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Risk of Fragility Fracture among Patients with Sarcoidosis: A Population-Based Study 1976–2013

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Abstract

Summary—Incidence of fragility fracture of a population-based cohort of 345 patients with sarcoidosis was compared with age and sex-matched comparators. The incidence of fragility fracture was higher among patients with sarcoidosis with hazard ratio (HR) of 2.18.

Introduction—Several chronic inflammatory disorders increase the risk of fragility fracture. However, little is known about the risk of fragility fracture in patients with sarcoidosis.

Methods—This study was conducted using a previously identified population-based cohort of 345 patients with incident sarcoidosis from Olmsted County, Minnesota. Diagnosis of sarcoidosis required physician diagnosis supported by biopsy showing non-caseating granuloma, radiographic evidence of intrathoracic sarcoidosis and compatible clinical presentations without evidence of other granulomatous diseases. Sex and age-matched subjects randomly selected from the same underlying population were used as comparators. Medical records of cases and comparators were reviewed for baseline characteristics and incident fragility fracture.

Results—Fragility fractures were observed in 34 patients with sarcoidosis, corresponding to a cumulative incidence of 5.6% at 10 years, while 18 fragility fractures were observed among comparators for a cumulative incidence of 2.4% at 10 years. The HR of fragility fractures among cases compared with comparators was 2.18 (95% confidence interval [CI], 1.23 – 3.88). The risk of fragility fracture by site was significantly higher among patients with sarcoidosis, and was due to higher rate of distal forearm fracture (HR 3.58; 95% CI 1.53 – 8.40). Statistically non-significant increased risk was also observed in proximal femur (HR 1.66; 95% CI 0.45 – 6.06) and proximal humerus (HR 3.27; 95% CI 0.66 – 16.21). Risk of vertebral fracture was not increased (HR 1.00; 95% CI 0.32 – 3.11).

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Conclusion—Patients with sarcoidosis have an increased risk of fragility fracture which is primarily driven by the higher incidence of distal forearm fracture.

Keywords

Sarcoidosis; Epidemiology; Fragility fracture; Glucocorticoids

Introduction

Chronic inflammation has been recognized as an independent risk factor for osteoporosis and fragility fracture. Inflammatory cytokines important in chronic inflammation, particularly interleukin-1 (IL-1) and tumor necrosis factor (TNF), have been found to play a role in accelerating bone resorption [1]. Several epidemiologic studies have demonstrated that patients with chronic inflammatory disorders, such as rheumatoid arthritis, inflammatory bowel disease and systemic lupus erythematosus, have a higher incidence of fragility fractures compared with the general population [2–4].

Sarcoidosis is a multi-organ, chronic inflammatory disorder characterized by the presence of non-caseating granulomas. The etiology of sarcoidosis is not known. It has been hypothesized that the interplay between genetic predisposition and environmental triggers plays a vital role in its pathogenesis [5, 6]. The incidence of sarcoidosis varies among different ethnic groups and sex, ranging from as low as 0.73 per 100,000 in Japanese males to as high as 71 per 100,000 in African-American females [7–9]. Glucocorticoids are commonly used for management of sarcoidosis.

Previous small cohort studies have demonstrated patients with sarcoidosis had a high prevalence of fragility fractures and vertebral deformities [10, 11]. A recent population-based cohort of patients with sarcoidosis using a database of general practitioners across the United Kingdom also showed an increased incidence of vertebral fracture [12].

To better characterize the risk of fragility fracture among patients with sarcoidosis, this study used a previously identified population-based cohort of patients with incident sarcoidosis from Olmsted County, Minnesota, United States [13] to compare the incidence of fragility fracture with age and sex-matched comparators.

Materials and Methods

Study population

The Rochester Epidemiology Project (REP) medical record-linkage system provides a unique opportunity to study the epidemiology and outcome of sarcoidosis. The data-linkage system allows complete access to medical records, both inpatient and outpatient, from all local healthcare providers, including the Mayo Clinic, the Olmsted Medical Center and their affiliated hospitals, local nursing homes and the few private practitioners, of all residents for over six decades. The potential use of the REP database for epidemiologic studies has been previously described [14].

Through the resources of the REP, a cohort of Olmsted County, Minnesota residents diagnosed with sarcoidosis between January 1, 1976 and December 31, 2013 was identified [13]. Potential cases of sarcoidosis were initially identified from the database using diagnostic codes related to sarcoidosis and non-caseating granuloma. Medical records of potential cases were then individually reviewed. Diagnosis of sarcoidosis required physician diagnosis supported by biopsy showing non-caseating granuloma, radiographic evidence of intrathoracic sarcoidosis and compatible clinical presentations without evidence of other granulomatous diseases such as tuberculosis and histoplasmosis. The exception for the requirement of histopathological confirmation was stage I pulmonary sarcoidosis that required only the presence of symmetric bilateral hilar adenopathy on thoracic imaging. Only cases with a diagnosis of sarcoidosis during residency in Olmsted County (i.e., incident cases) were included.

For each patient with sarcoidosis, one sex and age (±1 years) matched comparator subject without sarcoidosis at the time of the patient's sarcoidosis diagnosis was randomly selected from the same underlying population and assigned an index date that corresponded to the diagnosis date of sarcoidosis.

Medical records of cases and comparators were reviewed for baseline demographics and fragility fractures that occurred after index date. Fragility fracture was defined as fracture at vertebral, proximal femur, distal forearm or proximal humerus sites that occurred from a fall of standing height or less, without major trauma such as a motor vehicle accident. Data were collected for both groups. Data on systemic glucocorticoids treatment for cases, which included dose (more than or equal to 10 mg per day of oral prednisone equivalence versus less than 10 mg per day of oral prednisone equivalence) and duration (start and stop date) were also collected. Follow-up was continued until death, migration, or January 1, 2016.

Approval for this study was obtained from institutional review boards of Mayo Clinic and Olmsted Medical Center. The need for informed consent was waived.

Statistical analysis

Descriptive statistics (means, proportions, etc.) were used to summarize the data for cases and comparators. Cumulative incidence was estimated for fragility fracture overall and by site adjusted for the competing risk of death [15]. These methods are similar to the Kaplan-Meier method with censoring of patients who are still alive at last follow-up. Patients who die before experiencing a fragility fracture are appropriately accounted for to avoid overestimation of the rate of occurrence of fragility fractures, which can occur if such subjects are simply censored at death. Cox models were used to compare the rate of first fragility fracture between cases and comparators and to evaluate the association between use of glucocorticoids and fracture among cases. Glucocorticoid exposures were modeled using time-dependent covariates that modeled patients as unexposed until the time when they started treatment and exposed thereafter. These analyses were adjusted for sex, age and calendar year of sarcoidosis diagnosis. A p-value of less than 0.05 was considered statistically significant for all analyses. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) and R 3.1.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

For the years 1976–2013, 345 incident cases of sarcoidosis and 345 comparators were identified. Baseline characteristics of cases and comparators are described in table 1. The demographics were similar between the 2 groups except there were more non-White subjects among cases. The median length of follow-up was 12.9 years and 15.6 years for cases and comparators, respectively.

A total of 41 fragility fractures were observed in 34 patients with sarcoidosis (5 patients with 2 fragility fractures and 1 patient with 3 fragility fractures), while 19 fragility fractures were observed in 18 comparators (1 comparator subject had 2 fragility fractures). Cumulative incidence of first fragility fracture after diagnosis / index date for cases (5.6% at 10 years) and comparators (2.4% at 10 years) is shown in table 2 and figure 1. The hazard ratio (HR) of first fragility fracture among cases compared with comparators was 2.18 (95% confidence interval [CI], 1.23 – 3.88). The risk of fragility fracture by site was consistently higher among patients with sarcoidosis for proximal femur (HR 1.66; 95% CI 0.45 – 6.06), distal forearm (HR 3.58; 95% CI 1.53 – 8.40) and proximal humerus (HR 3.27; 95% CI 0.66 – 16.21). The risk of fragility fracture was not increased in the vertebrae in this cohort (HR 1.00; 95% CI 0.32 – 3.11).

A total of 100 patients with sarcoidosis were exposed to systemic glucocorticoids at some point during follow-up. Overall, the fragility fracture risk did not appear increased in those patients exposed to systemic glucocorticoids (HR 0.64; 95% CI 0.29 – 1.41). An assessment of fracture risk associated with exposure to higher doses of glucocorticoid (defined as more than or equal to 10 mg per day of oral prednisone equivalence) at longer duration (defined as at least 90 days) was undertaken. However, no increased fracture risk was found for patients with this extended exposure to higher dose glucocorticoids compared to the rest of the cohort (HR 0.51; 95% CI 0.20 – 1.34).

Discussion

Fragility fracture is a common medical problem that is associated with significant morbidity and mortality. For example, the in-hospital mortality rate among patients admitted for proximal femur fracture is as high as 10% [16, 17]. Therefore, identification of persons at higher risk of fragility fracture is the pivotal first step toward appropriate intervention for prevention.

The current study is the first to utilize a population-based cohort with individual medical record review to investigate the risk of fragility fracture among patients with sarcoidosis. Increased risk of fragility fracture was observed among patients with sarcoidosis which was primarily driven by the increased risk of distal forearm fracture. These results differ from a recent coding-based study that observed an increased risk of vertebral fracture, but not non-vertebral fracture, among patients with sarcoidosis [12]. The difference in the methods used to identify patients with sarcoidosis and the events of interest may explain the different observations, as the prior study relied primarily on diagnostic codes while individual medical record review was performed in the current study. Moreover, the current cohort was

predominately Caucasian while the ethnic composition of the prior cohort was not available, so it is possible that a difference in the ethnic background of the two cohorts may explain the difference in the findings.

The pathophysiologic mechanisms underlying this elevated risk are not known. Unlike other chronic inflammatory disorders, studies have demonstrated that the bone mineral density (BMD) of patients with sarcoidosis is not different from age and sex-matched persons from the general population [11, 18, 19]. Therefore, it seems unlikely the observed increased incidence of fragility fracture was a result of lower BMD. Interestingly, despite normal BMD, an increased level of bone turnover as reflected by increased level of bone resorption markers such as serum carboxy-terminal cross-linked telopeptide of type I collagen and increased level of bone formation marker such as serum procollagen type I amino-terminal propeptide has been observed in sarcoidosis [11]. It is possible that the increased fracture risk is a result of increased bone turnover, driven by inflammatory cytokines [20], with consequent microarchitectural changes and decreased bone strength. It is unknown whether patients with sarcoidosis have a higher tendency to fall compared to sex and age-matched subjects. This may be an interesting question for future sarcoidosis study.

Use of glucocorticoids is a well-established risk factor for osteoporosis and fragility fracture [21]. However, use of glucocorticoids was not a significant predictor of fragility fracture in this cohort. The utility of this analysis is limited by the lack of detailed information on glucocorticoid exposure. It is possible that a significantly increased risk of fragility fracture might be observed in a subgroup of patients who were exposed to moderate to high dose glucocorticoids for a long period of time. The current study may not have sufficient power to detect the association between fragility fracture and exposure to glucocorticoid due to the limited numbers of the event of interest and subjects who were exposed to glucocorticoids.

The incidence rate of fragility fracture among comparators of this study, whose mean age was 45.4 years, was similar to that reported in other studies. For example, incidence rate of fragility fracture among subjects younger than 50 years in a recent nationwide study from the United Kingdom was 20.7 per 10,000 person-years, which was approximately equivalent to the 10-year cumulative incidence of 2.1% [22]. Another study from Canada found 10-year cumulative incidence of approximately 2% and 3% among males and females aged 35 to 44 years, respectively [23].

The major strengths of this study are that it is a population-based cohort that represents the actual spectrum of sarcoidosis in the community, unlike studies based on referral cohorts that may consist of patients with higher disease severity. The long duration of follow-up allowed capture of the events of interest that occurred several years after the index date. Diagnosis of sarcoidosis in this study was confirmed by medical record, histopathology and radiographic study review. Therefore, the risk of disease misclassification was minimal, in contrast to studies that rely on just diagnostic codes. Similarly, the risk of misclassifying trauma-related fracture to fragility fracture was minimized.

The major limitations of the study are those inherent in the retrospective design as the clinical information were not systematically obtained and recorded. Generalizability of the

findings to other populations is another concern as the epidemiology and clinical manifestations of sarcoidosis are different among ethnic groups. The majority of residents of Olmsted County as well as the majority of patients in this cohort are Caucasian. Moreover, Olmsted County has higher proportion of healthcare workers who might have different patterns of healthcare utilization, who may have increased access to, and undergone more routine health screening, resulting in detection of more asymptomatic sarcoidosis or sarcoidosis at earlier stage.

Conclusion

Patients with sarcoidosis have an increased risk of fragility fracture. The increase in fragility fractures was primarily due to the increased risk of wrist fracture. Glucocorticoid therapy could not be identified as a significant predictor of fragility fracture, but he study may be underpowered to detect this association. Clinicians and patients should be aware that patients with sarcoidosis are at higher risk of fragility fracture its consequences.

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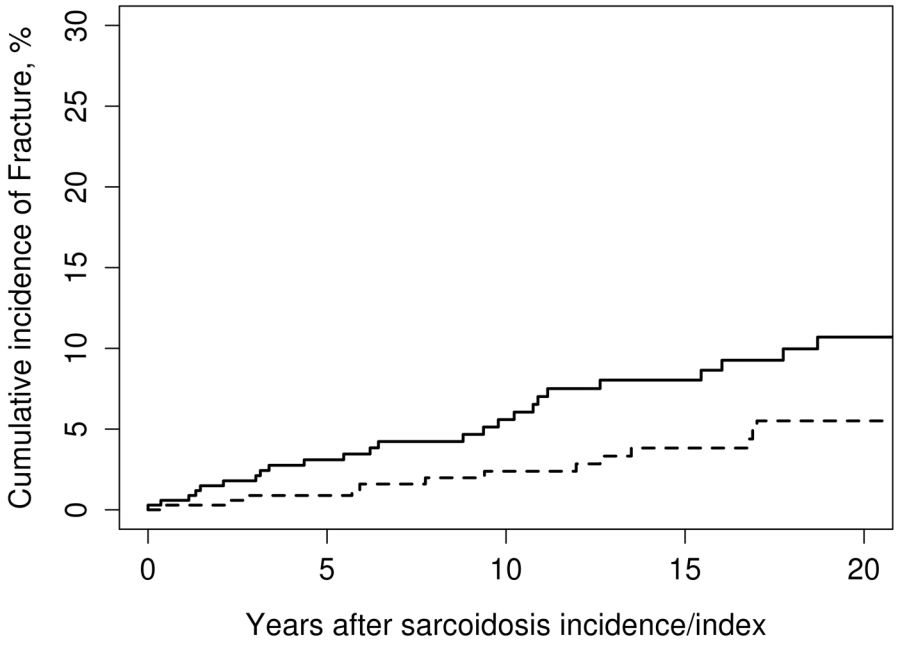

Figure 1.
Cumulative incidence of overall fragility fracture among patients with sarcoidosis (solid line) and comparators without sarcoidosis (dashed line).

Table 1

Baseline characteristics of patients with sarcoidosis and age and sex matched comparator subjects

	Sarcoidosis Cases (N = 345)	Comparators (N = 345)	P value
Mean age at diagnosis/index date in years (SD)	45.6 (13.6)	45.4 (13.7)	0.87
Female	50%	50%	1.0
Ethnicity			<0.001
Caucasian	90%	95%	
African-American	5%	1%	
Asian	2%	0%	
Native American	1%	0%	
Other	2%	4%	
Median length of follow-up in years	12.9	15.6	--

SD: standard deviation

Table 2

Cumulative incidence rate of fractures in 345 patients with sarcoidosis in 1976–2013 compared to 345 subjects without sarcoidosis

Fragility Fractures	Number of patients with events after index date in non-sarcoidosis / sarcoidosis	Cumulative incidence at 10 years for non-sarcoidosis subjects (95% CI)	Cumulative incidence at 10 years for sarcoidosis patients (95% CI)	Hazard ratio (95% CI) adjusted for age, sex and calendar year of index date	p-value
Any site	18 / 34	2.4 (0.6, 4.1)	5.6 (2.8, 8.3)	2.18 (1.23, 3.88)	0.008
Vertebral	6 / 6	0.6 (0.0, 1.5)	0.7 (0.0, 1.6)	1.00 (0.32, 3.11)	1.0
Femur	4 / 6	0.0 (0.0, 0.0)	0.4 (0.0, 1.1)	1.66 (0.45, 6.06)	0.45
Distal forearm	7 / 22	1.7 (0.2, 3.3)	3.8 (1.5, 6.1)	3.58 (1.53, 8.40)	0.003
Proximal humerus	2 / 6	0.0 (0.0, 0.0)	1.0 (0.0, 2.1)	3.27 (0.66, 16.21)	0.15

CI: confidence interval