (84.7%)	34 (82.9%)
Medical history (n (%))				
- Hypertension	83 (61.9%)	91 (56.2%)	144 (43.5%)	30 (73.2%)
- Myocardial infarction	14 (10.4%)	26 (16.0%)	29 (11.4%)	11 (26.8%)
- Angina pectoris	12 (9.0%)	21 (13.0%)	25 (9.8%)	8 (19.5%)
- Coronary artery disease	18 (13.5%)	39 (24.1%)	44 (17.3%)	13 (31.7%)
- CABG/PCI	13 (9.8%)	37 (22.8%)	37 (14.6%)	13 (31.7%)
- CVA/TIA	14 (10.4%)	14 (8.6%)	26 (10.2%)	2 (4.9%)
- Cancer	14 (10.4%)	22 (13.6%)	30 (11.8%)	6 (14.6%)
- COPD	15 (11.2%)	12 (7.4%)	23 (9.0%)	4 (9.8%)
- Peripheral arterial disease	7 (5.2%)	11 (6.8%)	15 (5.9%)	3 (7.3%)
Diabetic Sensory Polyneuropathy (n (%))				
- MNSI score > 3	53 (41.7%)	54 (41.5%)	82 (36.6%)	25 (75.8%)
Rotterdam Diabetic Foot Study				
Test Battery (median score, IQR)	17.0 (8.0 – 22.0)	14.0 (8.0 – 22.0)	15.0 (7.0 – 21.0)	21.0 (14.5 – 29.5)
- RDF-39				
Brief-BESTest (median score, IQR)	16.0 (10.0 – 21.3)	–	16.5 (11.8 – 22.0)	8.0 (0.50 – 15.0)
Retinopathy (n (%))	21 (25.0%)	28 (26.7%)	42 (25.8%)	7 (26.9%)
Single fallers (n (%))	25 (18.7%)	20 (12.3%)	45 (17.6%)	-
Recurrent fallers (n (%))	20 (14.9%)	21 (13.0%)	-	41 (100%)

Laboratory measurements				
HbA1c (median (mmol/L), IQR)	61.0 (52.5 – 69.0)	60.0 (53.0 – 70.5)	61.0 (53.0 – 70.0)	56.5 (52.3 – 65.8)
MDRD (median ml/min/1.73 m^2, IQR)	78.3 (60.2 – 96.7)	77.1 (53.0 – 70.5)	79.3 (60.9 – 96.2)	72.7 (57.3 – 96.3)
Total cholesterol (median (mmol/L), IQR)	4.1 (3.5 – 4.7)	4.0 (3.5 – 4.8)	4.0 (3.5 – 4.8)	4.0 (3.7 – 4.7)
LDL-C (median (mmol/L), IQR)	1.8 (1.3 – 2.5)	1.8 (1.4 – 2.5)	1.8 (1.4 – 2.5)	1.8 (1.5 – 2.4)
HDL-C (median (mmol/L), IQR)	1.4 (1.1 – 1.6)	1.3 (1.1 – 1.6)	1.3 (1.1 – 1.6)	1.2 (1.0 – 1.5)
Non-HDL-C (median mmol/L, IQR)	2.6 (2.1 – 3.3)	2.6 (2.2 – 3.2)	2.6 (2.1 – 3.2)	2.7 (2.3 – 3.6)
TG (median (mmol/L), IQR)	1.5 (1.0 – 2.4)	1.6 (1.0 – 2.4)	1.5 (1.0 – 2.3)	1.9 (1.3 – 3.1)
ApoB (median (g/L), IQR)	0.9 (0.8 – 1.1)	0.9 (0.8 – 1.1)	0.9 (0.8 – 1.1)	0.9 (0.7 – 1.0)
Microalbumin urine (median (mg/L), IQR)	14.0 (8.0 – 47.0)	18.0 (7.0 – 46.5)	16.0 (7.0 – 48.3)	21.0 (10.0 – 44.0)

M, male; F, female; 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; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; MNSI, Michigan Neuropathy Screening Instrument.

3.1.1. *Impact of sensory loss on balance parameters*

Fig. 1 shows that RDF-39 and Brief-BESTest total scores were significantly negatively associated (r_s = −0.446, p < 0.0005) with the RDF-39 sum score, accounting for 21.0% of the variation in total Brief-BESTest scores with adj. R^2 = 20.5%, despite considerable heterogeneity among patients. A Brief-BESTest score of 13 points correlates with a RDF-39 score of 22 points. Table 2 displays the relationship between increasing categories of RDF-scores, the separate Brief-BESTest subscores and the total MNSI score. The negative association seen in Fig. 1 is also present for each of the Brief-BESTest sub scores.

3.1.2. *Impact of balance and sensory loss on recurrent falls*

The Brief-BESTest had an acceptable ability to differentiate participants with and without a history of recurrent falls (AUC (CI) = 0.746 (0.624–0.868)). At the optimal probability cutoff point of 13 points, the Brief-BESTest yielded a sensitivity of 71.9% (correctly classifying the group with a history of recurrent falls during follow-up) and specificity of 70% (correctly classifying the group without a history of falls during follow-up).

The baseline RDF-39 score had an acceptable ability to predict participants with and without future recurrent falls during follow-up (AUC (CI) = 0.687 (0.596–0.779)). At the optimal probability cutoff point of 18 points, the RDF-39 yielded a sensitivity of 70.7% (correctly classifying the group with recurrent falls during follow-up) and specificity of 60.4% (correctly classifying the group without falls during follow-up). A total RDF-39 score of 18 points indicates aberrant S2PD and M2PD measurements, but intact vibration sense and protective sensation, as assessed with a 10 g monofilament (Fig. 1, Table 2).

3.1.3. *Brief-BESTest predictors*

Table 3 shows the results of univariate and multivariable linear regression analysis for total Brief-BESTest scores. A higher RDF-39 score at study entry (i.e. more severe degree of sensory loss; beta coefficient: −0.37), a higher age (beta: −0.35 per year), a higher weight (beta: −0.09 per kilogram), type 2 diabetes (beta: −6.59), a medical history of hypertension (beta: −4.80), myocardial infarction (beta: −4.75), COPD (beta: −4.24) or peripheral artery disease (beta: −8.56) significantly reduced the Brief-BESTest total score at the second follow-up, implying increased balance impairment. In the multivariable analysis, only a higher RDF-39 score at study entry (beta: −0.31), a higher age (beta: −0.21) and height (beta: 0.13) added independently and significantly to the prediction of the Brief-BESTest total score (p < 0.0005, adj. R^2 = 0.46).

3.1.4. *Predictors of falls*

Table 4 shows the results of univariate and multivariable binary logistic regression analysis for recurrent falls. A higher RDF-39 score (crude OR: 1.08) and a history of myocardial infarction (crude OR: 2.86) significantly increased the odds for recurrent falls during follow-up. The multivariable logistic regression model showed that a higher RDF-39 score (adj. OR: 1.12), male gender (adj. OR: 0.32) and age (adj. OR: 0.94) remained independently significant predictors for future falls (model $X^2(4)$ = 25.386, p < 0.0005; proportion of cases correctly classified: 86.2%). The RDF-39 score proved to be an indepen-

dent predictor of recurrent falls (BriefBESTest < 16: OR: 1.08, p = 0.11 versus BriefBESTest > 15: OR 1.07, p = 0.30).

3.1.5. *Incidence of falls, resource use and costs*

The incidence of recurrent falls in our cohort was 2.3 falls (95% CI: 1.6-3.3) per 100 person-years. Thirty-one patients made use of healthcare resources due to falls by visiting a general practitioner (n = 6), physiotherapist (n = 3) or were in need of secondary care (n = 24). Twelve patients (five women, seven men) suffered from fall-related fractures or ruptures (0.9 fractures (95% CI: 0.5-1.5) per 100 person-years). Two hip fractures were observed, one patella fracture, two broken ankles, one metatarsal bone fracture and two broken halluces. Upper extremity injuries included a fractured humerus, a broken wrist, a fractured digitus five and a rupture of the supraspinatus tendon. Total healthcare expenditures were $ 59,947.07, median costs of US$ 440.45 (IQR: 179–1162) per fall (2016 price level).

4. Discussion

Any person older than 65 years who has not fallen in the previous year has a pre-test probability of 19% to 36% to fall the next year [29,30]. As a previous fall is a sensitive prognosticator of future falls, exploration of its predictors appears sensible. Previous studies suggest that the highest potential yield comes from screening on balance and gait, as these factors are independent predictors of future falls and have more impact than orthostatic hypotension, visual impairment, medication use, limitation in activities of daily living and cognitive impairment [31]. This is important, because strategies to improve gait and balance of patients with diabetes have been proven effective to avoid falls [31–33]. So far, little attention has been given to the influence of degree of sensory loss at the feet in relation to both balance impairment and falls [12,14]. Our study showed that degree of sensory loss significantly relates to the risk for imbalance and risk of falls.

A previous study showed a positive association between peripheral neuropathy and pedal sensibility on the one hand and balance on the other, but sensibility was not assessed using an unambiguously outcome measure [14]. The advantage of the RDF-39 in assessing foot sensation lies in the fact that both early stages of sensory loss (i.e., S2PD, M2PD) as well as more advanced stages of sensory loss (e.g. loss of cold sensation, prior ulceration etc.) are measured with validated and easy to apply screening instruments. The RDF-39, a dichotomized version of the full RDF Study Test Battery, takes around 10 minutes to complete. This information enables quantifica-

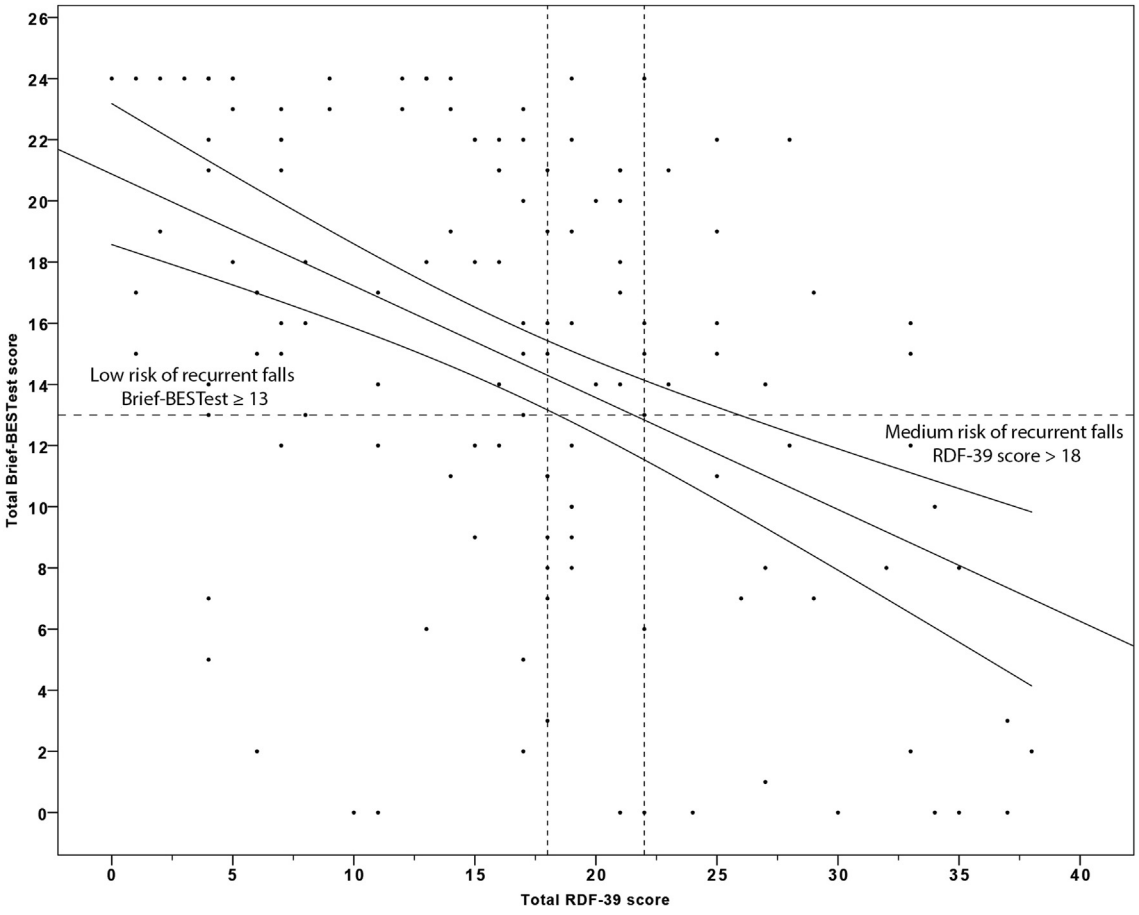

Fig. 1 – The correlation between balance, foot sensation and falls. ROC-analysis showed that a Brief-BESTest of 13 points was associated with a history of recurrent falls. A baseline RDF-39 score of 18 points was associated with future recurrent falls. The mean Brief-BESTest with 95% confidence intervals is displayed.

Table 2 – Brief-BESTest and several categories of incremental sensory loss (n = 134 subjects).

Total RDF-39 score*	Intact sensation (RDF-39: 0), n = 1	Loss of S2PD and/or M2PD (RDF-39: 1 ≤ 18), n = 80	Loss of vibration sense (RDF-39: 19 ≤ 22), n = 24	Loss of protective sensation (plantar) (RDF-39: 23 ≤ 29), n = 16	Aberrant Romberg test. Insensate to cold stimulus. Prior ulcer or amputation (RDF-39: 30 ≤ 39), n = 13	P-value
Median total Brief-BESTest score (IQR)	24 (0)	18 (10.5)	15.5 (10)	14 (11.25)	3 (11)	< 0.0005#
Median sub-scores (IQR)						
Section I: Biomechanical constraints	3 (0)	3 (1)	2 (2)	2 (3)	1 (2)	< 0.0005#
Section II: Stability limits	3 (0)	3 (1)	2 (1)	2.5 (1)	2 (2)	0.003#
Section III: Transitions-Anticipatory Postural adjustment						
- Left	3 (0)	2 (2)	1.5 (1)	1 (1.75)	0 (1)	< 0.0005#
- Right	3 (0)	2 (2)	1 (1)	1 (1.75)	0 (0)	< 0.0005#
Section IV: Reactive Postural Response						
- Left	3 (0)	3 (3)	2.5 (3)	2.5 (3)	0 (0.5)	0.075#
- Right	3 (0)	2 (3)	1 (3)	0.5 (3)	0 (0.5)	0.058#
Section V: Sensory orientation	3 (0)	3 (1)	1 (3)	1 (2.75)	0 (2)	0.001#
Section VI: Stability in gait	3 (0)	3 (0)	3 (0)	3 (0.75)	0 (3)	< 0.0005#
Total MNSI score (IQR)	3 (0)	2 (3)	3 (5)	5 (3.75)	8 (4)	< 0.0005#

A higher RDF-39 score indicates a higher degree of sensibility loss. A higher Brief-BESTest score indicates less balance impairment.
RDF-39, 39-item Rotterdam Diabetic Foot Study Test Battery.
* See *Supplementary Table A*; IQR, inter-quartile range.
# Kruskal-Wallis test; MNSI, Michigan Neuropathy Screening Instrument.

Table 3 – Univariate and multivariable linear regression analysis of balance status at second follow-up.

	Univariate model B (95% CI)	P-value	Multivariable model B (95% CI)	P-value
Male sex	1.002 (−1.594 to 3.598)	0.446		
Age (years)	−0.346 (−0.445 to −0.246)	<0.0005	−0.210 (−0.349 to −0.072)	0.003
Weight (kg)	−0.091 (−0.146 to −0.036)	0.001		
Height (cm)	0.075 (−0.045 to 0.195)	0.218	0.134 (0.018 to 0.250)	0.024
Duration of diabetes (years)	0.034 (−0.066 to 0.133)	0.503		
Diabetes type 2	−6.589 (−9.313 to −3.864)	<0.0005	−2.924 (−6.164 to 0.316)	0.076
Medical history				
- Hypertension	−4.804 (−7.260 to −2.348)	<0.0005		
- Myocardial infarction	−4.754 (−8.785 to −0.722)	0.021		
- Angina pectoris	−2.816 (−7.213 to 1.581)	0.207		
- CVA/TIA	−3.956 (−8.013 to 0.101)	0.056	−3.271 (−7.044 to 0.501)	0.088
- Cancer	−3.398 (−7.469 to 0.674)	0.101		
- COPD	−4.236 (−8.159 to −0.312)	0.035		
- Emphysema	−1.856 (−12.228 to 8.516)	0.724		
- Peripheral artery disease	−8.561 (−14.021 to −3.102)	0.002		
- Retinopathy	−1.429 (−5.112 to 2.255)	0.443		
Rotterdam Diabetic Foot Study Test Battery (score)				
- RDF-39	−0.366 (−0.487 to −0.244)	<0.0005	−0.307 (−0.462 to −0.152)	<0.0005

Dependent variable: Brief-BESTest total score (a higher score indicates less balance impairment); B, beta coefficient; CI, confidence interval; CVA, cerebrovascular accident; TIA, transient ischemic attack; COPD, chronic obstructive pulmonary disease; RDF-39, 39-item Rotterdam Diabetic Foot Study Test Battery.

Table 4 – Univariate and multivariable binary logistic regression analysis on risk of future falls at second follow-up.

	Univariate model OR (95% CI)	P-value	Multivariable model OR (95% CI)	P-value
Male sex	0.712 (0.364 to 1.379)	0.313	0.319 (0.126 to 0.811)	0.016
Age (years)	1.003 (0.975 to 1.031)	0.844	0.938 (0.899 to 0.979)	0.003
Weight (kg)	1.009	0.261		
Height (cm)	(0.994 to 1.024)	0.642		
	0.992 (0.961 to 1.025)			
Duration of diabetes (years)	0.996 (0.969 to 1.024)	0.783		
Diabetes type 2	2.413 (0.908 to 6.411)	0.077	3.157 (0.804 to 12.398)	0.100
Medical history				
- Hypertension	2.102 (1.009 to 4.379)	0.047		
- Myocardial infarction	2.857 (1.295 to 6.307)	0.009		
- Angina pectoris	2.221 (0.925 to 5.331)	0.074		
- CVA/TIA	0.452 (0.103 to 1.980)	0.292		
- Cancer	1.286 (0.499 to 3.312)	0.603		
- COPD	1.090 (0.357 to 3.332)	0.879		
- Peripheral artery disease	1.263 (0.349 to 4.570)	0.722		
- Retinopathy	1.061 (0.417 to 2.704)	0.901		
Rotterdam Diabetic Foot Study Test Battery (score)				
- RDF-39	1.080 (1.040 to 1.121)	<0.0005	1.124 (1.056 to 1.196)	<0.0005

Dependent variable: incidence of recurrent falls; OR, odds ratio; CI, confidence interval; CVA, cerebrovascular accident; TIA, transient ischemic attack; COPD, chronic obstructive pulmonary disease; RDF-39, 39-item Rotterdam Diabetic Foot Study Test Battery.

tion of the sensibility scores as it worsens over time [11,32,34]. Moreover, this study showed that at a cut-off of 18 points, patients become at increased risk for recurrent falls.

We used the Brief-BESTest to measure balance, of which reliability and its ability to discriminate between patients with and without a history of falls have been demonstrated [18,19]. Current study adds that the total Brief-BESTest score is also able to differentiate a history of recurrent fall status with favorable test characteristics when using a cut-off value of 13 points. Moreover, we found that the Brief-BESTest score is predominantly influenced by pedal sensation.

Neuropathy has long been considered the most dominant predictor of falls in diabetes, because diminishing somatosensory function of the lower extremity reduces the ability to detect changes in balance and make the necessary adjustments to avoid falls [35]. Yet, the basis of propriocep-

tion is related to cutaneous afferents, rather than joint afferents. Therefore, we restricted our attention in this study to cutaneous sensation [36]. Previous studies reported the influence of retinopathy and cataracts on contrast sensitivity and its contribution to balance impairments, which is important especially in low light conditions (e.g. bathroom visits at night) [37,38]. Only three out of 11 studies from the literature found visual impairment a statistically significant factor of the occurrence of falls (ORs ranging 1.6–2.0). We found that retinopathy was not significantly associated with the Brief-BESTest score or with falls. This suggests that it is not retinopathy alone and decreased foot sensation, rather than ocular changes, that is more likely to be responsible for balance impairment and associated with falls. Previous research has shown that vestibular dysfunction is 2.6 times more likely to be related to falls in the previous year [39]. However, the influence of diabetes on the quality and availability of vestibular information to the vestibulo-spinal tract to relay motor commands has not been examined in our study and may be accounted for in future studies [2,40].

In our study, the estimated incidence of falls was 2.3 per 100 person-years, which is less than other reports (125 per 100 person-years). This is mainly due to the unselected population of patients included in the RDF-study (both neuropathic and non-neuropathic subjects), compared to a study of patients with prior foot ulcers only (indicative of end-stage sensory loss) [22]. Our study also showed that falls lead to considerable burden for society. Falls account for approximately 10% of emergency department visits among elderly persons, with a strong age gradient. One in ten falls results in serious injury, such as fractures and brain or head injuries [30,41]. In the Dutch healthcare setting, average costs per fall were estimated to be € 9370 (2009 price level), which increased with being female, a higher age and comorbidity [41]. A US study found average costs per fall of US$ 9463 (2015 price level) [42]. In our study, we found lower costs, most likely related to the less serious or non-fatal injuries observed, differences in healthcare systems and the overall higher costs of healthcare in the United States. Moreover, we only included in-hospital costs, while out-of-hospital care (e.g. nursing homes) are known to account for considerable additional costs of approximately one-third of total costs [41].

Strengths of our study are the relatively large sample size, the prospective study design in an unselected group of patients with diabetes with substantial follow-up and the appreciation of pedal sensation as a new and valid measure of neuropathy instead of the conventional assessment of symptoms of neuropathy [15]. Several caveats relating to our study are important to highlight. Firstly, results of retrospective assessment of patients' fall status annually may have been sensitive to recall bias with a reported specificity of 91–95% and sensitivity of 80–89% when recalling falls in the previous year [43]. Secondly, selection bias may have played a role since 120 patients dropped-out from study start (n = 416) and 134 patients measured with the Brief-BESTest. However, the impact of selection bias appears limited. Selection bias due to mortality is likely to be absent as patients who died during follow-up had a slightly higher RDF-39 score at baseline, but this effect is explained by the correlation of a higher age and RDF-39 score. Withdrawals (n = 32) and patients lost-to-follow-up (n = 66) did not significantly differ with patients available for follow-up regarding age and duration of diabetes. Overall, sample size was sufficient to answer our hypothesis without the risk of under power with estimations unlikely to change with higher patient numbers tested. Thirdly, prognostic characteristics of RDF-39 and Brief-BESTest could not be compared head-to-head because the latter was not measured at study entry. Yet, the observed association between pedal sensory loss and balance deserves further investigation.

In summary, assessment of patient's sensory loss using the total RDF-39 score may help clinicians to better stratify patients at risk for balance impairment and falls. Patients already become at risk when having lost two-point discrimination. This information is important regarding patient information and may be used in recommendations on specific intervention strategies to prevent falls. One such intervention is decompressing lower extremity peripheral nerves in selected patients, which has been shown to restore sensation and improves balance [44,45]. We conclude that patients with loss of vibration sense should be subjected to a multifactorial falls risk assessment for prevention that includes gait and balance testing. The model suggests that patients can be categorized in medium and high-risk categories, which might be helpful in tailored preventive interventions.

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.

Author contributions

W.D.R., E.B., S.v.N. researched data, wrote the manuscript. M. C.C., J.v.N. and J.H.C. contributed to 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.

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Declaration of Competing Interest

No potential conflicts of interest relevant to this article were reported.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.107930.

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