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A Nationwide Register-Based Cohort Study

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ABSTRACT

Osteogenesis imperfecta (OI) is a hereditary, clinically heterogeneous, connective tissue disorder. The population prevalence of OI in Denmark is 10.6 in 100,000. A hallmark of the disease is frequent fractures that are often precipitated by minimal trauma. The aim of the current study was to compare the fracture rates across the lifespan of patients with OI with that of a reference population from the general population. The present study was a Danish nationwide, population-based, cohort study using register data. We identified 644 (55.6% females) patients in the OI cohort through the Danish National Patient Register and 3361 (55.2% females) persons, randomly selected from the Civil Registry System. A total of 416 patients with OI experienced a total of 1566 fractures during the observation period of median 17.9 years (interquartile range [IQR], 12.4 to 18.0 years), summing to 10137 person years. In comparison, 709 persons in the reference population experienced a total of 1018 fractures during follow-up. Both male and female patients with OI had an increased fracture rate throughout their life. The fracture rate ratio for participants aged 0 to 19 years was 10.7, for participants aged 20 to 54 years 17.2, and for participants aged 55 years and over 4.1 when compared to the reference population. The highest fracture rate was seen in males with OI aged 0 to 19 years (257 fractures per 1000 person-years). The fractures appear to follow the same pattern as in the general population, with a peak during the toddler and adolescent years (incidence rate [IR] 233.9 per 1000 person years), fewer fractures during adulthood (IR 84.5 per 1000 person years), and increased fracture rates in older women (IR 111.9 per 1000 person years). This is the largest register-based nationwide study on the fracture epidemiology of patients with OI. The risk of fractures seems largest in the childhood and adolescent years, and the relative risk of fracture declines with age in patients with OI compared to the general population. © 2016 American Society for Bone and Mineral Research.

KEY WORDS: OSTEOGENESIS IMPERFECTA; FRACTURE RATES; RARE BONE DISEASES; REGISTER-BASED STUDIES; EPIDEMIOLOGY; COLLAGEN

Introduction

Osteogenesis imperfecta (OI) is a hereditary, connective tissue disorder caused by mutations in the genes involved in the biosynthesis or post-transcription modification of collagen type 1.[1] The population prevalence of OI in Denmark has previously been shown to be 10.6 in 100,000.[2] The clinical severity of the disease varies from mild, with few or no signs of the disease, to perinatally lethal phenotypes.[3]

A hallmark of the disease is frequent fractures that are often precipitated by minimal trauma.[4] A British questionnaire study from 1984 comprising 45 women aged 60.5 ± 7.6 years of age

and 20 men aged 59.9 ± 10.9 years of age, showed a peak fracture rate of 1.6 per patient year in young men and 0.8 per patient year in young women, fewer fractures during adult life, and an increased fracture risk in women after menopause.[5] The study did not include a reference group and fractures were based on the patient's recollection. Other studies reporting fracture rates in patients with OI have used questionnaires, structured interviews, or patient chart review, but did not include a reference population.[6–8]

The unique personal identification number issued to all inhabitants of Denmark at birth or immigration enables individual-level record linkage between different health registries.[9] The Danish

National Patient Register (NPR) was established in 1977 and includes primary and supplementary diagnosis for all in-hospital contacts. Similarly, since 1995 all outpatient clinic and emergency visits have been included in this register.[10] NPR has a coverage above 99%, and the overall positive predictive value of a diagnosis in the register is above 95%.[11] Moreover, the Danish healthcare system is—with few minor exceptions that do not apply to fracture care—uniform, tax-financed, and covers all residents. Together, these conditions allow complete ascertainment and long-term follow-up of clinical conditions.[12]

Study objectives

The aim of the current study was to compare the fracture rates across the lifespan of patients with OI with that of the general population. We hypothesized that patients with OI would have a higher fracture rate than the reference population, but would have a similar fracture pattern throughout their life. Knowledge about fracture rates in patients with OI, under the current treatment regimen in Denmark, will aid the physicians' decisions in whom and how to treat patients with OI and furthermore give valuable information about what to expect from the current fracture prophylaxis regimes.

Patients and Methods

The study population is a subgroup of that described in Folkestad and colleagues (unpublished work). Mortality and causes of death in patients with osteogenesis imperfecta. A register-based national cohort study.

Study design

The present study is a nationwide, population-based, cohort study using register data from Denmark.

Data source

All data were supplied with encrypted personal identification numbers from the Statistics Denmark Division of Research Services Virtual Private Network (VPN) research servers (Project reference number: 704542). The Statistics Denmark is a government institution that provides statistics on both economic, social and health issues and administrates most of the Danish Health Registers.[12] Ethics committee approval was not required. The study was approved by the Danish Data Protection Agency. Analyses were conducted via VPN exclusively on deidentified microdata hosted with by Statistics Denmark with no access to subject names, social security numbers or other identifiers.

Study population

The patient cohort

All patients registered in the NPR (between January 1, 1977 and December 31, 2012) with a WHO International Classification of Diseases, 8th edition (ICD-8; 756.59) code or International Classification of Diseases, 10th edition (ICD-10; Q78.0) code for OI were included in the study.

The reference population

For every patient with OI, five persons, matched on gender and age (month and year of birth), were randomly selected from the background population using the Danish Civil Registration system. To limit the risk of misclassification bias of the reference population, patients could not be part of the reference population, and the persons in the reference population could not be first or second degree relatives to any of the patients.

Variables and data sources

Data on bone fractures were extracted from the NPR and included date of fracture and fracture site. The fracture groups and corresponding ICD-10 codes are shown in Table 1. Information on time of death was extracted from the Danish Register of Causes of Death. Information about migration was extracted from the Danish Civil Registration system. All data on the reference population and the OI cohort were extracted from the same data sources. Because the primary aim of the NPR is to facilitate managing of Danish healthcare services, a single event may be registered multiple times within a short period of time; eg, a fracture could be registered from the emergency room, the operating theater, and again from rehabilitation care.

Exposure and observation time

We counted all fractures occurring between January 1, 1995 and December 31, 2012 (the latest updated version of the NPR at the time of data extraction was July 27, 2014). A person was included in the cohort at January 1, 1995 if born prior to this date if still alive and living in Denmark at this date, at birth if born after 1995, or at the date of immigration to Denmark. Participants were excluded from the cohort as of the day they died, emigrated from Denmark, or the observation period ended.

Confounders and bias

Registration and classification bias of fractures in the NPR

Patients with OI are more likely to have complex fractures and to need more hospitalization and operative treatment for their

Table 1. ICD-10 Codes Used to Group Fractures

Fracture group	ICD-10 code	Fracture type
Spine fractures	S12	Cervical spine
	S220, S221	Thoracic spine
	S320	Lumbar spine
Upper arm	S422, S423, S424, S427, S428, S429	Humerus
	S420	Clavicle
	S421	Scapula
Forearm	S52	Forearm
Hip and pelvis	S720, S721, S722, S723	Hip
	S32 (excluding S320)	Pelvis
Femur	S724, S727, S728, S729	Femur
Lower leg and ankle	S82	Lower leg and ankle
Other fractures	S02	Head
	S222	Sternum
	S223, S224, S225	Ribs
	S62	Hand
	S92	Foot
	T02	Multiple body regions

fractures than participants in the reference population. Because only in-hospital care was registered in the period 1977 to 1995, patients treated as outpatients would not be registered during this time period. Thus, we avoided this possible bias by only including data from the NPR from 1995, where all hospital contacts were included in the register. Patients with OI could also have a higher frequency of complications and re-operations following a fracture than the reference population, thus artificially inflating the fracture rates. To limit possible bias, we introduced a 180-day "washout" period for each fracture, whereby any new fracture with the same ICD-10 code was ignored.

Fracture registration in the NPR does not differentiate left from right for fractures to the appendicular skeleton. Furthermore, fractures to the axial skeleton are only differentiated by lumbar, thoracic, and cervical fractures. This could result in exclusion of fractures to for example the left forearm, if a fracture had already been registered to the right forearm within the last 180 days. In patients with OI, where we would expect more frequent fractures than in the reference population, we risk under estimating the fracture rates. We could not correct for this possible bias.

We recognize that the typical immobilization period after a fracture is 40 to 60 days, and that the loss of bone and muscle mass seen during immobilization will increase the refracture rate shortly after the removal of a cast, which will result in under reporting of refractures. This is assumed to be lower than the risk of follow-up visit registrations with the same ICD fracture code during the first 180 days, which would result in inflation of the fracture rates in patients needing close follow-up after a fracture if the washout period was shorter than 180 days. Hence the fracture rates as reported here should be regarded as conservative.

Bisphosphonate treatment as a confounder

Since the late 1990s, patients with OI have been frequently treated with bisphosphonates.[13] This may lower their risk of fracture, although the effect has been questioned.[14,15] According to national guidelines, patients with OI treated with intravenous bisphosphonates should receive this at OI specialist centers, but hospital-administered drugs are not captured in the current prescription databases. The present study captures the fracture burden to patients with OI in Denmark given the current standard of care, which may or may not be lower than would be the case had the disease been allowed to take its natural course in all patients.

Fracture risk due to differences in age and gender

We have intentionally corrected for differences in fracture risk at different ages and between genders by matching the reference population to the OI cohort on age and gender.

Immortal time bias

To reduce the risk of immortal time bias (ie, the time during which a participant could suffer an event that would not be registered), we ended the observation period at the date of emigration. Patients experiencing fractures while travelling abroad would normally receive subsequent fracture care in Denmark and in most cases be captured in the registers.

Statistical analysis

All statistical analyses were done using Stata 14.1 (StataCorp, College Station, TX, USA).

Data are presented as mean $\pm$ SD or median (interquartile range [IQR] or range) as appropriate. Fracture rates (incidence rate [IR]) are presented as number of fractures per 1000 person years for each group and gender. We calculated the 95% confidence interval (CI) as IR $\pm$ (1.96 · IR/$\sqrt{\text{total number of fractures}}$). Incidence rate ratios (IRRs) between patients with OI and the reference population were considered significant if the 95% CI did not include the value 1. For illustrative purposes, we calculated the IR and 95% CI for fractures in 5-year age bands (Fig. 1, Supporting Table 1).

The association between OI (yes, no) and fracture rates adjusted for differences in gender and age was evaluated using a Poisson regression model with total number of fractures as the outcome variable, and logarithmic transformation of follow-up time within each age strata and calendar year as offset. Age groups were 0 to 19 years (to include fractures due to falls when toddlers and young children become more mobile, and the increased fracture risk during growth spurts in puberty and adolescents), 20 to 54 years (adult life), and 55 years and above (to include the increased fracture risk due to postmenopausal bone loss for women and age-related bone loss in men). The relatively large age bands were used to ensure sufficient events for statistical power to calculate the IRR between the OI cohort and the reference population. As we expected an interaction between age, gender, and OI, we introduced an three-way interaction term. We used the likelihood ratio test to identify statistically significant interactions, accepting a p value <0.05 as statistically significant. The independent variables in the final model were OI, age, gender, and the interaction term.

To control for any period effect, ie, the reduction in fracture rates caused by the introduction of bisphosphonates to treat patients at high risk of fracture, we included calendar year as an independent variable in the initial model. This variable was not significant, however, and was not included in the final model. We used Pearson's goodness-of-fit to evaluate model fit.

The analyses were stratified by the seven fracture diagnosis groups as described in Table 1. We ran individual models for each fracture group to calculate the IRR between patients with OI and the reference population of different fracture types over time.

We performed four sensitivity analyses to evaluate (1) the effect of the washout time for counting a new fracture at the same site—by removing the washout period from the NPR data; (2) the effect of the 180-day washout period—by using a 365-day washout instead; (3) the effect of including patients with only a referral diagnosis of OI registered in the NPR; and (4) the effect of suspected more severe phenotypes, defined as patients dying before the age of 10 years. We recognize that the majority of patients with moderate to severe phenotypes will live past the age of 10 years. A sensitivity analysis was performed as we assumed that patients who die before 10 years old would have the most severe phenotypes of OI and would theoretically have a much higher fracture rate than the general OI population.

Ethical considerations

The study was approved by the Danish Data Protection Agency. All data were deidentified by Statistics Denmark before being made accessible for analysis. The study was not eligible for ethics
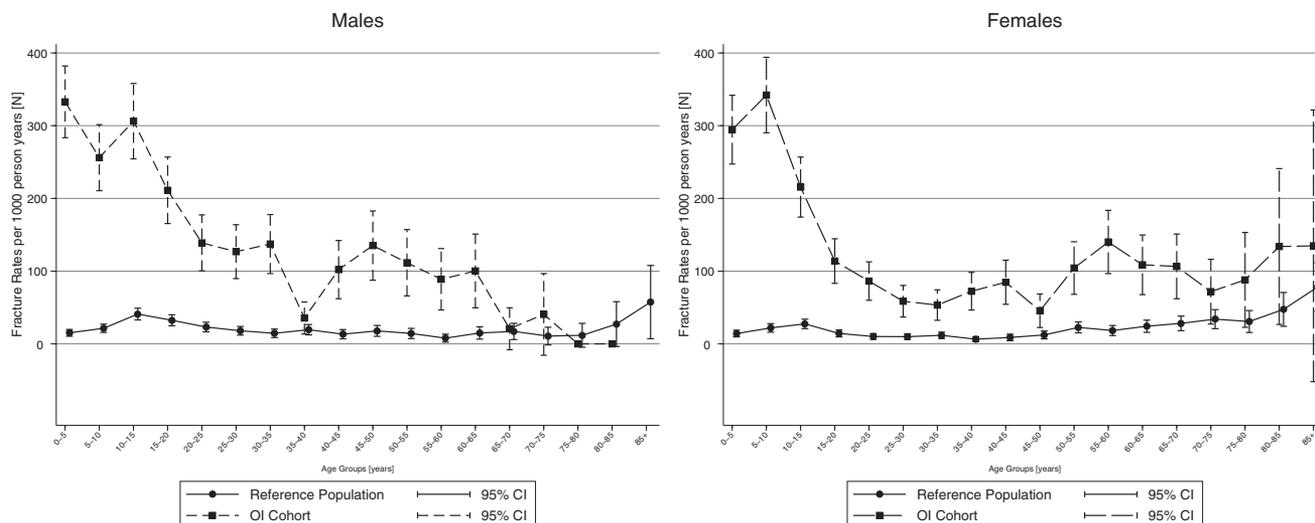
Fig. 1. Fracture rate in the OI cohort and the reference population by age, for males and females separately. Fracture rate is highest in the youngest patients with OI and then decreases during adult life. Especially in the reference population, the rate increases in women of postmenopausal age. The two groups were fully matched for age but shown here with a small offset on the *x* axis to provide space for confidence interval bars.

committee approval, nor was it a clinical trial. To avoid identification of confidential participant information we do not show results if the total number of events is lower than three.

Results

We identified 687 patients with OI from the NPR in 1977 to 2012, of whom 379 (55.2%) were females. Excluding all censored participants prior to 1995 (participants who had died or migrated prior to January 1, 1995), the OI cohort included 644 (55.6% females) patients and the reference population 3361 (55.2% females) persons for analysis (Table 2). During the period 2002 to 2013, 14 patients with median age 5.5 years (IQR, 2 to 12) were registered with a referral diagnosis of OI alone; ie, they did not have an outpatient or a hospital discharge OI diagnosis registered in the NPR. Six participants died before their 10th birthday during the observation period, with median age 0.2 years (range, 0 to 7.2). None of the reference population died in this age interval. The participants were followed for a median of 17.9 years (IQR, 12.6 to 18.0 years). Median age at the start of the observation was 15.0 years (range, 0 to 71 years) for the OI cohort and 15.0 years (range, 0 to 81 years) for the reference population.

Fracture rate in the OI cohort and the reference population

Figure 1 (and Supporting Table 1) shows the fracture rates for the OI cohort and the reference population in 5-year age groups. Of the 644 patients with OI, 416 experienced a total of 1566 fractures during the observation period. The median number of fractures was 1 per patient (range, 0 to 25 per patient), amounting to 0.15 fractures per person year. In the reference population, 709 persons experienced at least one fracture during the observation time, with a total of 1018 fractures. The median number of fractures was 0 per person (range, 0 to 9 per person). Comparing the patients with OI and the reference

population the fracture IRR was 8.1 (95% CI, 7.5 to 8.8). Analyzing the data according to three age groups, we found the fracture IRR for persons aged 0 to 19 years was 10.7, for persons aged 20 to 54 years was 6.2, and for persons aged 55 years and over was 4.1 (Table 3). The fracture rate was higher in postmenopausal women than in men over 55 years—this was the case for both patients with OI (IRR 1.6; 95% CI, 1.1 to 2.4) and for the reference population (IRR 2.1; 95% CI, 1.5 to 2.9). Among participants aged 55 years and over, women with OI had higher fracture rates than women in the reference population (IRR 8.0; 95% CI, 5.6 to 11.3), and men with OI had higher fracture rates than men in the reference population (IRR 4.9; 95% CI, 3.2 to 7.7).

Fracture sites

As shown in Table 4, the most frequent fracture sites in patients with OI were forearm, femur, and lower leg and ankle (see also Fig. 2 for females and Fig. 3 for males). Within the OI cohort, males aged 0 to 19 years had the highest rates of most fractures compared to middle-aged and older men. Among older (55+ years) patients with OI, women had a higher fracture rate than men of fractures in the upper arm, forearm, hip and pelvis, and lower leg and ankle. These fracture rates for older women with OI were higher than those for younger (20 to 55 years) women with OI. In the reference population, fracture rates for most fracture sites were highest for men and women aged 55 years and over.

Sensitivity analysis

The total number of fracture registrations in the NPR was higher when double registrations and readmissions were not excluded. The total number of fracture registrations in the NPR was 3441 in the OI cohort and 1772 in the reference population (IRR 7.9; 95% CI, 7.5 to 8.4). When a 365-day washout period was used instead of a 180-day period, the number of fracture registrations in the NPR was 980 in the OI cohort and 930 in the reference population (IRR 4.3; 95% CI, 4.0 to 4.8). No significant changes in

Table 2. Characteristics of the Patient Cohort With OI and the Reference Group From the General Danish Population

	OI cohort	Reference population
Number of participants, n	644	3361
Female participants, n, (%)	358 (56)	1854 (55)
Participants aged 0–20, n	416	2171
Participants aged 20–55, n	352	1802
Participants aged above 55, n	140	774
Total participation time (years)	10137	53328
Median observation time per individual (years)	17.9 (IQR, 12.4–18.0)	17.9 (IQR, 12.7–18.0)
Median age at end (years)	32.6 (IQR, 15.3–51.3)	32.2 (IQR, 16.0–52.5)
Total number of fractures, n	1566	1018

Because some of the participants could feature in more than one age strata, the numbers do not add to the total number of participants.
OI = osteogenesis imperfecta; IQR = interquartile range.

the IRR between the OI cohort and the reference population were seen when we excluded the 14 patients with only a referral diagnosis, or the six patients who died before the age of 10 years.

Discussion

In this register-based cohort study, male and female patients with OI had an increased fracture rate throughout their life, compared to the reference population. The highest fracture rate was seen in males with OI aged 0 to 19 years (257 fractures per 1000 person-years). Our study included 644 patients and appears to be the largest published population-based study aimed at evaluating fracture rates in patients with OI.

Throughout the observation period, the mean fracture rate in the OI cohort was 154.5 fractures per 1000 person years, or an annual rate of 0.15 per patient. In a Swedish study where fractures were determined from patients' medical charts, the annual fracture rate was 0.57 for patients with type I (n = 151, aged 22.4 ± 16.9 years), 3.83 for patients with type III (n = 29, aged 22.6 ± 18.7 years), and 1.33 for patients with type IV (n = 42, aged 19.6 ± 12.0 years).[8] A cross-sectional multicenter study of OI in North America that included 544 patients with a median age at inclusion at 12.6 years (range, 0 to 67 years) reported an average of 1.0 ± 3.0 fractures per individual in the year prior to enrolment.[7] Our data are more similar to a Norwegian population-based cohort study that included all known adult patients with OI, with a mean age of 44 ± 12 years (range, 25 to 83) at enrollment.[6] The authors reported an annual rate of 0.12 fractures per individual in the year prior to enrollment in the study.[6]

We acknowledge that our estimates of fracture rates may be conservative. This may be partly due to using the 180-day washout period before counting a fracture to the same anatomical site as a new fracture, and simultaneously not counting fractures to the contralateral anatomical site. This is a limitation to our study. However, the sensitivity analysis showed that even with no washout the IRR would be similar between the two groups. Patients with OI may have more frequent complications and reoperations than the reference population, and thus we may have inflated their fracture rates had we not stipulated a reasonable long washout period. Some fracture types are likely to be underreported in the registries, such as spinal fragility fractures that often do not result in radiographs or hospitalization and could even be asymptomatic in the short term. No data are available on the positive and negative predictive value of the NPR for symptomatic spine fractures. However, the register-based incidence of symptomatic spine fractures in Denmark in 2011 was 4.3 times lower than the incidence reported by the International Osteoporosis Foundation, which was based on radiographic data.[16] Furthermore, in a 1982 Danish study, 52 of 289 seventy-year-old women had experienced at least one spine crush fracture when evaluated by radiographs.[17] This is much higher than what we found via the Danish health registers. Vertebral fractures are frequent in patients with OI. In a study including 97 adult patients with OI using radiographs in the anteroposterior and lateral positions to evaluate the spine, 67% had at least one vertebral deformity,

Table 3. Comparison of Fracture Rates by Age Group in the OI cohort and the reference population

	OI cohort			Reference population			
	Fractures (n)	Person-years at risk	IR per 1000 person years (95% CI)	Fractures (n)	Person years at risk	IR per 1000 person years (95% CI)	IRR (95% CI)
All							
0–19 years	1078	4610	233.9 (219.9–247.8)	531	24265	21.9 (20.0–23.7)	10.7 (9.6–11.9)
20–54 years	338	3988	84.8 (75.7–93.8)	277	20329	13.6 (12.0–15.2)	6.2 (5.3–7.3)
55+ years	150	1540	97.4 (81.8–113.0)	210	8735	24.0 (20.8–27.3)	4.1 (3.3–5.0)
Females							
0–19 years	515	2421	212.7 (194.3–231.1)	219	12403	17.7 (15.3–20.0)	12.1 (10.3–14.1)
20–54 years	160	2351	68.1 (57.5–78.6)	134	11617	11.5 (9.6–13.5)	5.9 (4.7–7.4)
55+ years	114	1019	111.9 (91.3–132.4)	168	5745	29.2 (24.8–33.7)	8.0 (5.6–11.4)
Males							
0–19 years	563	2188	257.3 (236.0–278.5)	312	11862	26.3 (23.4–29.2)	9.8 (8.5–11.2)
20–54 years	178	1637	108.7 (92.8–124.7)	143	8712	16.4 (13.7–19.1)	6.6 (5.3–8.2)
55+ years	35	521	69.1 (46.6–91.7)	42	2988	14.1 (9.8–18.3)	4.9 (3.2–7.7)

Because some of the participants could feature in more than one age strata, the numbers do not add to the total number of participants.
OI = osteogenesis imperfecta; IR = incidence rate; IRR = incidence rate ratio (calculated using a Poisson regression model).

Table 4. Fracture Rates in the OI Cohort and Reference Population by Fracture Site and Age Group, for Men and Women Separately

	OI cohort			Reference population			
	Person years at risk	Fractures (*n*)	IR per 1000 person years (95% CI)	Person years at risk	Fractures (*n*)	IR per 1000 person years (95% CI)	IRR (95% CI)
Females							
Upper arm fractures							
0–19 years	2421	63	26.0 (19.6–32.5)	12403	25	2.0 (1.2–2.8)	12.9 (8.1–20.5)
20–54 years	2351	11	4.7 (1.9–7.4)	11617	15	1.29 (0.6–1.9)	3.6 (1.7–7.9)
55+ years	1019	19	18.7 (10.3–27.0)	5745	24	4.17(2.5–5.6)	4.5 (2.4–8.2)
Forearm fractures							
0–19 years	2421	125	51.6 (42.7–60.7)	12403	75	6.1 (4.7–7.4)	8.4 (6.3–11.4)
20–54 years	2351	25	10.6 (6.47–14.8)	11617	27	2.3 (1.5–3.2)	9.3 (4.6–18.9)
55+ years	1019	23	22.6 (13.3–31.8)	5745	48	8.3 (6.0–10.7)	5.7 (1.9–17.8)
Spine fractures							
0–19 years	2421	5	1.6 (0.5–2.6)	12403	4	0.3 (0.0–0.6)	6.4 (1.7–23.9)
20–54 years	2351	9	2.1 (0.3–3.9)	11617	—[a]	NA	NA
55+ years	1019	4	3.9 (0.1–7.8)	5745	9	1.6 (0.5–2.6)	2.5 (0.8–8.1)
Hip fractures							
0–19 years	2421	19	7.8 (4.3–11.4)	12403	—[a]	NA	NA
20–54 years	2351	8	3.4 (1.0–5.8)	11617	5	0.4 (0.1–0.8)	7.9 (2.6–24.2)
55+ years	1019	14	13.7 (6.5–20.9)	5745	26	4.52 (2.79–6.26)	3.4(1.6–5.8)
Femur fractures							
0–19 years	2421	86	35.52 (28.01–43.03)	12403	—[a]	NA	NA
20–54 years	2351	17	7.2 (3.8–10.7)	11617	—[a]	NA	NA
55+ years	1019	9	8.8 (3.1–14.6)	5745	18	1.7 (0.7–2.8)	5.1 (2.1–12.5)
Lower leg and ankle							
0–19 years	2421	89	36.8 (29.1–44.4)	12403	15	1.2 (0.6–1.8)	30.4 (17.6–52.5)
20–54 years	2351	26	11.1 (6.8–15.3)	11617	22	1.9 (1.1–2.7)	5.8 (3.3–10.3)
55+ years	1019	18	17.7 (9.5–25.8)	5745	14	2.4 (1.2–3.7)	7.3 (3.6–14.6)
Other fractures							
0–19 years	2421	128	52.9 (43.7–62.0)	12403	99	8.0 (6.4–9.6)	6.6 (3.6–5.6)
20–54 years	2351	64	27.2 (20.6–33.9)	11617	63	5.4 (4.1–6.8)	5.0 (3.6–7.1)
55+ years	1019	27	26.5 (16.5–36.5)	5745	37	6.4 (4.4–8.5)	4.1 (2.5–6.8)
Males							
Upper arm fractures							
0–19 years	2188	63	28.8 (21.7–35.9)	11862	37	3.1 (2.1–4.1)	9.2 (6.2–13.9)
20–54 years	1637	16	9.8 (5.0–14.6)	8712	17	2.0 (1.0–2.9)	5.0 (2.5–9.9)
55+years	521	6	11.5 (2.3–20.7)	2989	3	1.0 (–0.1 to 2.1)	11.5 (2.9–45.9)
Forearm fractures							
0–19 years	2188	109	49.8 (40.5–59.2)	11862	70	5.9 (4.5–7.3)	8.5 (6.4–11.4)
20–54 years	1637	21	12.8 (7.3–18.3)	8712	12	1.4 (0.6–2.2)	9.3 (4.6–18.9)
55+years	521	6	11.5 (2.3–20.7)	2989	6	2.0 (0.4–3.6)	5.7 (1.9–17.8)
Spine fractures							
0–19 years	2188	10	4.6 (1.7–7.4)	11862	3	0.3 (–0.3 to 0.5)	8.4 (6.3–11.4)

Table 4. (*Continued*)

	OI cohort			Reference population			
	Person years at risk	Fractures (n)	IR per 1000 person years (95% CI)	Person years at risk	Fractures (n)	IR per 1000 person years (95% CI)	IRR (95% CI)
20–54 years	1637	5	3.1 (0.4–5.7)	8712	3	0.3 (–0.1 to 0.7)	9.3 (4.6–18.9)
55+years	521	3	5.8 (−0.8–12.3)	2989	—a	NA	NA
Hip fractures							
0–19 years	2188	20	9.1 (5.1–13.1)	11862	—a	NA	NA
20–54 years	1637	9	5.5 (1.9–9.1)	8712	2	0.2 (–0.1 to 0.5)	24.0 (5.2–110.9)
55+ years	521	4	7.7 (0.2–15.2)	2989	13	4.4 (2.0–6.7)	1.8 (0.6–5.4)
Femur fractures							
0–19 years	2188	91	41.6 (33.0–50.1)	11862	3	0.3 (–0.3 to 0.5)	164.4 (52.1–519.2)
20–54 years	1637	12	7.3 (3.2–11.5)	8712	—a	NA	NA
55+years	521	4	7.7 (0.2–15.2)	2989	—a	NA	NA
Lower leg and ankle fractures							
0–19 years	2188	135	61.7 (51.3–72.1)	11862	35	3.0 (2.0–3.9)	20.9 (14.4–30.3)
20–54 years	1637	37	22.6 (15.3–29.9)	8712	18	2.1 (1.1–3.0)	10.9 (6.2–19.2)
55+years	521	5	9.6 (1.2–18.0)	2989	5	1.7 (0.2–3.1)	5.7 (1.7–19.8)
Other fractures							
0–19 years	2188	135	61.7 (51.3–72.1)	11862	164	13.8 (11.71–15.9)	4.5 (3.6–5.6)
20–54 years	1637	78	47.6 (37.1–58.2)	8712	91	10.5 (8.3–12.6)	4.6 (3.4–6.2)
55+ years	521	8	15.4 (4.7–26.0)	2989	13	4.4 (2.0–6.7)	3.5 (1.5–8.5)

OI = osteogenesis imperfecta; IR = incidence rate; IRR = incidence rate ratio (calculated using a Poisson regression model); NA = not applicable.

aDue to a very low number of fractures, the number is not provided (and the IRR not calculated) to avoid identification of confidential participant information.

most frequently in the mid-thoracic region.[18] The spinal fracture prevalence was lowest in patients with OI type I and highest in patients with OI type III.[18] We acknowledge that we will underestimate the rates of vertebral fractures using a register-based approach, as vertebral fractures are known to be underreported by most healthcare systems.

Fracture rates across the lifespan

Our patients with OI had the highest fracture rate during their first two decades of life. We saw the highest rates of forearm, femur, and lower leg and ankle fractures in the youngest age group. This indicates that children with OI are likely to be more susceptible to long-bone fractures when they start to walk and become more active. In a British study of childhood fractures, the peak fracture rates were at age 11 to 15 years.[19] The skeleton adapts to the need of increased bone strength in the growing skeleton, but there seems to be a lag in bone strength during periods of accelerated growth as seen during the pubertal growth spurt.[20] We speculate that the disconcordance in bone strength and growth could explain some of the increased fracture rates seen in patients with OI during the first two decades of life.

Although several fracture types showed increased IRR among women with OI aged 55 years and over, IRR was lower in men with OI in this age group. However, this may be due to the low number of older men in our cohort as a result of higher mortality.[21] Patients with the most severe phenotypes of OI will have increased risk of early death[22]; this could lead to a positive selection of patients with milder phenotypes, and thus fewer fractures, in the older age strata.

In postmenopausal women with OI the fracture rate was almost twice as high as that of premenopausal women. Also, the IRR was 8.0 (95% CI, 5.6 to 11.4) between OI cohort postmenopausal women and the reference population women, suggesting that bone loss associated with menopause has an important role in the fracture risk of OI patients. Paterson and colleagues[5] reported increased fracture rates after menopause, with the highest being 0.5 fractures per patient year at 25 years after menopause.

Effect of bisphosphonate use on fracture rates

We had no data on bisphosphonate use in our cohort, but we did not see a period effect when we entered calendar year into our Poisson model, as would be expected had the prognosis of fractures suddenly improved with the more widespread use of bisphosphonates in the late 1990s. In a Cochrane review[15] that included randomized studies with young patients with OI, the authors saw little evidence of fracture prevention by bisphosphonates. In contrast, a meta-analysis including randomized studies on adult patients showed a reduced fracture rate
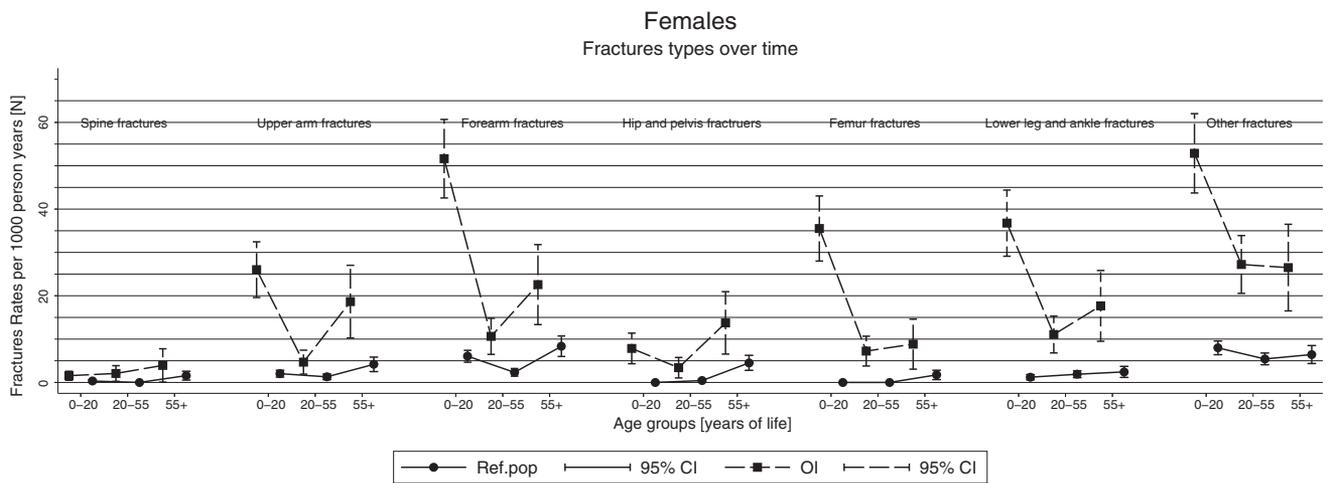
Females
Fractures types over time

Fig. 2. Fracture site by age group in females in the OI cohort and in the reference population. In the OI cohort, the rate of fractures to the forearm, femur, and lower leg and ankle were highest in the youngest age group and lowest for women aged 19 to 54 years. The two groups were fully matched for age but shown here with a small offset on the *x* axis to provide space for confidence interval bars.

during bisphosphonate treatment (Relative Risk 0.71; 95% CI, 0.52 to 0.96).[14] The authors concluded, however, that the evidence for fracture prevention with bisphosphonates was weak due to underpowered and heterogeneous studies.[14] The rates reported in the present study are representative of the burden of fractures in Danish patients with OI under the current standard of care in the country, including the potential use of bisphosphonate treatment.

Fracture reporting and information on OI subtypes

Clinical experience shows that some patients with OI experience fractures so frequently that they sometimes treat fractures themselves by self-immobilizing and analgesics. This could potentially lead to underreporting of fractures in our study, because we only have access to information on fractures treated by the hospital. Thus, our data may reflect the fracture burden posed to the healthcare system and not necessarily that experienced by the patient. The extent of undertreatment is unknown, but we must consider the possibility that the proportion of self-treated fractures may be larger in the more severe phenotypes than in the milder phenotypes. The reliability of fracture records in the NPR is generally high, with a concordance of 94% for hip, 84% for forearm, and 83% for humerus in self-reported fractures among Danish female nurses.[23] However, this has not been tested specifically for OI patients.
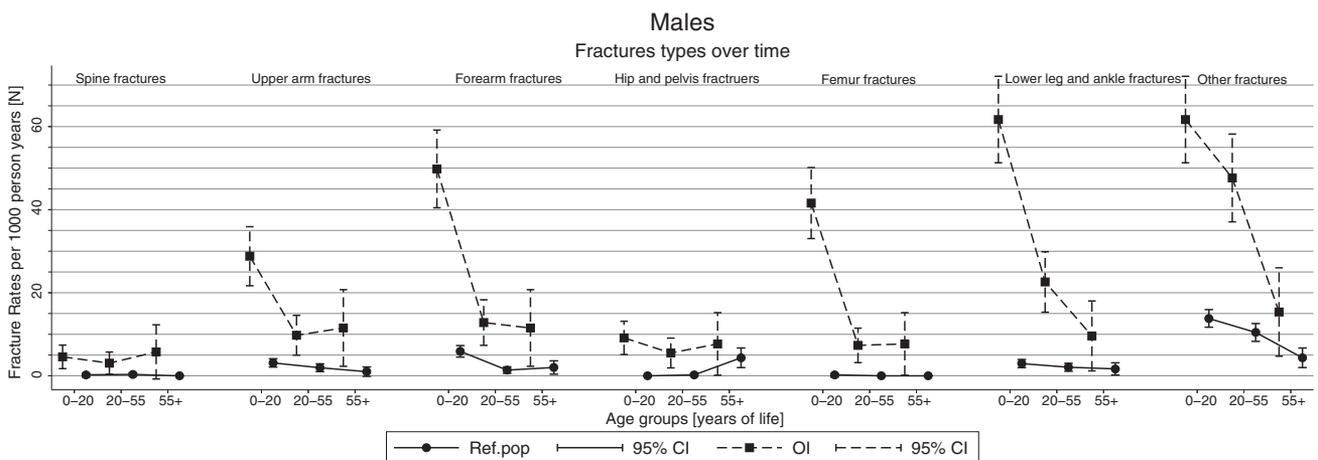
Males
Fractures types over time

Fig. 3. Fracture site by age group in males in the OI cohort and in the reference population. In the OI cohort, the fractures rates of the upper arm, forearm, femur, and lower leg and ankle fractures were highest in the youngest age group and decreased with age. The two groups were fully matched for age but shown here with a small offset on the *x* axis to provide space for confidence interval bars.

A major limitation to our study is the lack of data on clinical or genetic OI subtypes in our population. There is significant overlap between clinical phenotypes of OI, and for the more severe phenotypes (II to XV) genotypic information can be used to classify the patients within these forms of OI.[1] In the Norwegian population-based study, the patients with type I OI reported to have suffered between 1 and 170 fractures since birth, and patients with the more severer forms of OI (types III to IV) reported having suffered four to 300 fractures since birth.[6] Data on fractures were collected through a structured interview.[6] This method of fracture assessment is prone to recall bias among patients. In a sensitivity analysis excluding the six patients thought to suffer from the most severe phenotypes in our study, we saw no significant change in the fracture rates in the OI population. In a population of 644 patients, at least 120 patients would be expected to have moderate to severe OI. The fracture rates in these patients will be underestimated. The life expectancy in patients with moderate OI phenotypes is lower than the general population, but in 1996, Paterson and colleagues[24] found that the remaining life expectancy in patients with a moderate phenotype of OI was 72 years in women and 69 years in men at birth. A substantial portion of patients with moderate to severe phenotypes will survive into adulthood.

Validity of the OI diagnosis

We had no data on the specificity, sensitivity, or positive/negative predictive value of having an ICD-8 or ICD-10 diagnosis for OI in the NPR. A Danish study from 1989 estimated the prevalence of OI in the Danish population to be 10.6 per 100,000 persons.[2] Because the population of Denmark in 2012 comprised 5,230,310 citizens, we would have expected to identify 554 patients and we identified 687 persons with OI, of whom 112 died during the observation period, leaving 575 patients in the population. Thus it is likely that we have identified most patients with OI in Denmark. In a Danish study, 91 patients registered with an OI diagnosis in hospital treatment databases (which should reflect what is reported to the NPR) were clinically evaluated. An OI diagnosis could not be confirmed in six of these patients.[25] Three patients had idiopathic familial osteoporosis and three patients were first-degree relatives to patients with OI but had themselves too few classic OI symptoms to allow the authors to accept the registered OI diagnosis in the hospital treatment databases.[25] We saw no significant change in the IRR between patients with OI and the reference population when we omitted patients with only a referral diagnosis for OI. Misclassification bias cannot be ruled out, but if non-OI patients had been included in the OI cohort, it would lead to a false reduction in the ratio between the OI cohort and the reference population.

Our study had several strengths. It was population-based and included all patients registered with an OI diagnosis. Patients were identified via high-quality national databases on hospital discharges, outpatient clinic visits, and emergency department visits. Furthermore, fracture data for the patient and the reference populations were collected from the same databases, and were not prone to recall bias in the same way as self-report and interview data.

We confirm that patients with OI have increased risk of fractures throughout their life compared to the general population. Though the relative risk declines with age, fractures as a whole appear to follow the same pattern in terms of absolute rates as that of the general population, with a peak fracture rate during the toddler and adolescent years (IR 233.9 per 1000 person years), fewer fractures during adulthood (IR 84.5 per 1000 person years), and increased fracture rates in older women (IR 111.9 per 1000 person years).

Disclosures

Acknowledgments

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