Contents available at ScienceDirect

Diabetes Research and Clinical Practice

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

Standard complication screening information can be used for risk assessment for first time foot ulcer among patients with type 1 and type 2 diabetes

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ARTICLE INFO

Article history:
Received 14 November 2018
Received in revised form
21 March 2019
Accepted 12 April 2019
Available online 18 April 2019

Keywords:
Type 1 Diabetes
Type 2 Diabetes
Complications
Foot ulcers
Diabetic foot ulcers

ABSTRACT

Aim: Diabetic foot ulcer (DFU) is a major complication of both Type 1 Diabetes (T1D) and Type 2 Diabetes (T2D); however research into risk factors for DFU does not separate between these two types. The purpose of the present investigation was to identify risk factors for development of first time DFU (FTDFU) over a period of 15 years in patients with T1D and T2D separately.

Methods: This retrospective cohort study included 25,220 feet from 5588 patients with T1D and 7113 patients with T2D treated in the period 2001–2015. Data on baseline characteristics and comorbidities were collected from electronic patient records. Influences of various risk factors for the development of FTDFU were assessed by hazard ratios (HR) from Cox proportional hazard regression models on time from enrolment to FTDFU diagnosis or end-of-follow-up.

Results: In T1D independent risk factors were male sex, age >60 years, high HbA1c, long diabetes duration, history of cardiovascular disease, macro-albuminuria, decreased visual acuity, advanced diabetic retinopathy, decreased/absent vibration sense, presence of patient reported symptoms of neuropathy, and absence of foot pulses. In T2D the independent risk factors were the same except age >60 years, a history of cardiovascular disease, and long diabetes duration.

Conclusions: This study documents that much of the standard clinical information obtained as part of the routine follow-up are also independent risk factors for development of FTDFU. This may be used to create a basis for in which patient and when prevention should be started.

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https://doi.org/10.1016/j.diabres.2019.04.021
0168-8227/

1. Background

Diabetic foot ulcer (DFU) is a serious complication and a large burden for health care systems [1]. It has been estimated that 25% of all patients with diabetes develop DFU during their lifetime and DFUs precede 80% of all lower leg amputations in patients with diabetes [2]. Foot ulcers occur predominantly in feet with polyneuropathy and in approximately 50% peripheral vascular disease (PAD) is present [3]. This combination often complicated by infection, results in poor outcome including recurrent ulceration, amputation and increased mortality [4,5]. Therefore, risk factors for DFU should be identified and linked to increased adoption of prevention strategies of proven effectiveness [6]. There is a comprehensive body of studies into risk factors for DFU. A systematic review of 71 studies examined more than a hundred potential risk factors from the patient's history, symptoms and signs and from diagnostic tests [7] and a meta-analysis of 16 cohorts with data from more than 16,000 people with diabetes [8] have recently been published. Essentially, the primary risk factors for DFU were peripheral neuropathy, PAD and foot deformity. Additionally, previous or present ulceration and amputation were important risk factors for recurrent ulceration. A simplified prognostic model of only three risk factors has been developed: a history of foot ulceration, an inability to feel a 10 g monofilament and at least one absent foot pulse [8].

However, only few studies focused on risk factors for first time DFU (FTDFU). Furthermore, the majority of patients studied suffered from type 2 diabetes (T2D), and when type 1 diabetes (T1D) patients were included, the impact of the risk factors was assumed the same for the two types. The review [7] concluded that further studies on large numbers of patients are required.

We have previously examined a large cohort of people with T1D and T2D followed in a hospital specialized in diabetes mellitus observed over the period 2001–2014, and have reported decreasing incidence of DFU [9], increased healing [10] and a major decrease of leg amputations [11]. The aim of the present investigation was to examine to which extent results of standard clinical information available and obtained as part of the routine follow-up and treatment in relation to both T1D and T2D such as age, BMI, albuminuria, retinopathy and neuropathy are independent risk factors for FTDFU in the same cohort, but now observed over the period 2001–2015, and separately for patients with T1D and T2D.

2. Research design and methods

Data for the analyses in the present paper were compiled from the patient records of an outpatient clinic in the greater Copenhagen area specialized in people with diabetes. This clinic serves as an integrated part of the public health care system in the Copenhagen region of Denmark. In Denmark all patients with T1D are cared for in hospital outpatient clinics. Most of the T2D patients, i.e. 80–90% are cared for by their GP. This group of patients typically does not have diabetes complications, and if they have, the medical treatment is uncomplicated. If the GPs find it difficult to reach the therapeutic goals, they can refer the patient to the hospital outpatient clinics. Here the treatment is optimized typically over a period of 6–9 months after which the patients are referred back to their GPs again. In the period 2001–2015 typically 300–500 of this type of patients were referred on a yearly basis. Finally, T2D patients with more advanced micro- or macrovascular complications are to a wide extent cared for permanently in hospital outpatient clinics; this group of patients is called a tertiary referral population.

In the study clinic an electronic patient record system was introduced in the beginning of 2001, the present study is based on information extracted from this system. This means that part of the patients had been attending the center before 2001; this applies to approximately 40% of the T1D patients and 10–15% of the T2D patients. However, the majority of the patients included in the study where referred to the center after 2001. Patients with T1D and complicated T2D were typically followed in the center until they died, but some have moved geographically and hence stopped the control in the center. Finally, the patients referred for optimization of T2D treatment have typically only been followed for less than 1 year.

As part of routine care in the clinic a yearly foot examination is performed by a diabetologist or a diabetes nurse. Patients without a history of DFU were classified as at high risk of developing DFU, and therefore referred to a multidisciplinary foot service, if they had at least one of the following criteria:

- Symptoms or signs of peripheral neuropathy,
- lacking foot pulsations in minimum one foot,
- Presence of any deformities of the feet including the nails and skin,
- Poor physical health,
- Poor vision,
- Nephropathy,
- Peripheral oedema.

All patients were informed and urged to contact the multidisciplinary immediately if they developed an ulcer.

Extensive information on all these foot service contacts, and any other contacts with the clinic, including patient characteristics, diagnoses, visits, measurements, complications and medication, has been recorded in an electronic patient record system since 2001.

The present study is based on information from electronic patient records of 5588 T1D and 7113 T2D patients treated in the clinic in the period 2001–2015. We extracted the data from the records from the first year of treatment; for patients already in treatment in 2001 we extracted the data from the records from 2001. Amputated feet and feet with a prior or present DFU diagnosis were excluded from the study. We obtained data on sex, age, body mass index (BMI), type of diabetes, duration of diabetes, smoking, cardiovascular disease (CVD), glycated hemoglobin (HbA1c), visual acuity, results of a retinal examination, urinary albumin excretion and information on insulin treatment (only for patients with T2D). Furthermore, for each foot, data was obtained on presence of

Table 1 – Background characteristics of individual feet with diabetes with and without foot ulcer.

	Feet with type I diabetes (N = 11108)			Feet with type II diabetes (N = 14112)		
	No foot ulcer (n = 10416) n (%)	Foot ulcer (n = 692) n (%)	Sign.	No foot ulcer (n = 13164) n (%)	Foot ulcer (n = 948) n (%)	Sign.
Gender (females)	4802 (46.1)	255 (36.9)	***	5531 (42.0)	254 (26.8)	***
Age			***			***
<40 years	5069 (48.7)	110 (15.9)		994 (7.6)	31 (3.3)	
40–59 years	3849 (37.0)	342 (49.4)		5419 (41.2)	370 (39.0)	
60–79 years	1369 (13.1)	222 (32.1)		6109 (46.4)	500 (52.7)	
80+ years	129 (1.2)	18 (2.6)		642 (4.9)	47 (5.0)	
BMI			n.s.			***
Missing	211 (2.0)	7 (1.0)		350 (2.7)	18 (1.9)	
<18	219 (2.1)	13 (1.9)		41 (0.3)	4 (0.4)	
18–25	6408 (61.5)	430 (62.1)		2442 (18.6)	133 (14.0)	
25–30	2892 (27.8)	185 (26.7)		4633 (35.2)	381 (40.2)	
30–35	581 (5.6)	50 (7.2)		3319 (25.2)	256 (27.0)	
>35	105 (1.0)	7 (1.0)		2379 (18.1)	156 (16.5)	
Smoking			***			***
Missing	322 (3.1)	22 (3.2)		645 (4.9)	21 (2.2)	
No	3718 (35.7)	134 (19.4)		6346 (48.2)	285 (30.1)	
Yes	6376 (61.2)	536 (77.5)		6173 (46.9)	642 (67.7)	
Insulin			N/A			***
No	–	–		6782 (51.5)	279 (29.4)	
Yes	–	–		6382 (48.5)	669 (70.6)	
CVD						
Missing			***	2 (0.0)		***
No	9661 (92.7)	557 (80.5)		10,472 (79.6)	652 (68.8)	
Yes	755 (7.3)	135 (19.5)		2690 (20.4)	296 (31.2)	
HbA1C			***			***
Missing	92 (0.9)	12 (1.7)		227 (1.7)	9 (1.0)	
Well regulated (<58 mmol/mol)	2178 (20.9)	58 (8.4)		4650 (35.3)	219 (23.1)	
Medium regulated (58–69 mmol/mol)	3181 (30.5)	156 (22.5)		3170 (24.1)	200 (21.1)	
Poorly regulated (>69 mmol/mol)	4965 (47.7)	466 (67.3)		5117 (38.9)	520 (54.9)	
Treatment start			***			***
Before 1995	4379 (42.0)	522 (75.4)		1001 (7.6)	216 (22.8)	
1995–2000	1415 (13.6)	74 (10.7)		2094 (15.9)	323 (34.1)	
2001–2005	1160 (11.1)	41 (5.9)		4075 (31.0)	223 (23.5)	
2006–2100	1685 (16.2)	32 (4.6)		3165 (24.0)	118 (12.5)	
After 2010	1777 (17.1)	23 (3.3)		2829 (21.5)	68 (7.2)	
Diabetes duration			***			***
Missing	102 (1.0)			257 (2.0)	5 (0.5)	
<5 years	2211 (21.2)	27 (3.9)		5247 (39.9)	151 (15.9)	
5–20 years	4268 (41.0)	148 (21.4)		6848 (52.0)	669 (70.6)	
>20 years	3835 (36.8)	517 (74.7)		812 (6.2)	123 (13.0)	
Albuminuria			***			***
Missing	551 (5.3)	28 (4.1)		749 (5.7)	33 (3.5)	
Normal	8317 (79.9)	388 (56.1)		8918 (67.8)	451 (47.6)	
Microalbuminuria	1031 (9.9)	183 (26.5)		2615 (19.9)	319 (33.7)	
Macroalbuminuria	517 (5.0)	93 (13.4)		882 (6.7)	145 (15.3)	
Visual acuity			***			***
Missing	1180 (11.3)	54 (7.8)		1278 (9.7)	33 (3.5)	
>0.8	8635 (82.9)	480 (69.4)		10,560 (80.2)	728 (76.8)	
0.3–0.8	470 (4.5)	120 (17.3)		1134 (8.6)	141 (14.9)	
0.1–0.3	107 (1.0)	22 (3.2)		148 (1.1)	36 (3.8)	
Blind (<0.1)	24 (0.2)	16 (2.3)		44 (0.3)	10 (1.1)	

(*continued on next page*)

Table 1 – (*continued*)

	Feet with type I diabetes (N = 11108)			Feet with type II diabetes (N = 14112)		
	No foot ulcer (n = 10416) n (%)	Foot ulcer (n = 692) n (%)	Sign.	No foot ulcer (n = 13164) n (%)	Foot ulcer (n = 948) n (%)	Sign.
Vibration			***			***
Missing	910 (8.7)	14 (2.0)		1580 (12.0)	16 (1.7)	
<30	5700 (54.7)	192 (27.8)		6362 (48.3)	171 (18.4)	
30–50	1598 (15.3)	192 (27.8)		2937 (22.3)	287 (30.3)	
>50	2208 (21.2)	294 (42.5)		2285 (17.4)	474 (50.0)	
Pulse			***			***
Missing	611 (5.9)	10 (1.5)		1216 (9.2)	13 (1.4)	
Yes	9440 (90.6)	545 (78.8)		10,921 (83.0)	749 (79.0)	
No	635 (3.5)	137 (19.8)		1027 (7.8)	186 (19.6)	
Neuropathy			***	1773 (13.5)	56 (5.9)	***
Missing	1101 (10.6)	33 (4.8)		8070 (61.3)	331 (34.9)	
No	8049 (77.3)	365 (52.8)		3321 (25.2)	561 (59.2)	
Yes	1266 (12.1)	294 (42.5)				
Retinopathy			***			***
Missing	1020 (9.8)	57 (8.2)		772 (5.9)	26 (2.7)	
No diabetic neuropathy	4306 (41.3)	93 (13.4)		7637 (58.0)	222 (23.4)	
Non-proliferative background retinopathy	1186 (11.4)	38 (5.5)		1120 (8.5)	53 (5.6)	
Advanced non-proliferative retinopathy	2715 (26.1)	218 (31.5)		3213 (24.4)	514 (54.2)	
Proliferative retinopathy	735 (7.1)	150 (21.7)		346 (2.6)	108 (11.4)	
Previous laser treatment	454 (4.4)	136 (19.7)		76 (0.6)	25 (2.6)	

*Significant at 5% level based on χ^2-test
**significant at 1% level based on χ^2-test
***significant at 0.1% level based on χ^2-test.

symptoms of neuropathy as reported by the patients, foot vibration sense (measured by biothesiometry) and presence of foot pulse.

Patients were classified as having CVD if they had been hospitalized for cardiovascular complications before or in the initial year of their follow-up. HbA1c was measured in mmol/mol according to IFCC standard. Visual acuity was based on the patient's best seeing eye and divided into four stages ranging from normal (>0.8) to blind (<0.1). The extent of diabetic retinopathy was determined by the retinal examination result for the poorest eye and classified according to a modification of the EURODIAB grading scale into four levels of retinopathy [12]. Urine albumin excretion was based on the results of three consecutive urine collections and classified into: <30 mg/24 h (no albuminuria), 30–300 mg/24 h (microalbuminuria) and >300 mg/24 h (macroalbuminuria), if at least two were within one of the respective ranges. Results of the biothesiometry were divided into three groups: <30 mV (normal), 30–50 mV (abnormal) and >50 mV (absent).

DFU diagnoses were also obtained from the electronic patient record system and for each foot the time for registration of start to FTDFU was recorded for the analyses.

2.1. *Statistical analysis*

Differences in patient- and foot characteristics between feet of patients with or without development of FTDFU within the study period were analyzed with chi-squared tests for patients with T1D and T2D separately. The influences of the various risk factors for FTDFU development were assessed by hazard ratios (HR) from Cox proportional hazard regression models on time from treatment- or registration start to FTDFU diagnosis; the risk time for each foot was censored at end-of-study. Effects of the potential risk factors were assessed individually in univariable regression models, and with three degrees of adjustment for confounding in multivariable regression models: Model I adjusts for sex, age, year of treatment start at the clinic, and diabetes duration, Model II adjusts additionally for BMI, smoking, CVD and insulin treatment (for T2D only), Model III includes all potential risk factors. In additional analyses interactions between sex and age, and each of the other risk factors in the full multivariable regression model one at a time to investigate whether a risk factor's influence differed relative to the patient's sex and age.

In all models, the inherent correlation between the two feet of the same person was adjusted for by using a robust sandwich estimator of the variance.

The proportional hazard assumption was tested in the full multivariable model by adding the interactions between each risk factor and the logarithm of time until first DFU to the model; a joint test of these interactions tests the assumption. If the proportional-hazard assumption was violated, i.e. one or more of the interactions was significant; the hazard function was estimated, in all the models, separately within the strata of the corresponding covariates as to be able to assume proportional hazards for the remaining variables in the model. The stratified estimation of the hazard function was constructed sequentially, adding to the stratification the

Table 2 – Comparative incidence rates of diabetic foot ulcer according to various risk factor categories among type I diabetes patients.

	Univariable regression (all variables included one at a time)				Multivariable regression I (variables in grey included one at a time), n = 9679				Multivariable regression II (variables in grey included one at a time), n = 9467				Multivariable regression III, n = 8482			
Variable	HR	95% CI	p-value	n	HR	95% CI	p-value	n	HR	95% CI	p-value	n	HR	95% CI	p-value	n
Sex				9752												
Male	1			0.0000	1			0.0000	1			0.0000	1			0.0000
Female	0.66	[0.54–0.81]	0.0000		0.65	[0.53–0.80]	0.0000		0.62	[0.50–0.76]	0.0000		0.60	[0.48–0.75]	0.0000	
Age				9752												
<40 years	0.31	[0.23–0.43]	0.0000	0.0000	0.38	[0.27–0.53]	0.0000	0.0000	0.41	[0.29–0.57]	0.0000	0.0000	0.50	[0.35–0.70]	0.0000	0.0000
40–59 years	1				1				1				1			
60–79 years	1.66	[1.31–2.10]	0.0000		1.60	[1.27–2.03]	0.0000		1.60	[1.25–2.03]	0.0001		1.58	[1.19–2.09]	0.0016	
80+ years	1.88	[0.97–3.65]	0.0633		2.09	[1.06–4.11]	0.0339		1.73	[0.83–3.61]	0.1466		2.15	[0.99–4.67]	0.0545	
BMI				9665				9592								
<18	1.01	[0.41–2.50]	0.9756	0.5179	0.95	[0.38–2.37]	0.9044		1.00	[0.40–2.48]	0.9980	0.0859	0.74	[0.25–2.21]	0.5863	0.0070
18–25	1				1			0.1318	1				1			
25–30	0.86	[0.69–1.08]	0.1982		0.76	[0.61–0.96]	0.0202		0.74	[0.59–0.93]	0.0103		0.60	[0.46–0.79]	0.0002	
30–35	1.12	[0.77–1.63]	0.5665		1.11	[0.75–1.63]	0.6165		1.07	[0.72–1.59]	0.7432		0.90	[0.58–1.39]	0.6273	
>35	1.58	[0.57–4.36]	0.3808		1.52	[0.54–4.29]	0.4323		1.53	[0.55–4.25]	0.4180		0.91	[0.39–2.11]	0.8279	
Smoking				9619				9550								
No	1			0.0220	1			0.0737	1			0.1061	1			0.2286
Yes	1.37	[1.05–1.78]	0.0220		1.31	[0.97–1.76]	0.0737		1.27	[0.95–1.70]	0.1061		1.21	[0.89–1.65]	0.2286	
CVD				9752				9679								
No	1			0.0000	1			0.0007	1			0.0026	1			0.3554
Yes	2.18	[1.68–2.85]	0.0000		1.56	[1.21–2.01]	0.0007		1.50	[1.15–1.96]	0.0026		1.16	[0.85–1.58]	0.8489	
Insulin				–				–								
No	1				1				1				1			
Yes	–	[–]	–		–	[–]	–		–	[–]	–		–	[–]	–	
Treatment start				9752												
Before 1995	1.65	[1.09–2.52]	0.0191	0.0018	0.75	[0.48–1.17]	0.1997	0.0495	0.68	[0.43–1.07]	0.0950	0.0089	0.70	[0.43–1.15]	0.1615	0.0025
1995–2000	1.03	[0.63–1.71]	0.8952		0.86	[0.51–1.46]	0.5850		0.80	[0.47–1.37]	0.4118		0.82	[0.45–1.47]	0.5009	
2001–2005	1				1				1				1			
2006–2010	0.83	[0.45–1.53]	0.5402		1.02	[0.55–1.91]	0.9430		1.09	[0.57–2.06]	0.8003		1.22	[0.60–2.46]	0.5859	
After 2010	1.62	[0.82–3.22]	0.1682		1.74	[0.89–3.40]	0.1071		1.97	[1.00–3.89]	0.0503		2.47	[1.18–5.17]	0.0161	
Diabetes duration (years)				9679												
<5 years	1				1			0.0000	1			0.0000	1			0.0073
5–20 years	2.22	[1.32–3.74]	0.0027	0.0000	2.47	[1.42–4.29]	0.0014		2.47	[1.41–4.33]	0.0016		2.06	[1.11–3.85]	0.0230	
>20 years	5.16	[3.09–8.60]	0.0000		4.54	[2.60–7.92]	0.0000		4.63	[2.64–8.12]	0.0000		2.77	[1.43–5.37]	0.0026	
Urinary Albumin Excretion				9752				9679				9467				
Normal	1			0.0000	1				1				1			
Microalbuminuria	3.06	[2.42–3.86]	0.0000		–	[–]	–		–	[–]	–		–	[–]	–	
Macroalbuminuria	3.18	[2.34–4.31]	0.0000		–	[–]	–		–	[–]	–		–	[–]	–	
Visual acuity				9133				9087				8949				
>0.8	1			0.0000	1			0.0000	1			0.0000	1			0.0325
0.3–0.8	2.95	[2.17–4.00]	0.0000		1.94	[1.41–2.68]	0.0000		1.97	[1.43–2.71]	0.0000		1.55	[1.09–2.20]	0.0154	
0.1–0.3	1.67	[0.87–3.22]	0.1254		1.00	[0.49–2.01]	0.9935		1.03	[0.52–2.08]	0.9251		0.95	[0.47–1.90]	0.8842	
Blind (<0.1)	5.01	[2.66–9.43]	0.0000		3.16	[1.62–6.18]	0.0008		3.02	[1.49–6.15]	0.0022		1.93	[0.95–3.92]	0.0678	
Vibration				9752				9679				9467				
<30	1			0.0000	1				1				1			
30–50	3.25	[2.56–4.13]	0.0000		–	[–]	–		–	[–]	–		–	[–]	–	
>50	4.80	[3.84–5.99]	0.0000		–	[–]	–		–	[–]	–		–	[–]	–	
Retinopathy				9061				9019				8883				
No diabetic neuropathy	1			0.0000	1			0.0000	1			0.0000	1			0.0000
Non-proliferative background retinopathy	1.23	[0.76–1.99]	0.3976		1.00	[0.62–1.63]	0.9983		1.07	[0.65–1.75]	0.7862		1.14	[0.69–1.87]	0.6077	

Table 2 – (continued)

Variable	Univariable regression (all variables included one at a time)				Multivariable regression I (variables in grey included one at a time), n = 9679				Multivariable regression II (variables in grey included one at a time), n = 9467				Multivariable regression III, n = 8482			
	HR	95% CI	p-value	n	HR	95% CI	p-value	n	HR	95% CI	p-value	n	HR	95% CI	p-value	n
Advanced non-proliferative retinopathy	2.53	[1.84–3.48]	0.0000		1.68	[1.18–2.39]	0.0039		1.81	[1.26–2.60]	0.0012		1.45	[1.00–2.12]	0.0509	
Proliferative retinopathy	4.71	[3.26–6.80]	0.0000		2.92	[1.93–4.42]	0.0000		3.20	[2.10–4.89]	0.0000		2.83	[1.51–3.75]	0.0002	
Previous laser treatment	5.95	[4.07–8.68]	0.0000		3.99	[2.58–6.17]	0.0000		4.02	[2.56–6.32]	0.0000		3.00	[1.86–4.84]	0.0000	
Pulse				9654				9583				9388				0.0000
Yes	1			0.0000	1			0.0000	1			0.0000	1			
No	4.04	[3.11–5.24]	0.0000		2.63	[2.01–3.43]	0.0000		2.42	[1.81–3.22]	0.0000		1.88	[1.37–2.58]	0.0000	
HbA1C				9690				9617				9409				0.0000
Well regulated (<58 mmol/mol)	0.69	[0.47–1.01]	0.0588	0.0000	0.88	[0.59–1.30]	0.5098	0.0000	0.88	[0.59–1.31]	0.5359		1.00	[0.65–1.53]	0.9877	
Moderately regulated (58–69 mmol/mol)	1				1				1			0.0000	1			
Poorly regulated (>69 mmol/mol)	1.82	[1.44–2.30]	0.0000		2.13	[1.68–2.70]	0.0000		2.20	[1.73–2.80]	0.0000		2.01	[1.56–2.59]	0.0000	
Symptoms of neuropathy				9465				9392				9199				
No	1			0.0000	1			0.0000	1			0.0000	1			0.0000
Yes	2.87	[2.29–3.60]	0.0000		2.21	[1.75–2.78]	0.0000		2.20	[1.73–2.78]	0.0000		1.93	[1.50–2.49]	0.0000	

covariate with the lowest P value for the interaction until the joint test of all remaining interactions was insignificant.

Since the influences of the stratification variables could not be evaluated, the stratification for the corresponding risk factor was not performed for the univariable assessment of these risk factors to anyway give an influence assessment; one in which the proportional hazard function is violated.

All analyses were performed with SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). A p-value of 1% is considered significant.

3. Results

In the 15-year study period 11,108 feet of 5588 persons with T1D were at risk of developing a FTDFU, which occurred in 692 (6.23%) feet. and 14,112 feet of 7113 persons with T2D were at risk of developing a FTDFU which occurred in 948 (6.72%) feet. Both people with T1D and T2D in whom FTDFU developed were more likely to older, male patients, smokers and suffering from CVD. They were less well controlled as documented by a higher HbA1c, had longer diabetes duration and a longer treatment history and were suffering from more advanced microvascular complications as evidenced from higher rates of micro- and macro albuminuria, poor visual acuity, advanced retinopathy and poor vibration sense (Table 1).

T1D: Table 2 shows the differences in incidence rate of DFU, expressed as HR, for the investigated risk factors for patients with T1D. Unadjusted analyses show, similarly to the crude comparison in Table 1, that all risk factors except BMI are associated with DFU incidence. Violations of the proportional hazard assumption are found for vibration sense and urine albumin excretion; the multivariable analyses are therefore stratified for these two variables. The unadjusted association with smoking is seen gradually explained from Model I through III by the combined risk factors. The (unadjusted) associations with CVD and visual acuity disappear when all the clinical information, also results of complications screening, are included in Model III. An adjusted association with BMI appears gradually from Model I through III which indicates that this association was hidden by confounding with the other risk factors. However, gradually adjusting the analyses for larger subsets of the risk factors shows that most risk factors remain significantly associated to DFU incidence. This indicates that for patients with T1D most of the selected risk factors are independent predictors for DFU. Additional analyses for interactions of the risk factors with age and sex do not show significant age or sex differences in the association of these risk factors with DFU incidence.

T2D: Table 3 shows the differences in incidence rate of DFU, expressed as HR for the investigated risk factors for patients with T2D. The adjusted analyses show that (Table 3), contrary to the crude comparison in Table 1, many risk factors are not seen associated with DFU incidence; Violations of the proportional hazard assumption are found for vibration sense and HbA1c; the multivariable analyses are therefore stratified for these two variables. Risk factors that are not associated with DFU incidence in unadjusted analysis, generally do not appear associated with increasing adjustment for the other risk factors. Only the year of treatment start gradually

Table 3 – Comparative incidence rates of diabetic foot ulcer according to various risk factor categories among type 2 diabetes patients.

	Univariable regression (all variables included one at a time)				Multivariable regression I (variables in grey included one at a time), n = 12230				Multivariable regression II (variables in grey included one at a time), n = 11756				Multivariable regression III, n = 10436			
Variable	HR	95% CI	p-value	n	HR	95% CI	p-value	n	HR	95% CI	p-value	n	HR	95% CI	p-value	n
Gender				12,397												
Male	1			0.0000	1			0.0000	1			0.0000	1			0.0000
Female	0.51	[0.43–0.62]	0.0000		0.51	[0.42–0.61]	0.0000		0.48	[0.40–0.59]	0.0000		0.47	[0.38–0.58]	0.0000	
Age				12,397												
<40 years	0.62	[0.39–1.00]	0.0483	0.2546	0.79	[0.49–1.27]	0.3255	0.6930	0.78	[0.48–1.27]	0.3137	0.5391	1.10	[0.66–1.83]	0.7241	0.7548
40–59 years	1				1				1				1			
60–79 years	0.93	[0.78–1.11]	0.4199		0.93	[0.77–1.11]	0.4068		0.96	[0.79–1.15]	0.6463		0.94	[0.77–1.15]	0.5468	
80+ years	0.92	[0.63–1.35]	0.6763		0.98	[0.66–1.46]	0.9263		1.18	[0.78–1.79]	0.4298		1.15	[0.71–1.86]	0.5804	
BMI				12,243				12,085								
<18	1.79	[0.37–8.81]	0.4718	0.1112	1.23	[0.16–9.56]	0.8455	0.0528	1.25	[0.16–9.80]	0.8327	0.0460	1.67	[0.20–13.82]	0.6361	0.0638
18–25	1				1				1				1			
25–30	1.32	[1.04–1.69]	0.0235		1.24	[0.97–1.59]	0.0852		1.24	[0.96–1.59]	0.0969		1.18	[0.90–1.55]	0.2405	
30–35	1.39	[1.08–1.80]	0.0114		1.42	[1.09–1.85]	0.0092		1.43	[1.10–1.86]	0.0085		1.41	[1.05–1.88]	0.0210	
>35	1.37	[1.03–1.83]	0.0307		1.51	[1.13–2.04]	0.0062		1.53	[1.13–2.07]	0.0057		1.53	[1.11–2.13]	0.0102	
Smoking				12,050				11,886								
No	1			0.6552	1			0.6061	1			0.5286	1			0.2208
Yes	0.96	[0.80–1.15]	0.6552		1.06	[0.86–1.29]	0.6061		1.07	[0.87–1.31]	0.5286		1.15	[0.92–1.43]	0.2208	
CVD				12,395				12,228								
No	1			0.3592	1			0.5993	1			0.9983	1			0.7531
Yes	1.09	[0.91–1.30]	0.3592		1.05	[0.87–1.26]	0.5993		1.00	[0.83–1.21]	0.9983		1.04	[0.84–1.27]	0.7531	
Insulin				12,397				12,230								
No	1			0.4013	1			0.3087	1			0.4358	1			0.0423
Yes	0.92	[0.77–1.11]	0.4013		0.90	[0.75–1.10]	0.3087		0.93	[1.62–1.13]	0.4358		0.80	[0.64–0.99]	0.0423	
Treatment start				12,397												
Before 1995	1.04	[0.82–1.31]	0.7610	0.0731	0.87	[0.67–1.12]	0.2672	0.0200	0.86	[0.66–1.14]	0.2941	0.0347	0.64	[0.47–0.88]	0.0054	0.0000
1995–2000	0.96	[0.77–1.20]	0.7072		0.88	[0.70–1.11]	0.2802		0.88	[0.68–1.12]	0.2930		0.72	[0.55–0.94]	0.0157	
2001–2005	1				1				1				1			
2006–2010	1.05	[0.79–1.40]	0.7259		1.02	[0.76–1.35]	0.9191		1.04	[0.78–1.39]	0.7965		1.07	[0.78–1.46]	0.6941	
After 2010	1.61	[1.13–2.29]	0.0084		1.58	[1.11–2.26]	0.0117		1.62	[1.12–2.35]	0.0101		1.95	[1.32–2.89]	0.0009	
Diabetes duration (years)				12,230												
<5 years	1			0.0000	1			0.0000	1			0.0000	1			0.0305
5–20 years	1.66	[1.32–2.09]	0.0000		1.79	[1.40–2.30]	0.0000		1.78	[1.78–2.30]	0.0000		1.43	[1.08–1.88]	0.0116	
>20 years	1.70	[1.23–2.34]	0.0012		2.06	[1.44–2.94]	0.0000		2.11	[1.46–3.05]	0.0000		1.24	[0.83–1.86]	0.2957	
Urinary Albumin Excretion				11,890				11,733				11,330				
Normal	1			0.0000	1			0.0022	1			0.0042	1			0.2563
Microalbuminuria	1.38	[1.15–1.66]	0.0007		1.23	[1.02–1.49]	0.0324		1.24	[1.02–1.50]	0.0342		1.08	[0.88–1.33]	0.4678	
Macroalbuminuria	1.68	[1.32–2.13]	0.0000		1.53	[1.19–1.96]	0.0008		1.51	[1.17–1.95]	0.0016		1.25	[0.96–1.63]	0.1001	
Visual acuity				11,830				11,720				11,326				
>0.8	1			0.0150	1			0.0005	1			0.0003	1			0.0444
0.3–0.8	1.23	[0.97–1.55]	0.0895		1.45	[1.14–2.19]	0.0030		1.45	[1.13–1.86]	0.0037		1.32	[1.01–1.72]	0.0426	
0.1–0.3	1.89	[1.14–3.13]	0.0137		2.28	[1.29–4.00]	0.0043		2.41	[1.35–4.31]	0.0031		1.91	[1.02–3.58]	0.0432	
Blind (<0.1)	1.88	[0.88–4.04]	0.1073		2.13	[0.99–4.55]	0.0525		2.37	[1.06–5.31]	0.0367		1.89	[0.78–4.59]	0.1602	
Vibration				12,397				12,230				11,756				
<30	1			0.0000	1				1				1			
30–50	3.00	[2.42–3.71]	0.0000		–	[–]	–		–	[–]	–		–	[–]	–	
>50	6.32	[5.13–7.79]	0.0000		–	[–]	–		–	[–]	–		–	[–]	–	
Retinopathy				11,900				11,786				11,389				
No diabetic neuropathy	1			0.0000	1			0.0000	1			0.0000	1			0.0000

(continued on next page)

Table 3 – (continued)

Variable	Univariable regression (all variables included one at a time)				Multivariable regression I (variables in grey included one at a time), n = 12230				Multivariable regression II (variables in grey included one at a time), n = 11756				Multivariable regression III, n = 10436			
	HR	95% CI	p-value	n	HR	95% CI	p-value	n	HR	95% CI	p-value	n	HR	95% CI	p-value	n
Non-proliferative background retinopathy	1.21	[0.83–1.77]	0.3164		1.14	[0.78–1.67]	0.4845		1.18	[0.81–1.73]	0.3904		1.27	[0.86–1.86]	0.2285	
Advanced non-proliferative retinopathy	2.44	[2.00–2.97]	0.0000		2.44	[1.97–3.03]	0.0039		2.55	[2.04–3.18]	0.0000		2.30	[1.82–2.90]	0.0000	
Proliferative retinopathy	2.92	[2.15–3.97]	0.0000		3.17	[2.28–4.42]	0.0000		3.38	[2.42–4.73]	0.0000		2.40	[1.66–3.48]	0.0000	
Previous lasertreatment	3.60	[2.09–6.21]	0.0000		4.11	[2.35–7.18]	0.0000		4.60	[2.60–8.12]	0.0000		3.26	[1.60–6.65]	0.0012	
Pulse																0.0000
Yes	1			12,146	1			11,993	1			11,550	1			
No	1.95	[1.59–2.40]	0.0000	0.0000	1.87	[1.52–2.30]	0.0000	0.0000	1.81	[1.46–2.25]	0.0000		1.68	[1.32–2.15]	0.0000	
HbA1C				12,397				12,230				11,756				
Well regulated (<58 mmol/mol)	1.15	[0.90–1.45]	0.2616		–	[–]	–		–	[–]	–		–	[–]	–	
Medium regulated (58–69 mmol/mol)	1				1				1				1			
Poorly regulated (>69 mmol/mol)	1.46	[1.19–1.79]	0.0002	0.0005	–	[–]	–		–	[–]	–		–	[–]	–	
Symptoms of neuropathy				12,028				11,875				11,438				
No	1			0.0000	1			0.0000	1			0.0000	1			0.0000
Yes	2.14	[1.80–2.55]	0.0000		2.12	[1.77–2.54]	0.0000		2.10	[1.75–2.53]	0.0000		1.95	[1.61–2.37]	0.0000	

showed association from Model I through III. The unadjusted association with diabetes duration and with visual acuity is explained from Model III by clinical diabetes-related measurements that, among others, include retinopathy. The results in Table 3 indicate that DFU incidence is primarily predicted by clinical diabetes-related measurements and that many of the conventional, more general, predictors seem not much informative in the present selection of patients with T2D. Additional analyses for interactions of the risk factors with age and sex reveal a significant interaction between age and retinopathy, i.e. the association of retinopathy with DFU incidence is different between age-groups: the dose-response-like association between retinopathy and DFU incidence is most pronounced in older patients (especially patients 60–79 years of age). Including this interaction in Model III does not meaningfully affect the associations of the other risk factors.

4. Discussion

To the best of our knowledge the present series is the first study documenting the pattern of risk factors for diabetic foot ulcers separately in T1D and T2D. The study shows that a number of factors routinely obtained as part of the routine diabetes care are independent predictors of development of FTDFU. Many of the factors, but not all, predicted risk in both in T1D and T2D. This applies to male gender, poor metabolic control, reduced visual acuity and advanced retinopathy, reduced vibration sensitivity, symptoms of neuropathy, and absence of at least on pedal pulse. In T1D, but not T2D, high age, presence of CVD, and macroalbuminuria were also associated with increased risk

There are only few studies documenting risk factors for FTDFU. The risk factors established previously are: peripheral neuropathy measured by biothesiometry, Michigan DPN upon reflexes and muscle strength or insensation to 10-g monofilament [13–15]. Moreover, absence of at least one pedal pulse and long duration of diabetes [7], increased plantar pressure, consumption of alcohol [13] and age [14,15] have all been reported as risk factors. Our finding of peripheral neuropathy, absence of pedal pulses and duration of diabetes are in accordance with the literature. Differences can be explained by different patient selection. Thus, for example, in the series of Abbott et al. [14,15], all patients had neuropathy, while in the series of Kästenbauer et al. [13] PAD was excluded and in the series of Crawford et al. [7] the patients were selected from several series. Moreover, the risk factors selected for analysis were not identical. Overall our results corroborates well with those previously reported and add some other strong and independent risk factors, which are all routinely recorded in the care of the patients in diabetes clinics.

It has been suggested, that in T1D with a clustering of microvascular complications, i.e. retinopathy and nephropathy, there is an increased prevalence of cardiovascular disease [16]. The present results in T1D as well as T2D also show this clustering with increased risk of FTDFU. We are not aware of any previous studies focusing on this association. In a study of people diagnosed with T2D before age 65 and treated in primary care it was reported that male gender, presence of

peripheral neuropathy, retinopathy, albuminuria and absence of pulse were all independent risk factors for amputations [17], i.e. the same risk factors as found in the present study.

The present study was performed in a hospital specialized in treating patient with diabetes, the hospital clinic serves as an integrated part of the public health care system in the Greater Copenhagen Region of Denmark. The general relevance of the present results therefore depends on the patients included in the study. In Denmark close to 100% of patient with T1D are treated in hospital outpatient clinics. Data from the national Danish diabetes quality database [18] shows that patients with T1D followed in our clinic do not differ from other patients with diabetes with regard to duration of diabetes, metabolic control and rate of complications. T2D patients are to a large degree cared for in general practice. However, two groups of patients are seen in hospital outpatient clinics. One group comprises patients for whom it is difficult to reach treatment goals in primary care, typically in relation to HbA1c. These are then referred to the outpatient clinics, where treatment is optimized and after typically 6–12 months the majority of these patients return to primary care. Another group comprises patients with both micro- and macrovascular complications, approximately 10% of all T2D patients who are typically followed life-long in outpatient clinics. Hence, the group of T2D patients included in the present study typically are more complicated and with longer disease duration than the average T2D patients.

4.1. *Limitations of the study*

The aim of the present investigation was to examine to which extent results of standard clinical information available and obtained as part of the routine follow-up and treatment of patients with T1D or T2D. A large number of risk factors for DFU documented in the literature and many of these are not included in the present study, therefore we cannot assess whether the present combinations perform better or poorer than other risk factors or set of risk factors. The present results are based on analysis of a cohort of T1D patients that are representative of the total Danish diabetes population, while the T2D cohort is selected as describe previously. It may well be that some of the differences between the set of risk factors for FTDFU identified for T1D and T2D patients are due this selection.

Decreased renal function as measured by decreased GFR is a risk factor for DFU. In the present study macroalbuminuria is a marker of abnormal renal function, we did however not include measures of the glomerular filtration rate (eGFR), which could have further characterized the degree of loss of renal function. This could have identified a group of patient with some degree of loss of renal function, on the other hand there will be only few patients with severe loss of renal function, i.e. eGFR < 30 and end stage renal disease, in the data of the present study, as in Denmark this group of patients is cared for in hospital departments of nephrology. Thus it may be that we failed to identify e-GFR as an independent risk factor.

In patients who stopped treatment at the center we have no information as to whether they developed a DFU. For T1D patients the length of observation is quite large and therefore incidence assessments pertain to the general T1D population. This is also the case for the complicated T2D patients who are the majority of the T2D patients in the data. The less complicated T2D patients are only followed shorter periods and DFU incidences on this group may not be generalizable to all uncomplicated T2D patients. Note that these limitations do not bias the measures of impact of the risk factors; these HRs are ratios of incidence rates which are relative measures.

4.2. *Strength of the study*

The present study is to our knowledge the first which focuses on the development of FTDFU and which tries to assess to which extent there may be differences between T1D and T2D. The study includes at large number of observations and in relation to T1D they are likely to be representative of the general T1D population, while the T2D patients in our sample can be viewed representative of T2D patients needing secondary care attention. Finally, the study investigates standard recordings in relation to diabetes care implying no extra recordings relating to more specific issues are needed.

We suggest that studies are undertaken where the risk factors identified in the present study are systematically obtained at regular intervals, e.g. every second year, and related to the risk of developing foot ulcers. As the risk factors are part of the routine care of diabetes patients this is possible. Based on this it may be possible to develop risk stratification for the development of FTDFU which can be integrated in electronic record systems, and thereby made useful for routine care.

Authors' contributions

All authors contributed to the design and acquisition of data. SH and VS conducted the data analysis and tables. SH, TA, VS and PH drafted the manuscript. All authors had full access to all data and statistical reporting of the trial and can take full responsibility for the integrity of data and accuracy of data analysis. All authors revised and approved the final version of the manuscript.

Conflicts of interest

AR, TA, AAN, KEN report ownership of shares in NovoNordisk. SH, VS and PH have no conflicts of interest.

Funding

The authors received no funding from an external source.

REFERENCES

[1] Boulton AJ, Vileikyte L, Ragnarson-Tennwall G, Appleqvist J. The global burden of diabetic foot disease. Lancet 2005;366:1719–24.
[2] Singh N, Armstrong DG, Lipsky BA. Preventing foot ulcers in patients with diabetes. JAMA 2005;293(2):217–28.

[3] Prompers L, Huijberts M, Apelqvist J, Jude E, Piaggesi A, Bakker K, et al. High prevalence of ischaemia, infection and serious comorbidity in patients with diabetic foot disease in Europe. Baseline results from the Eurodiale study. Diabetologia 2007;50(1):18–25.
[4] Prompers L, Schaper N, Apelqvist J, Edmonds M, Jude E, Mauricio D, et al. Prediction of outcome in individuals with diabetic foot ulcers: focus on the differences between individuals with and without peripheral arterial disease. The EURODIALE study. Diabetologia 2008;51(5):747–55. https://doi.org/10.1007/s00125-008-0940-0.
[5] Boulton AJ. The pathogenesis of diabetic foot problems: an overview. Diabet Med 1996;13(Suppl 1):S12–6.
[6] Jeffcoate WJ. Stratification of foot risk predicts the incidence of new foot disease, but do we yet know that the adoption of routine screening reduces it? Diabetologia 2011;54(5):991–3.
[7] Monteiro-Soares M, Boyko EJ, Ribeiro J, Ribeiro I, Dinis-Ribeiro M. Predictive factors for diabetic foot ulceration: a systematic review. Diabetes Metab Res Rev 2012;28:574–600. https://doi.org/10.1002/dmrr.2319.
[8] Crawford F, Cezard G, Chapell M, et al. The deveopment and validaiton of a mutivariable prognostic model to predict foot ulceration in diabates using a systematic review and individual patient data metaanalysis. Diabet Med 2018. https://doi.org/10.1111/dme.13797.
[9] Rasmussen A, Almdal T, Anker Nielsen A, Nielsen KE, Jørgensen ME, Hangaard S, et al. Decreasing incidence of foot ulcer among patients with type 1 and type 2 diabetes in the period 2001–2014. Diabetes Res Clin Pract 2017 Aug;130:221–8. https://doi.org/10.1016/j.diabres.2017.05.025.
[10] Almdal T, Nielsen AA, Nielsen KE, Jørgensen ME, Rasmussen A, Hangaard S, et al. Almdal Increased healing in diabetic toe ulcers in a multidisciplinary foot clinic – an observational cohort study. Diabetes Res Clin Pract 2015 Dec;110(3):315–21. https://doi.org/10.1016/j.diabres.2015.10.003.
[11] Jørgensen ME, Færch K, Almdal T. Reduced incidence of lower-extremity amputations in a Danish diabetes population from 2000 to 2012. Diabet Med 2013 Sep 25. https://doi.org/10.1111/dme.12320.
[12] Aldington SJ, Kohner EM, Meuer S, Klein R, Sjølie K. Methodology for rethinal photography assessment of diabetic rethinopathy: the EURODIAB IDDM Complications Study. Diabetologia 1995;38:437–44.
[13] Kästenbauer T, Suaseng S, Sokol G, Auinger M, Irsiger K. A prospective study of predictors for foot ulceration in ype 2 diabetes. J Am Podiatr Med Assoc 2001;91(7):343–50.
[14] Abbott CA, Vileikyte L, Williamson S, Carrington AL, Boulton AJ. Multicenter study of the incidence of and predictive risk factors for diabetic neuropathic ulceration. Diabetes Care 1998;21:1071–5.
[15] Abbott CA, Carrington AL, Ashe H, et al. The Northe-West Diabetes Foot Care study: incidence of, and risk factors for new diabetic foot ulceration in a community based cohort. Diabetic Med 2002;19:377–84.
[16] Deckert T, Feldt-Rasmussen B, Borch-Johnsen K, Jensen T, Kofoed-Enevoldsen A. Albuminuria reflects widespread vascular damage. The Steno hypothesis. Diabetologia 1989 Apr;32(4):219–26.
[17] Bruun C, Siersma V, Guassora AD, Holstien P, de Fine Olivarius N. Amputation and foot ulcers in patients with type 2 diabetes mellitus and observed for 19 years. The role of gender and co.morbidity. Diabetic Med 2013;30:964–72. https://doi.org/10.1111/dme.12196.
[18] Jørgensen ME, Kristensen JK, Reventlov Husted G, Cerqueira C, Rossing P. The Danish adult diabetes registry. Clin Epidemiol 2016 Oct;25(8):429–34.