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The clinical course and mortality of persons with diabetic Charcot foot

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ABSTRACT

INTRODUCTION. The aim was to study the mortality and the clinical course of diabetic Charcot foot.

METHODS. This was a retrospective cohort study including all persons with diabetes and a Charcot diagnosis from 2000 to 2016.

RESULTS. In the mortality sub-study, 164 persons had the Charcot diagnosis, 52 (31.1%) died in the follow-up period. The mortality rate was 4.6/100 person-years at risk. Rate ratios for death were insignificantly different among smokers and non-smokers, among persons with type 1 and type 2 diabetes, among persons with a diabetes duration below or above ten years and among persons with a glycated haemoglobin (HbA_{1c}) level above or below 60 mmol/mol after adjustment for age and gender. In the clinical course sub-study, 114 persons with Charcot were identified whereof 97 (85%) had an active Charcot. The duration from start of symptoms to diagnosis was ten weeks, the treatment period was 7.5 months and 46 (40%) had bony prominences (rocker bottom) in the planta at follow-up.

CONCLUSIONS. The mortality rate among persons with Charcot was 4.6/person-years at risk, which was unaffected by smoking, diabetes type, diabetes duration and HbA_{1c} level. The persons with Charcot had a long delay from symptom onset to diagnosis, a long treatment period and often developed complications.

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TRIAL REGISTRATION. not relevant.

Diabetic Charcot foot (DCF) is a disabling and devasting foot complication with an incidence of 0.3/year in persons with diabetes who are often dysregulated and have neuropathy [1, 2]. The pathogenesis consists of neuropathy, acute inflammation and progressive destruction of the bones and joints of the foot and/or ankle [2, 3]. Clinically, active DCF is warm with a difference of > 2 °C between the two feet, erythematous, oedematous and occasionally painful and with palpable pulses [2]. A triggering incident such as a trauma or increased load is occasionally reported by the person affected by DCF.

DCF is costly for the healthcare system as it requires close observation in the outpatient clinic and often hospitalisation. If detected late, a severe deformity may result in a secondary ulceration, infection and need for amputation [2]. Immobilisation in the early stages is essential, but severe deformity may still develop [2]. The impact on the person with DCF is substantial and includes isolation, metabolic dysregulation, physical disability and reduced quality of life [4]. The restrictions imposed on persons with active DCF may seem illogical due to the neuropathy-reduced sensitivity. The benefit of the restrictions cannot always be perceived and may therefore be

regarded as futile by the patient. Thus, even though persons with active DCF and the involved healthcare professionals may share the same objective of clinical remission, their motivation differs.

A recent study has shown a mean mortality of 29% within five years according to studies published since 2007, which is similar to mortality for all reported cancers (31% in five years) [5].

A few recent studies have described the clinical course of DCF. A UK study has explored factors associated with the development and resolution of acute DCF and found that removable off-loading was used more than non-removable off-loading [1], even though the total contact cast (TCC) is the gold standard [6]. In a Danish study, 95% of persons with acute DCF were treated with a removable walker for an average duration of 8.3 months [7].

The most common location and deformity of the DCF is in the midfoot. Deformity in this area may cause severe deformity (rocker bottom deformity) [1, 2, 8, 9]. The CDUK study demonstrated that 35% of patients with DCF had a foot ulcer [1].

The aim of the present study was to determine the mortality among persons with DCF, to compare baseline characteristics of persons with DCF who died or survived in the follow-up period and to study the rate ratio of selected risk factors for mortality among persons with DCF.

Furthermore, we aimed to study the clinical course of DCF with a focus on symptom duration before the diagnosis, the diagnostic process, the localisation of the DCF incident and the development of complications (deformities, recurrence of DCF, a new DCF process on the contralateral foot, foot ulcers and amputations). In addition, we aimed to record retainment of occupation, the ability to exercise/be physically active and marital status at follow-up.

METHODS

This was a retrospective cohort study including all persons with a DCF diagnosis at the Steno Diabetes Centre Copenhagen (SDCC) from 2000 to 2016 in a mortality sub-study. In the clinical course sub-study, persons from 2003 to 2016 with relevant clinical information regarding DCF were included, as relevant data were not retrievable from 2000 to 2003. The study was approved by the Danish Patient Safety Authority.

The Steno Diabetes Centre is an outpatient clinic integrated in public Danish healthcare. In 2000-2016, 3,500 persons with type 1 diabetes and 2,000 persons with complicated type 2 diabetes were followed. Persons with type 2 diabetes were referred from primary care for optimisation of treatment, typically for a 6-12-month period. Those with micro- or macrovascular complications were offered life-long control at the SDCC. In general, persons at the SDCC were representative of people living in Denmark with type 1 diabetes and the 10% most complicated persons with type 2 diabetes. All had a foot examination once a year. In case of neuropathy, loss of sense of vibration, ischaemia, DCF, minor or major amputations or a previous or present foot ulcer, the persons were referred to our multidisciplinary foot clinic [10].

The diagnosis and treatment of DCF was standardised according to national and international recommendations. To diagnose DCF, all patients had their skin temperature measured and an X-ray performed and/or a bone scintigraphy and/or magnetic resonance imaging (MRI). In the first years of the present study, MRI was unavailable. Therefore, the diagnosis was confirmed by a synthesis of clinical appearance, clinical path and supplementary MRI, bone scintigraphy and X-ray. Sprains, uric acid arthritis, fracture, neuropathic pain, infections and other rheumatological disorders were excluded. Once the diagnosis had been established, the DCF was considered active/acute when the temperature difference between the two feet exceeded 2 °C.

The acute phase treatment was immobilisation in a removable cast (RC) (Aircast, DonJoy, USA) with custom

made insoles or therapeutic sandals if a RC was not feasible due to physical disability. When the temperature difference between the feet was < 2 °C at two subsequent visits separated by a minimum four-week interval, persons with DCF were offered careful transition from RC to sandals with rocker bottom and custom insoles. Persons with DCF were followed closely in the foot clinic until bespoke footwear had been delivered and approved.

Corrective surgery was considered if conservative off-loading was inadequate for healing of a foot ulcer. Foot infections were treated according to severity: superficial infections in the outpatient clinic, deep infections during admission with surgical drainage and revision, if required. Revascularisation was performed in case of critical ischaemia, if possible. Following healing of the DCF, we recommended lifelong treatment by a primary care podiatrist and a minimum of one annual control in the foot clinic at the SDCC.

Data included information on co-morbidities, symptoms, lifestyle habits, treatment, medication and objective measurements used in daily clinical practice. The basic characteristics and medication from the latest available information at enrolment are displayed in **Table 1**.

TABLE 1 Baseline characteristics at Charcot diagnosis for the mortality sub-study – total and divided into deceased and surviving patients.

	Total (N = 164)	Deceased (n_{dec} = 52)	Survivors (n_{sur} = 112)
Age at Charcot diagnosis, yrs, mean ± SD	56.3 ± 11.4	61.3 ± 10.0	54.0 ± 11.4*
Men, %	61	63	60
Diabetes duration, yrs, mean ± SD	25.0 ± 14.6	24.2 ± 15.3	25.3 ± 14.3
Type 1diabetes, % (95% CI)	54 (46-62)	40 (27-55)	60 (50-70)*
Non-smoker, % (95% CI)	46 (39-54)	35 (22-49)	52 (42-61)*
BMI, kg/m², mean ± SD	28.2 ± 5.8	29.1 ± 5.4	27.7 ± 5.9
Systolic BP, mmHg, mean ± SD	138 ± 20	143 ± 21	136 ± 19
Diastolic BP, mmHg, mean ± SD	78 ± 9	76 ± 11	79 ± 9
HbA_{1c} concentration, mmol/mol (%), mean ± SD	70 (8.6) ± 19 (1.7)	67 (8.3) ± 19 (1.8)	71 (8.7) ± 19 (1.7)
Haemoglobin concentration, mmol/l, mean ± SD	8.2 ± 1.1	7.9 ± 1.2	8.3 ± 0.9*
Creatinine concentration, µmol/l, median (Q1-Q3)	93 (72-118)	115 (88-161)	85 (69-109)*
LDL concentration, mmol/l, mean ± SD	2.4 ± 0.9	2.5 ± 0.9	2.3 ± 0.9
Urine albumin creatinine ratio, mg/g, median (Q1-Q3)	31 (11-200)	33 (11-200)	31 (11-221)
Vibration threshold > 25 V, % (95% CI)	80 (73-86)	81 (67-90)	79 (71-87)
Vibration threshold > 50 V, % (95% CI)	48 (40-55)	54 (39-68)	45 (35-54)
Diabetic foot ulcer, % (95% CI)	43 (36-51)	48 (34-62)	41 (32-51)
Antihypertensives[a], % (95% CI)	87 (81-92)	85 (72-93)	88 (81-94)
Statins[b] (95% CI), %	53 (45-61)	42 (29-57)	58 (48-67)
Antithrombotic[c] agents, % (95% CI)	59 (51-66)	71 (57-83)	53 (43-62)*
Insulin[d], % (95% CI)	69 (61-76)	58 (43-71)	74 (65-82)*
Non-insulin antidiabetic agents[e] % (95% CI)[f]	58 (47-69)	48 (30-67)	64 (49-77)

ACE = angiotensin-converting enzyme; ARBs = angiotensin receptor blockers; BP = blood pressure; CI = confidence interval; HbA_{1c} = glycated haemoglobin; LDL = low-density lipoprotein; NPH = neutral protamine hagedorn; Q = quartile; SD = standard deviation.
*) p < 0.05 compared with deceased.
a) ACE inhibitors, ARBs, diuretics, β-blockers, calcium channel blockers, moxonidine and/or doxazosine.
b) Simvastatin, atorvastatin, pravastatin and rosuvastatin.
c) Acetylsalicylic acid, clopidogrel, dipyridamole, vitamin K antagonists and non-vitamin K antagonist oral anticoagulants.
d) Insulin aspart, insulin glargine, insulin detemir, insulin degludec, NPH insulin and/or regular insulin.
e) Biguanides, sulfonylureas, dipeptidyl peptidase-4 inhibitors, sodium glucose cotransporter 2 inhibitors and/or glucagon-like peptide-1 analogues.
f) Only persons without type 1 diabetes.

Normo-albuminuria was defined as a urine albumin creatinine ratio < 30 mg/g. A person may or may not have been treated with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers.

Vibration threshold was measured by biothesiometry in volts using Bio-Thesiometer (USA) on the tip of the first toe. Persons were grouped according to a vibration threshold > 25 V and > 50 V.

Foot ulcers were classified as neuropathic, neuro-ischaemic or critically ischaemic ulcers.

Information on date of death was extracted from the Civil Registration System Registry.

DCF was classified according to Sanders & Frykberg [11], comprising five areas: *I.* interphalangeal/metatarsophalangeal joint, *II.* tarsometatarsal, *III.* naviculo-cuniform, *IV.* talonavicular and *V.* calcaneo-cuboid. Similarly, deformity was classified into four categories: no visible deformities, development of a bone prominence in the planta (rocker bottom foot), dislocation of the ankle and a flat foot with a large volume. DCF recurrence was defined as a new incident in the same area; a new DCF was defined as a new incident in another area.

Information on retainment of occupation and marital status was extracted from the medical file.

Exact 95% confidence intervals (CIs) were calculated for percentages and compared between groups using χ^2-tests or Fisher's exact test, as appropriate. The Wilcoxon rank sum test was used to compare group differences for continuous variables. Statistical analyses were conducted using SAS Enterprise Guide 7.1 (SAS Institute, Cary, NC, USA).

Mortality rates were estimated by dividing the number of outcomes by person-years at risk. Years at risk were calculated as the time difference between date of entry and date of exit. Date of entry was the date when DCF was diagnosed. For deceased individuals, the date of exit was set to the date of death. For survivors, the date of exit was end of study or the date of the last consultation if the person had stopped attending the SDCC. We did not have access to cause of death for the individual deceased persons.

Rate ratios from Poisson regression analyses were adjusted for age and gender.

No allowance was made for multiplicity of statistical tests, an alpha-level of 5% being used throughout.

Trial registration: not relevant.

RESULTS

In the mortality sub-study, 164 persons had the DCF diagnosis and 52 (31.1%) died in the follow-up period (Table 1). Compared with survivors, persons who died were significantly older, less frequently had type 1 diabetes, more often were smokers, had a lower haemoglobin level and a higher creatinine level and were more frequently treated with antithrombotic agents than survivors (Table 1).

The deceased patients lived for 1,973 days (mean, range: 219-4,895), i.e., 5.4 years after their diagnosis. All were followed for a total of 1,122 years, median 6.0 years/person (Q1-Q3 = 3.2-10.0). The mortality rate was 4.6/100 person-years at risk.

Rate ratios for death were not significantly different among persons with a diabetes duration below or above ten years, among persons with type 1 and type 2 diabetes, among smokers and non-smokers, among persons with a glycated haemoglobin (HbA_{1c}) level above or below 60 mmol/mol or among persons with or without a diabetic foot ulcer - either in the univariate analyses or after adjustment for age and gender (**Table 2**).

TABLE 2 Rates of mortality and rate ratios for the mortality sub-study.

		Rate ratio (95% CI)	
	Rate per 100 person-years at risk	**unadjusted**	**adjusted for age and gender**
Diabetes duration, yrs	< 10: 2.6 versus > 10: 5.2	0.49 (0.21-1.15)	0.53 (0.23-1.25)
Diabetes type	Type 1: 3.9 verus Type 2 + other: 6.4	0.61 (0.35-1.07)	0.84 (0.46-1.53)
Smoking	Yes: 4.8 versus No: 4.6	0.96 (0.54-1.69)	1.09 (0.61-1.94)
HbA_{1c} concentration, mmol/mol (%)	< 60 (7.6): 4.0 versus > 60 (7.6): 6.2	0.63 (0.36-1.10)	0.73 (0.41-1.27)
Diabetic foot ulcers	Yes: 5.8 versus No: 3.9	1.49 (0.86-2.57)	1.41 (0.81-2.47)

CI = confidence interval; HbA_{1c} = glycated haemoglobin.

In the clinical course sub-study, 114 persons with DCF were identified. The duration from symptom onset to diagnosis was median ten weeks (**Table 3**).

TABLE 3 Clinical results at baseline and follow-up for the clinical course sub-study (N = 114).

Duration of symptoms before diagnosis, wks, median (range)	10 (1-51)
Diagnosis based on a combination of, n (%)	
X-ray	80 (70)
Scintigraphy	77 (67)
MRI	21 (18)
Localisation of the Charcot incident in 102 (89%) persons: Anatomic Classification, n (%)	
Area I: distal and proximal interphalangeal joint and metatarsophalangeal joint	12 (10)
Area II: tarsometatarsal joints, Lisfrancs	47 (41)
Area III: naviculo-cunieform joints, talo-navicular joint, calcaneocuboid joint	42 (37)
Area IV: ankle joint, subtalar joint	14 (12)
Area V: calcaneus	8 (7)
Number with information on deformities or not, n (%)	
No visible deformities	23 (20)
Developed a prominence on the plantar (rocker bottom)	46 (40)
With a varus or valgus deformity in the hindfoot	9 (8)
With a flat foot with increased volume	4 (4)
Subtotal	82 (72)
Persons with a minimum of one recurrence of Charcot, n (%)	12 (10)
Persons with a new Charcot incident during follow-up, n (%)	12 (10)
Persons with foot ulcers on the Charcot foot during follow-up, n (%)	34 (29)
Persons with a major amputation, all due to an infection, n (%)	4 (3)
Persons returned to their occupation after the diagnosis of Charcot foot, n (%)	22 (19)
Persons by marital status after the Charcot had progressed, n (%)	
Lived alone	50 (44)
Married or had a partner	53 (47)
Married and had children still living at home	9 (8)
Subtotal	112

The localisation of the DCF, with most incidents occurring in the midfoot (area II + area III), the complications and other indicators are presented in Table 3. Time from symptom onset includes patient delay, referral delay

and time from presentation of a hot, red and swollen foot in the clinic to confirmation by either bone scintigraphy, MRI or X-ray. Off-loading treatment was initiated at clinical suspicion at presentation in the clinic.

A total of 97 (85%) had an active DCF. DCF triggers included previous fractures, trauma, overloading and previous foot surgery. However, most commonly, the trigger was unknown, but presumably due to neuropathy (data not shown).

The type of insoles used in the cast or sandals was described in 51 (45%) cases. All persons with DCF were offered prescribed footwear for prevention of foot complications when their DCF had healed. A total of 37 (32%) persons were recommended exercising on a bicycle.

DISCUSSION

Our study showed a mortality rate of 4.6/100 person-years at risk (52 (31.1%) died during a median 6.0-year follow-up). Previous studies of DCF patients have reported mortality rates of 50% per 7.88 years [12]; 44.7% after 3.7 years [13], 15% after 40 months [14] and 28% after five years [15]. A study on DCF patients from our clinic covering the period from 1984 to 1994 showed that only two out of 115 persons died during a median 48-month follow-up period [8], and a recent Danish study recorded a 14% five-year mortality rate, which is comparable to that of persons with diabetes in general [7]. The difference in mortality may be explained by different proportions of persons with type 1 diabetes, different age groups, different diabetes durations and different complication statuses; even so, our study found no significant difference in mortality rate between persons with type 1- and type 2 diabetes, between short or a long diabetes duration or between smokers and non-smokers. This may likely be explained by a lack of power in our study. The low mortality rate in our and other Danish studies [7, 8] makes it even more important to reduce the risk of complications to DCF.

Persons with DCF have had a long course with symptoms before their diagnosis. The combination of patient and referral delay may be due to the subtle symptoms due to neuropathy or to the fact that symptoms were misinterpreted as infection, inflammation or trauma. The frequent localisation of DCF in the midfoot (area II + area III) and the fact that 46 (40%) had bony prominences in the planta at the end of the treatment are in line with findings reported from other studies [1, 2, 5]. One fifth did not develop deformities. Previous studies have shown severe deformities, which are difficult to off-load [2] and the risk of ulceration is high.

In our study, we used the RC even though TCC is the gold standard [16]. Most other centres in Denmark are using RC in the treatment of DCF [7], and Christensen et al. showed that treatment with less restrictive off-loading is safe [17]. The RC affords the person with DCF the possibility of taking a shower without the cast and of inspecting his or her feet daily. However, the use of RC instead of the gold standard (TCC) in this study may have prolonged the treatment period.

Only 22 (19%) (Table 3) returned to their previous occupation. It seems reasonable to inform persons with DCF of this and to include work rehabilitation in their treatment.

The strengths of the present retrospective cohort study include the well-described baseline characteristics, the thorough description recorded during follow-up including information on complications to the DCF (DCF recurrence, occurrence of a new DCF, diabetic foot ulcers and amputation), retainment of occupation and marital status. Furthermore, the long follow-up period with calculation of years at risk was a strength.

The study was limited by lacking information on occupation at baseline, but reported information on retainment of occupation. Furthermore, we had missing data on some of the reported variables.

CONCLUSIONS

The mortality rate among persons with DCF was 4.6%/person-years at risk, which was unaffected by smoking, diabetes type, diabetes duration and HbA_{1c} level.

In our study, persons with DCF had a delay from symptom onset to diagnosis, a long treatment period and frequent complications. Persons with DCF typically lived alone and only a few returned to their previous occupation after receiving their diagnosis. Further research is needed to identify risk factors for and prevention of development of deformities.

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