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ORIGINAL ARTICLE

The pattern of incident fractures according to fracture site in people with T1D

N. H. Rasmussen[1] · C. Sarodnik[2] · S. P. G. Bours[3,4] · N. C. Schaper[3,4] · P. C. Souverein[5] · M. H. Jensen[1,6] · J. H. M. Driessen[2,5,7,8] · J. P. W. van den Bergh[2,3,9,10] · P. Vestergaard[1]

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Abstract

Summary Higher incidences of fractures are seen in people with type 1 diabetes (T1D), but knowledge on different fracture sites is sparse. We found a higher incidence mainly for distal fracture sites in people with T1D compared to controls. It must be further studied which fractures attributed to the higher incidence rates (IRs) at specific sites.

Introduction People with T1D have a higher incidence of fractures compared to the general population. However, sparse knowledge exists on the incidence rates of individual fracture sites. Therefore, we examined the incidence of various fracture sites in people with newly treated T1D compared to matched controls.

Methods All people from the UK Clinical Practice Research Datalink GOLD (1987–2017), of all ages with a T1D diagnosis code ($n=6381$), were included. People with T1D were matched by year of birth, sex, and practice to controls ($n=6381$). Fracture IRs and incidence rate ratios (IRRs) were calculated. Analyses were stratified by fracture site and sex.

Results The IR of all fractures was significantly higher in people with T1D compared to controls (IRR: 1.39 (CI95%: 1.24–1.55)). Compared to controls, the IRR for people with T1D was higher for several fracture sites including carpal (IRR: 1.41 (CI95%: 1.14–1.75)), clavicle (IRR: 2.10 (CI95%: 1.18–3.74)), foot (IRR: 1.70 (CI95%: 1.23–2.36)), humerus (IRR: 1.46 (CI95%: 1.04–2.05)), and tibia/fibula (IRR: 1.67 CI95%: 1.08–2.59)). In women with T1D, higher IRs were seen at the ankle (IRR: 2.25 (CI95%: 1.10–4.56)) and foot (IRR: 2.11 (CI95%: 1.27–3.50)), whereas in men with T1D, higher IRs were seen for carpal (IRR: 1.45 (CI95%: 1.14–1.86)), clavicle (IRR: 2.13 (CI95%: 1.13–4.02)), and humerus (IRR: 1.77 (CI95%: 1.10–2.83)) fractures.

Conclusion The incidence of carpal, clavicle, foot, humerus, and tibia/fibula fractures was higher in newly treated T1D, but there was no difference at other fracture sites compared to controls. Therefore, the higher incidence of fractures in newly treated people with T1D has been found mainly for distal fracture sites.

Keywords Fracture pattern · Incident fractures · Type 1 diabetes

✉ N. H. Rasmussen
nicklas.rasmussen@rn.dk

1 Steno Diabetes Center North Denmark, Aalborg University Hospital, Aalborg, Denmark

2 NUTRIM Research School, Maastricht University, Maastricht, The Netherlands

3 Department of Internal Medicine, Maastricht University Medical Centre+, Maastricht, The Netherlands

4 CAPHRI Research School, Maastricht University, Maastricht, The Netherlands

5 Division of Pharmacoepidemiology & Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands

6 Department of Health Science and Technology, Aalborg University, Fredrik Bajers Vej 7, 9210 Aalborg, Denmark

7 Department of Clinical Pharmacy and Toxicology, Maastricht University Medical Centre+, Maastricht, The Netherlands

8 Cardiovascular Research Institute Maastricht (CARIM), Maastricht University, Maastricht, The Netherlands

9 Department of Internal Medicine, VieCuri Medical Center, Venlo, The Netherlands

10 Faculty of Medicine and Life Sciences, University of Hasselt, Hasselt, Belgium

Introduction

People with diabetes have an increased risk of fractures compared with the general population [1]; however, important knowledge gaps exist. In most studies, the incidence of any fracture is increased in people with diabetes, although highest in T1D [2, 3]. A meta-analysis showed an increased relative risk (RR) of any fracture with T1D of 3.16 (95% confidence interval (CI) 1.51–6.63) and a relative risk (RR) of hip fracture of 3.78 (95% CI 2.05–6.98) as compared to people without diabetes [4].

T1D is often diagnosed in childhood, which could influence the development of the bone and thus the accretion of peak bone mass [5]. A low peak bone mass could lead to fractures at a younger age. Also, younger people probably fracture at different sites compared to people aged > 60 years, who, e.g., more frequently suffer from hip fractures [6]. Diabetes duration, and different body composition with body mass index (BMI) in the lower normal range or frank underweight, has been associated with an increased risk of fractures in T1D [7]. However, most studies have been conducted in people aged > 40 years or older, with different aims, diabetes duration, trauma mechanism, and fracture sites as secondary endpoints, which complicate comparisons. Only a few studies have addressed the incidence of fractures in the younger population [8]. Two studies have found a modest increase of any fractures and hip fractures in people with T1D aged 0–19 [6, 9]. Although, most studies have focused on the total amount of fractures or one fracture site such as the hip. To our knowledge, no study exists on the fracture pattern and incidences on newly diagnosed people with T1D, thus leaving a need for studies on other fracture sites to comprehend a better understanding of fracture patterns at an early stage of T1D.

Therefore, the primary aim was to examine the incidence of various fracture sites in people with newly treated T1D compared to people without T1D and after stratification of sex.

Materials and methods

Source of data

Data were extracted from the UK Clinical Practice Research Datalink (CPRD) GOLD. The CPRD contains anonymized electronic medical records of 674 primary care practices in the UK, representing approximately 6.9% of the total UK population in 2013. The data recorded in CPRD include patient demographics, medical history, laboratory test results, prescription details, specialist referrals, hospital admissions, and major outcomes since 1987, with ongoing data collection. The population within the CPRD is widely representative of the UK population, and it was reported that the accuracy and completeness of data, especially about age and sex, is satisfactory. This study protocol (Protocol 18_275R) was approved as a descriptive study by the Independent Scientific Advisory Committee (ISAC) for Medicines and Healthcare products Regulatory Agency (MHRA) database research. Informed consent was not required in this study, since all data on patients are stored anonymously in the CPRD.

Study design and population

In order to address the research question, we performed a population-based retrospective cohort study of people of all ages identified in the CPRD database between January 1, 1987, and December 31, 2017. The cohort consisted of all people with newly treated T1D (from now on "T1D") ($n = 6381$) and their matched controls ($n = 6381$); the selection of the study population is shown in Fig. 1. People with newly diagnosed (incident) T1D were identified by a first-ever redeemed prescription of insulin, which determined the index date, with at least 1 year of valid data collection before this index date. People who also received non-insulin antidiabetic drugs (NIADs) ($n = 625$) on the index date, people who received insulin without a T1D Read code before the index date in the CPRD database ($n = 2193$), or people without a specific diabetes diagnosis code ($n = 6299$) were excluded. Each person with T1D was matched by year of birth, sex, and practice to a person (1:1) without an insulin prescription (a control person) using incidence density sampling. The inclusion date for follow-up of the control persons started on the same day as the index date of their matched person with T1D. Control persons were censored when they received an insulin prescription or when a diabetes diagnosis Read code was recorded. A Read code is a clinical code that is used in primary care in the UK to register several medical events such as the diagnosis of a disease. The coding quality on estimates of the incidences of diabetes in the UK CPRD has improved over time [10]. To reduce miscoding and misclassification of diabetes diagnoses, Read codes should be combined with prescribing information as it was in this study [11, 12].

Outcomes

People with T1D and controls were followed from their index date up to the date of death, the end of data collection, the end of the study period, or the date of the fracture (for every fracture site), whichever came first. Fractures were identified by Read codes and stratified by the following fracture sites:

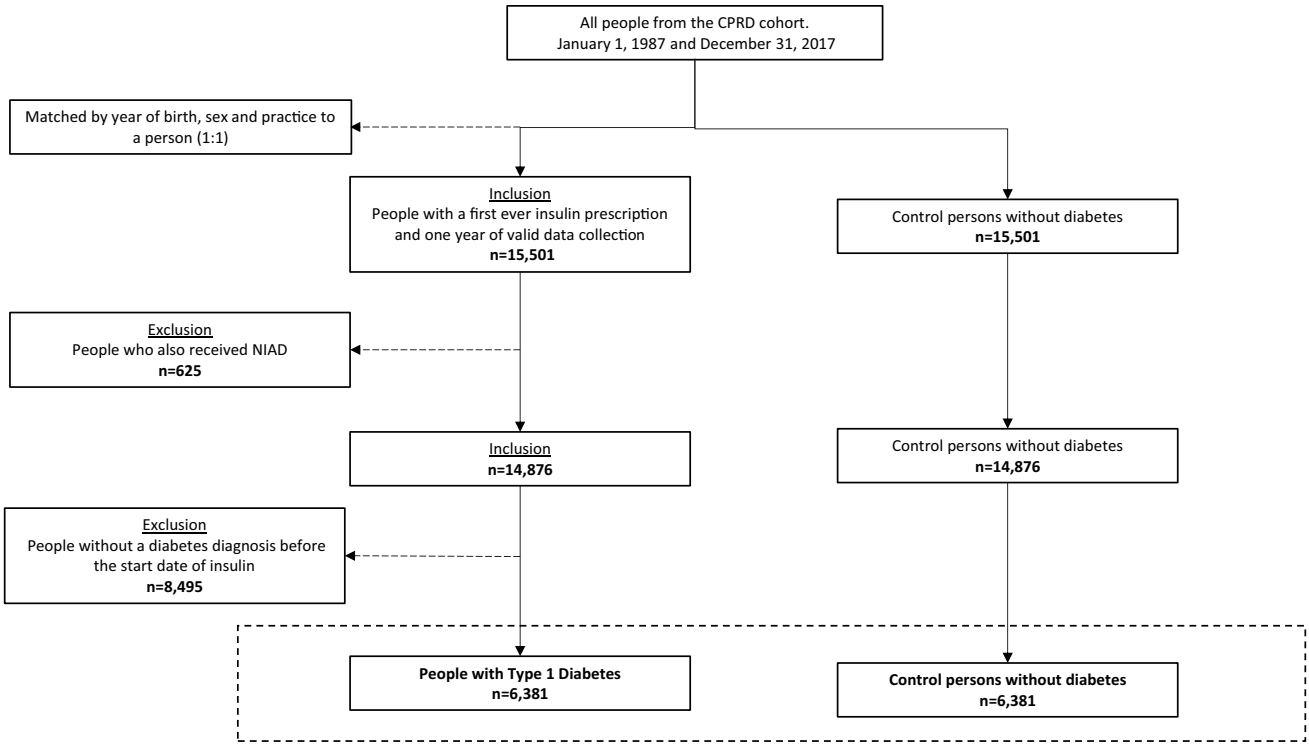

Fig. 1 Flow chart for the inclusion of people with T1D and their matched controls by sex and age and practice (1:1). The cohort was extracted from the UK CPRD data cohort. People with a first-ever prescription and 1 year of valid data collection ($n = 15{,}501$) were included. People with NIAD at the index date ($n = 625$) and people without a diabetes Read code before the start of treatment ($n = 8495$) were excluded. The final cohort comprised of 6381 people with T1D and their matched control (1:1). The median time between the first T1D Read code and first prescription was 15 days, with an IQR from 5 to 60 days. Abbreviations: T1D, type 1 diabetes; NIAD, non-insulin antidiabetic drugs; CPRD, Clinical Practice Research Datalink

ankle, carpal, clavicle, femur unspecified, foot, hip, humerus, other, patella, pelvis, radius/ulna, ribs, scapula, skull, tibia/fibula, and clinical symptomatic vertebral fractures. Additional outcomes included all fractures, which was the first incident fracture after the index date. A high level of validity of hip and vertebral fractures within the CPRD database has been reported previously [7].

In a sensitivity analysis, low-energy, high-energy, and fall-related fractures were studied. Probable low-energy fractures included MOFs, proximal hip, and spine fractures. Probable fall-related fractures included all forearm fractures, and probable high-energy fractures included all other fractures.

Demographics

The following characteristics were determined at baseline: age, sex, most recent BMI, smoking status, and alcohol use.

Statistical analyses

Baseline characteristics were presented with a mean (standard deviation (SD)) or median (interquartile range (IQR)) in case continuous data and categorical data were expressed as numbers (proportion).

Fracture site incidence rates (IRs) were calculated by dividing the number of fractures (per fracture site) by the total number of person-years at risk and presented per 1000 person-years (PYs). In addition, a Poisson model with Wald confidence limits was used to calculate the incidence rate ratios (IRRs) and 95% confidence intervals (CI95%). Furthermore, the analysis was stratified by fracture site and sex.

Furthermore, in a sensitivity analysis, we stratified the analysis by age < 20 and ≥ 20 years and high/low-energy

and fall-related fractures. In another sensitivity analysis, we also adjusted our results for BMI, smoking, and alcohol and tested whether the adjusted results differed significantly from the original results [13].

All statistical analyses were performed in SAS 9.4. The significance level was set at a *p*-value of less than 0.05 for two-sided testing.

Table 1 Baseline characteristics of patients with T1D and their matched controls

	People with T1D		Controls without diabetes	
	n = 6381	%	*n* = 6381	%
Mean follow-up time (years, SD)	8.4	5.9	8.3	5.8
Time to fracture (years, SD)	4.7	3.8	4.7	4.1
Women	2589	40.6	2589	40.6
Age				
Mean age (years, SD)	27.6	20.6	27.6	20.6
< 20	3100	48.6	3100	48.6
20–29	797	12.5	797	12.5
30–39 years	788	12.3	788	12.3
40–49 years	596	9.3	596	9.3
50–59 years	449	7.0	449	7.0
60–69 years	350	5.5	350	5.5
70–79 years	220	3.4	220	3.4
80 + years	81	1.3	81	1.3
BMI				
Mean BMI (kg/m^2, SD)	23.7	5.8	25.2	6.1
< 20.0 kg/m^2	1565	24.5	639	10.0
20.0–24.9 kg/m^2	2013	31.5	1329	20.8
25.0–29.9 kg/m^2	1245	19.5	1037	16.3
30.0–34.9 kg/m^2	489	7.7	427	6.7
≥ 35.0 kg/m^2	226	3.5	203	3.2
Missing	843	13.2	2746	43.0
Smoking status				
Never	2995	46.9	2573	40.3
Past	885	13.9	776	12.2
Current	1354	21.2	1191	18.7
Missing	1147	18.0	1841	28.9
Alcohol use				
No	1166	18.3	627	9.8
Yes	2786	43.7	2444	38.3
Missing	2429	38.1	3310	51.9

Abbreviations: *T1D*, type 1 diabetes; *BMI*, body mass index; *SD*, standard deviation

Results

Table 1 shows the baseline characteristics of people with T1D and the matched controls at the index date (both $n = 6381$). The cohorts had in general similar demographics, with a proportion of women of 40.6%, a mean age of 27.6 years and approximately half of the people were < 20 years of age (48.6%) in both groups. The mean duration of follow-up was 8.4 years (in total 53,600 person-years) in the T1D cohort and 8.3 years (in total 52,935 person-years) in the control cohort. The mean BMI was lower in the T1D cohort and was on average 23.7 kg/m^2 compared to 25.2 kg/m^2 in the control group. Furthermore, the proportion of people with T1D with a BMI < 20 kg/m^2 was 2.5-fold higher than the control group (24.5% versus 10.0%).

Figure 2 shows a forest plot of the IRs and IRRs of any fracture and different fracture sites in people with T1D versus controls. People with T1D had a significantly overall higher incidence for any fracture compared to controls (13.8 and 10.0 per 1000 PYs, respectively), with an IRR of 1.39 (CI95%: 1.24–1.55). Furthermore, the IRRs were higher for several fracture sites including carpal (1.41 (CI95%: 1.14–1.75)), clavicle (2.10 (CI95%: 1.18–3.74)), foot (1.70 (CI95%: 1.23–2.36)), humerus (1.46 (CI95%: 1.04–2.05)) and tibia/fibula (1.67 (CI95%: 1.08–2.59)). The IRs of fractures at the other fracture sites were not statistically significantly different in people with T1D compared to controls, none of the fracture sites studied displayed lower fracture rates in people with T1D as compared to controls.

Table 2 shows the IRs and IRRs of fractures for men or women with and without T1D. Higher IRs of fractures were seen in women at the ankle (IRR 2.25 (CI95%: 1.10–4.56)) and foot (IRR 2.11 (CI95%: 1.27–3.50)). Among men, higher fracture incidence risk was seen for carpal (IRR 1.45 (CI95%: 1.14–1.86)), clavicle (IRR 2.13 (CI95%: CI95%: 1.13–4.02)), and humerus fractures (IRR 1.77 (CI95%: 1.10–2.83).

Table 3 shows the IRs and IRRs for different fracture sites of our sensitivity analysis, where we stratified by age (< 20 and ≥ 20 years). Among people with T1D aged < 20 years higher, IRs were seen for carpal (IRR 1.32 (CI95%: 1.01–1.73)), foot (IRR 1.71 (CI95%: 1.05–2.78)), and humerus fractures (IRR 1.86 (CI95%: 1.14–3.04)) as compared to people without T1D aged < 20 years. Among people with T1D aged ≥ 20 years, higher IRs were seen for carpal (IRR 1.52 (CI95%: 1.06–2.18)), clavicle (IRR 3.09 (CI95%: 1.23–7.79)), foot (IRR 1.71 (CI95%: 1.10–2.65)), and radius/ulna fractures (IRR 1.63 (CI95%: 1.07–2.48)).

Table 4 shows the crude IRRs versus BMI, smoking, and alcohol adjusted IRRs for people with and without

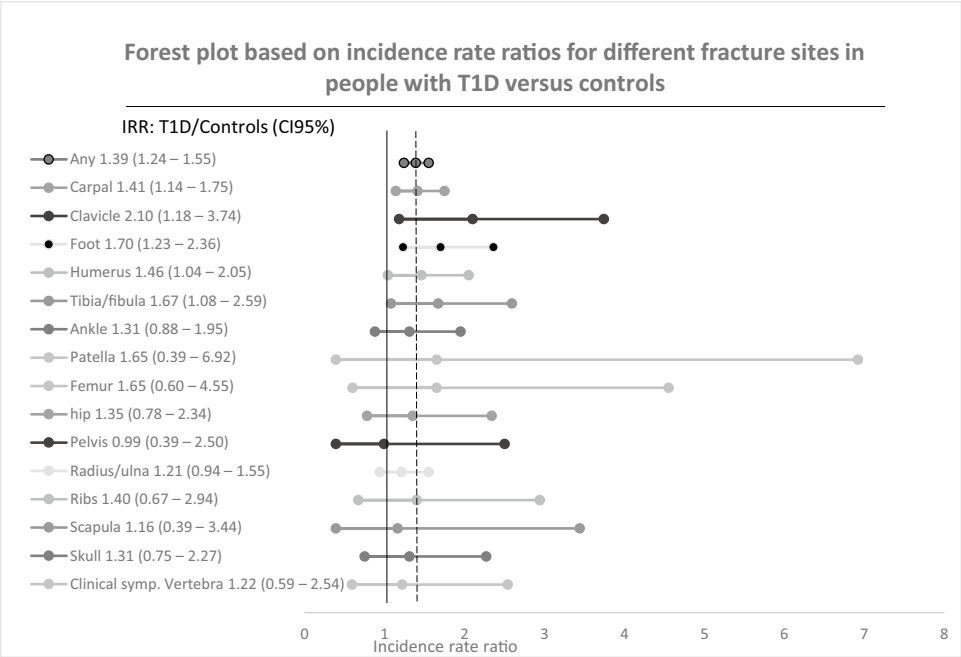

Fig. 2 Abbreviations: T1D, type 1 diabetes; IRR, incidence rate ratios

T1D at different fracture sites. The adjusted IRRs were slightly higher than the crude IRRs for all fracture sites except for the foot, which was slightly lower. The adjusted IRR was only significantly higher for any fractures (IRR-crude/IRRBMI 1.06 (CI95%: 1.01–1.12)).

Table 5 shows another sensitivity analysis of different IRRs for probable low- and high-energy and fall-related fractures in people with and without T1D. High-energy fractures were higher among people with T1D compared with controls ((IRR 1.43 (CI95%: 1.27–1.62)) whereas low-energy fractures and fall-related were not.

Discussion

In this study, we examined the incidence of fractures according to fracture sites in people with and without T1D. The overall incidence of fractures was higher in people with T1D, and the IRs varied according to the fracture site, which offered an insight into a potential different fracture pattern for people with T1D compared to people without T1D. In general, the incidence of any fracture in this study was lower compared with other studies, as a prior meta-analysis showed an increased RR of any fracture with T1D of 3.16 (CI95%: 1.51–6.63) [4]. However, in these studies, a relatively long disease duration, a mix between T1D and T2D types, prevalent and incident cases of diabetes, are regularly seen. Furthermore, people with T1D included from the UK CRPD cohort in this study were younger, had shorter disease duration, and probably limited diabetic complications, which could explain the lower incidences of different fracture sites compared to previous studies. Therefore, to gain additional insight into the complex matter of diabetic bone disease, this study aimed to describe fracture patterns in people with newly treated T1D.

Fracture pattern and the pathogenesis of different fractures sites

In this study, the incidence of different fracture sites was significantly higher at the carpal, foot, humerus, tibia/fibula, and clavicle in people with newly treated T1D. These fracture types are similar to other studies, as a recent meta-analysis showed a higher incidence of low-energy fractures at the distal forearm, wrist/hand, and proximal humerus in people with diabetes (RR 1.5 (CI95%: 1.1–1.8)) [2]. However, no available results from this study distinguished between people with T1D or T2D, diabetes duration, or fracture pattern. Furthermore, another meta-analysis on T1D and T2D and the risk of fractures at specific sites found an increased risk of fractures at the upper arm (RR 1.47 (CI95%: 1.02–2.10)) and ankle (RR 1.24 (CI95%: 1.10–1.4)) [1]. Though, in that study, people with T1D had a greater risk of total (RR: 1.24; CI95%: 1.08 to 1.41; $p = 0.002$), hip (RR: 3.43; CI95%: 2.27 to 5.17; $p < 0.001$), and ankle fractures (RR: 1.71; CI95%: 1.06 to 2.78; $p = 0.029$) compared to people with T2D. Fractures at different sites may have different pathogenesis and causality and the link to T1D differs per fracture site which may be due to several factors such as bone fragility, age, diabetes duration, falls, body composition, diabetic complications, and medication.

Table 2 The incidence rates and incidence rate ratios for different fracture sites in men and women with T1D versus men and women without T1D

Fracture site	Men with T1D ($n=3792$)		Men without T1D ($n=3792$)		IRR T1D/controls (CI95%)	Women with T1D ($n=2589$)		Women without T1D ($n=2589$)		IRR T1D/controls (CI95%)
	Number of fractures	IR (/1000 PYs)	Number of fractures	IR (/1000 PYs)		Number of fractures	IR (/1000 PYs)	Number of fractures	IR (/1000 PYs)	
Any	470	15.0	336	10.8	**1.39 (1.21–1.60)**	268	12.2	192	8.8	**1.38 (1.15–1.66)**
Ankle	32	1.0	32	1.0	0.99 (0.61–1.62)	25	1.1	11	0.5	**2.25 (1.10–4.56)**
Carpal	155	4.9	106	3.4	**1.45 (1.14–1.86)**	47	2.1	36	1.7	1.29 (0.84–1.99)
Clavicle	30	1.0	14	0.4	**2.13 (1.13–4.02)**	6	0.3	<6	0.1	1.98 (0.49–7.90)
Femur unspecified	<6	0.1	<6	0.1	0.99 (0.25–3.98)	6	0.3	<6	0.1	2.96 (0.60–14.68)
Foot	51	1.6	35	1.1	1.45 (0.94–2.23)	47	2.1	22	1.0	**2.11 (1.27–3.50)**
Hip	12	0.4	<6	0.1	2.98 (0.96–9.25)	18	0.8	18	0.8	0.99 (0.51–1.90)
Humerus	48	1.5	27	0.9	**1.77 (1.10–2.83)**	36	1.6	30	1.4	1.19 (0.73–1.92)
Patella	<6	0.1	<6	0.1	1.99 (0.36–10.86)	<6	0.0	<6	0.0	0.99 (0.06–15.79)
Pelvis	<6	0.1	<6	0.1	0.66 (0.11–3.97)	7	0.3	6	0.3	1.15 (0.39–3.43)
Radius/ulna	75	2.4	62	2.0	1.20 (0.86–1.68)	60	2.7	49	2.2	1.21 (0.83–1.76)
Ribs	10	0.3	10	0.3	0.99 (0.41–2.39)	7	0.3	<6	0.1	3.46 (0.72–16.64)
Scapula	<6	0.1	<6	0.1	0.99 (0.14–7.06)	<6	0.2	<6	0.2	1.23 (0.33–4.60)
Skull	26	0.8	20	0.6	1.29 (0.72–2.32)	<6	0.1	<6	0.1	1.48 (0.25–8.87)
Tibia/fibula	36	1.1	23	0.7	1.56 (0.92–2.63)	18	0.8	9	0.4	1.98 (0.89–4.40)
Clinically symptomatic vertebrae	7	0.2	7	0.2	0.99 (0.35–2.83)	9	0.4	6	0.3	1.48 (0.53–4.16)

Abbreviations: *T1D*, type 1 diabetes; *IR*, incidence rates; *RR*, incidence rate ratios

Table 3 The incidence rates and incidence rate ratios for different fracture sites in people age < 20 years and age ≥ 20 years with T1D versus people without T1D

Fracture type	Age < 20 years				IRR T1D/controls (CI95%)	Age ≥ 20 years				IRR: T1D/controls (CI95%)
	People with T1D (*n* = 3100)		People without T1D (*n* = 3100)			People with T1D (*n* = 3281)		People without T1D (*n* = 3281)		
	Number of fractures	IR (/1000 PYs)	Number of fractures	IR (/1000 PYs)		Number of fractures	IR (/1000 PYs)	Number of fractures	IR (/1000 PYs)	
Any	383	15.2	286	12.0	**1.27 (1.09–1.48)**	355	12.6	242	8.3	**1.51 (1.28–1.78)**
Ankle	25	1.0	19	0.8	1.25 (0.69–2.27)	32	1.1	24	0.8	1.37 (0.81–2.33)
Carpal	128	5.1	92	3.8	**1.32 (1.01–1.73)**	74	2.6	50	1.7	**1.52 (1.06–2.18)**
Clavicle	18	0.7	11	0.5	1.55 (0.73–3.29)	18	0.6	6	0.2	**3.09 (1.23–7.79)**
Femur unspecified	< 6	0.2	< 6	0.1	1.26 (0.28–5.65)	6	0.2	< 6	0.1	2.06 (0.52–8.24)
Foot	45	1.8	25	1.0	**1.71 (1.05–2.78)**	53	1.9	32	1.1	**1.71 (1.10–2.65)**
Hip	< 6	0.0	< 6	0.0	0.95 (0.06–15.16)	29	1.0	21	0.7	1.42 (0.81–2.49)
Humerus	47	1.9	24	1.0	**1.86 (1.14–3.04)**	37	1.3	33	1.1	1.15 (0.72–1.85)
Patella	< 6	0.0	< 6	0.0	0.95 (0.06–15.16)	< 6	0.1	< 6	0.1	2.06 (0.38–11.25)
Pelvis	< 6	0.1	0	N/A	########	7	0.2	9	0.3	0.80 (0.30–2.15)
Radius/ulna	78	3.1	75	3.1	0.99 (0.72–1.35)	57	2.0	36	1.2	**1.63 (1.07–2.48)**
Ribs	< 6	0.1	< 6	0.0	1.90 (0.17–20.92)	15	0.5	11	0.4	1.40 (0.65–3.06)
Scapula	< 6	0.1	< 6	0.0	2.85 (0.30–27.36)	< 6	0.1	< 6	0.2	0.82 (0.22–3.07)
Skull	19	0.8	12	0.5	1.50 (0.73–3.09)	10	0.4	10	0.3	1.03 (0.43–2.47)
Tibia/fibula	29	1.2	17	0.7	1.62 (0.89–2.94)	25	0.9	15	0.5	1.72 (0.91–3.26)
Clinically symptomatic vertebrae	< 6	0.1	< 6	0.2	0.47 (0.09–2.59)	14	0.5	9	0.3	1.60 (0.69–3.70)

Abbreviations: *T1D*, type 1 diabetes; *IR*, incidence rates; *IRR*, incidence rate ratios; *CI*, confidence interval

Table 4 Crude incidences rate ratios versus BMI, smoking, and alcohol adjusted incidence rate ratios and test of difference

Fracture type	Crude IRR IRR T1D/controls (CI95%)	Adjusted IRR IRR T1D/controls (CI95%)	Test for sig. difference IRRcrude/IRRadj (CI95%)
Any	**1.39 (1.24–1.55)**	**1.45 (1.28–1.64)**	**1.06 (1.01–1.12)**
MOF	**1.27 (1.05–1.54)**	**1.27 (1.03–1.56)**	1.01 (0.93–1.10)
Ankle	1.31 (0.88–1.95)	1.33 (0.87–2.04)	1.04 (0.89–1.21)
Carpal	**1.41 (1.14–1.75)**	**1.46 (1.15–1.85)**	1.05 (0.95–1.17)
Clavicle	**2.10 (1.18–3.78)**	**2.27 (1.20–4.27)**	1.09 (0.84–1.42)
Femur unspecified	1.65 (0.60–4.55)	2.02 (0.67–6.11)	1.26 (0.78–2.05)
Foot	**1.70 (1.23–2.36)**	**1.52 (1.08–2.15)**	0.91 (0.82–1.02)
Hip	1.35 (0.78–2.34	1.34 (0.75–2.39)	1.00 (0.84–1.20)
Humerus	**1.46 (1.04–20.5**)	**1.47 (1.02–2.12)**	1.02 (0.88–1.18)
Patella	1.65 (0.39–6.92)	1.75 (0.38–8.03)	1.08 (0.63–1.86)
Pelvis	0.99 (0.39–2.50)	0.86 (0.32–2.29)	0.88 (0.66–1.18)
Radius/ulna	1.21 (0.94–1.55)	1.20 (0.91–1.59)	1.01 (0.90–1.14)
Ribs	1.40 (0.67–2.94)	1.19 (0.56–2.54)	0.88 (0.72–1.07)
Scapula	1.16 (0.39–3.44)	1.07 (0.34–3.40)	0.95 (0.67–1.34)
Skull	1.31 (0.75–2.27)	1.74 (0.93–3.28)	**1.38 (1.00–1.89)**
Tibia/fibula	**1.67 (1.08–2.59)**	**1.83 (1.12–2.98)**	1.11 (0.90–1.38)
Clinical symptomatic vertebrae	1.22 (0.59–2.54)	1.05 (0.49–2.25)	0.87 (0.69–1.08)

Abbreviations: *T1D*, type 1 diabetes; *IR*, incidence rates; *IRR*, incidence rate ratios; *CI*, confidence interval; *BMI*, body mass index

Table 5 Incidence rate ratios for fractures in people with and without T1D divided into probable low-, high-energy, and fall-related fractures

Fracture type	People with T1D ($n=6381$)		People without T1D ($n=6381$)		IRR T1D/controls (CI95%)
	Number of fractures	IR (/1000 PYs)	Number of fractures	IR (/1000 PYs)	
Probable low-energy fractures	41	0.8	37	0.7	1.10 (0.70–1.71)
Probable high-energy fractures	631	11.8	437	8.3	**1.43 (1.27–1.62)**
Probable fall-related fractures	135	2.5	111	2.1	1.21 (0.94–1.55)
Men	Men	Men	IRR (T1D men control men)		
Probable low-energy fractures	14	0.4	14	0.4	0.99 (0.47–2.09)
Probable high-energy fractures	411	13.1	290	9.3	**1.41 (1.21–1.64)**
Probable fall-related fractures	75	2.4	62	2.0	1.20 (0.86–1.68)
Women	Women	Women	IRR (T1D women control women)		
Probable low-energy fractures	27	1.2	23	1.1	1.16 (0.66–2.02)
Probably high-energy fractures	220	10.0	147	6.7	**1.48 (1.20–1.82)**
Probable fall-related fractures	60	2.7	49	2.2	1.21 (0.83–1.76)

Abbreviations: *T1D*, type 1 diabetes; *IR*, incidence rates; *IRR*, incidence rate ratios; *CI*, confidence interval

Bone mineral density (BMD) measured by dual-energy x-ray absorptiometry (DXA) is diagnostic for osteoporosis and predicts fracture risk [14]. However, people with T1D have a lower BMD compared to people without T1D [15–17]. The lower BMD does not fully explain the observed proportion of fractures seen in people with T1D [18]. Hence, BMD cannot solely explain the increased fracture burden in T1D. Newer studies have suggested that people with T1D may also have an increased bone fragility from decreased bone quality, which partly explains the increased risk of fractures [19–21].

Clavicle, forearm, and upper arm fractures are indicative of fall-related and high-energy traumatic fracture, whereas spine and hip fractures are more indicative of

decreased bone biomechanical competence (low-energy and osteoporotic fractures). In this study, people with T1D were included at the onset of the disease, which diminishes the likelihood of fractures due to diabetic complications, increased bone fragility, and low BMD. Instead, it favors fall-related and high-energy traumatic distal fractures due to, e.g., insulin treatment and rapid changes in body composition. Hence, another fracture pattern should be considered at the onset of T1D compared to later stages of T1D. Over time, the fracture pattern probably changes as the diabetes duration progresses, which later results in increased bone fragility and low-energy MOFs.

Weight loss often occurs in people with T1D, especially before diagnosis, then followed by a period of weight gain in the later management of the disease with insulin [22, 23]. After the start of insulin treatment, at least some weight is regained; still, the BMI/weight can be relatively low. In this study, the BMI adjusted IRRs were slightly higher than the crude IRRs for all fracture sites except for the foot, which was slightly lower. A recent meta-analysis by De Laet et al. showed that much of the fracture risk conveyed by BMI was in fact mediated by BMD [24]. Hence, at the onset of T1D, BMD should be similar in people with T1D compared with the general population. People with T1D are often underweight compared to their pears at the time of their diagnosis, which corresponds to our study findings. In general, being underweight is thought to increase the risk of falls and fractures, due to sarcopenia, a low BMD, fatigue, malnutrition, and less soft tissue padding [25, 26]. In addition, hypoglycemia related to insulin treatment in people with T1D is associated with an increased risk of fractures [27]. Weight loss and under insulin treatment can in some people add to the risk of sarcopenia in the years after the diagnosis [28].

Skeletal maturity and peak height are normally reached around age 20 and peak BMD is attained between age 20 and 30. People with T1D are often diagnosed at a young age, which results in a lower peak BMD, an earlier risk of developing osteoporosis, a longer diabetes duration, and a higher risk of developing complications that require pharmacological treatment [29]. Therefore, the younger age in people with T1D may be associated with another falling and fracture pattern (i.e., a higher proportion of accidental falls and high-energy fractures) compared to older people diagnosed with T1D above the age of 60 [30, 31]. A recent study showed an increased risk of falls in young people with T1D compared with people of the same age group without diabetes and suggested an increased risk of a distal injury pattern [31]. The increased risk of falls also increased the risk of injuries and accidental fractures. In this study, similar results were shown in a sensitivity analysis as probable high-energy fracture types at the carpal, foot, and humerus were higher in people with T1D younger than 20 years of age.

Fractures that involve the carpal bones account for approximately 18% of hand fractures, and scaphoid fractures account for 80% of carpal bone fractures [32, 33]. A scaphoid fracture usually occurs due to a fall onto an outstretched hand, with a full impact of the body weight when landing on the palm of the hand. Fractures at the foot are commonly caused by repetitive stress, falls, twisting, or the direct impact of a foot against a hard object [34]. The majority of ankle fractures are caused by low-energy trauma [35]. Stress fractures of the foot are common and occur in time due to an excessive overload of the bone [36]. Most clavicle fractures occur when a person falls onto an outstretched arm or horizontally on the shoulder [37, 38]. These fracture types are a combination of different factors as osteoporosis, bone biomechanical properties, bone stress, low-energy trauma, accidental fractures, and a different falling pattern [39]. Consequently, another pattern of incidence of fractures could to some extent be explained by the different changes in BMI, body composition, BMD, or diabetic complications.

Hence, the combination of T1D, osteoporosis with a low BMD and a decreased bone quality, altered body composition, different types of falls, and increased risk of falls could contribute to the increased proportion of distal fractures, which probably vary over time, among different age groups and in disease duration. In general, the younger people with T1D presumably fracture directly from falling and indirectly from being underweight, whereas the elderly with T1D and a longer disease duration probably also fracture due to a lower BMD.

Strengths

This study had several advantages for describing the incidence of fractures in people with T1D. First, the large study cohort from the CPRD GOLD database allowed for population-based estimates of incidences and characterization of fracture patterns in T1D. Second, people with T1D were included at the time of their first treatment, which allowed for descriptive analyses of fracture patterns in newly treated people with T1D. Furthermore, the period until the diagnosis of T1D is often short and with a rapid and acute debut [40]. Hence, the estimated duration of disease and time of diagnosis is relatively accurate in people with T1D. Secondly, the matched control group represented the general population, which allowed us to make robust fracture incidence risk estimations. Finally, we included people with T1D in a broad time window between January 1, 1987, and December 31, 2017. In this timespan, the management of T1D with insulin has been consistent with only minor changes. This makes the people similar in the complete study period and minimizes the risk of misclassification and miscoding.

Limitations

Several limitations should be considered in this study. First, a variety of missing values of BMI, smoking, and alcohol was reported. The proportion of missing BMI recordings were slightly higher in the control group compared to people with T1D. Lifestyle variables as BMI are in general poorly recorded in the CPRD database due to a lack of regulation and requirement of maintenance of these data. However, this was improved in the year 2004, when the Quality of Outcomes (QOF) framework was introduced [41]. From 2004 and forward, the GPs are paid to record certain lab values, lifestyle variables, or certain diseases. However, this did not influence the results directly as only minor changes were observed in the adjusted analysis [42]. Second, this was a descriptive study, and no associations could be studied. We included people with T1D based on diagnosis and insulin treatment without any NIAD. Misclassification of people with T2D could have occurred in case of treatment with insulin in monotherapy due to the conditioning of the disease. However, few of these cases exist and would probably have underestimated the results. Third, due to the use of Read codes, no data exists on the origin of fractures (spontaneous and asymptomatic vertebral fractures were not included in this study) or BMD. However, the main aim of this study was to determine the pattern of incident fractures according to various fracture sites in people with T1D from a descriptive perspective instead of risk estimation of factors associated with fracture risk. Furthermore, CPRD data is highly valuable as a high level of validity of hip and vertebral fractures within the database has been reported previously [43]. The positive predictive value for vertebral fractures in CPRD was reported to be 88.1% (81.3–93.0%) [44]. Other types of fractures have not yet been validated. Although, the registration of fractures would expectably be similar among people with T1D and people without. However, vertebral fractures identified from symptomatic back pain could be higher due to detection bias as people with T1D have more visits to the physician, but this was not the scope of this article. Fourth, no information on BMD or bone quality assessment was available in this study. However, at the time of the T1D diagnosis, BMD is probably similar compared with the general population. Hence, the distribution between osteoporotic/low-energy and high-energy/fall-related fractures in newly diagnosed people with T1D probably changes over time. Fracture patterns are not static but develop over time as diabetes progresses.

Conclusion

In conclusion, this study showed that beyond a higher overall fracture incidence, people with newly treated T1D also have a higher incidence of probable high-energy fractures at several sites with predominantly higher IRs at distal fracture sites such as carpal, foot, and ankle. Adjusted results did not change the outcome of a distal fracture pattern. It must be further studied which fractures attributed to the higher IRs at specific sites to better understand the underlying mechanisms and to which extent diabetes duration affects the fracture pattern. This is a door opening on the topic of diabetes and fractures and a call for more rigorous and robust research to better understand any potential benefits and harms related to people with T1D and fracture patterns.

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Data availability Data that was obtained from the Clinical Practice Research Datalink (CPRD) GOLD is not available for review.

Code availability Data that was obtained from the Clinical Practice Research Datalink (CPRD) GOLD is not available for review.

Declarations

Ethics approval This research was in accordance with the principles of the Helsinki declaration and its later amendments or comparable ethical standards. Our study protocol (Protocol 18_275R) was approved by the Independent Scientific Advisory Committee (ISAC) for Medicines and Healthcare products Regulatory Agency (MHRA) database research.

Consent to participate This study was a retrospective study and all data on patients are stored anonymously in the Clinical Practice Research Datalink (CPRD). For this type of study, formal consent is not required.

Consent for publication This study was a retrospective study and all data on patients are stored anonymously in the Clinical Practice Research Datalink (CPRD). For this type of study, formal consent is not required.

Conflicts of interest Peter Vestergaard is head of research in the Steno Diabetes Center North Jutland sponsored by the Novo Nordisk Foundation. Joop van den Bergh is involved in the research that is sponsored by Amgen, Eli Lilly, and UCB. The other authors, Nicklas Rasmussen, Cindy Sarodnik, Sandrine Bours, Nicolaas Schaper, Patrick Souverein, Morten Jensen, and Johanna Driessen, declare that they have no conflict of interest.

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