Pronounced Risk of Fractures among Elderly Men Affected by Granulomatosis with Polyangiitis

Mikkel Faurschou, Bo Baslund, and Niels Obel

ABSTRACT. ***Objective.*** It is unknown whether patients affected by granulomatosis with polyangiitis (GPA) are at increased risk of fractures, and whether the fracture risk in GPA varies with age and sex. The aim of the present study was to compare the fracture risk among patients with GPA with that among age- and sex-matched population controls.

Methods. We established a monocentric cohort of patients treated for GPA at a Danish tertiary care center from 1995 to 2010 (n = 159) and a register-derived GPA cohort identified from the Danish National Hospital Register (n = 402). Each patient was matched with 7 population controls. The occurrence of fractures among patients was compared with that among controls by calculation of incidence rate ratios (IRR).

Results. In the monocentric cohort, an increased fracture risk was observed among men aged ≥ 55 years at the time of first hospitalization for GPA (IRR 3.5, 95% CI 1.6–7.6), but not among men < 55 years (IRR 0.3, 95% CI 0.04–2.1) or women (IRR women ≥ 55 yrs: 1.0, 95% CI 0.4–2.7 and IRR for women < 55 yrs: 0.7, 95% CI 0.2–2.4). In the register-derived cohort, an increased fracture risk was also observed among men aged ≥ 55 years at study baseline (IRR 2.0, 95% CI 1.2–3.5), whereas the incidence rate of fractures was not significantly increased among younger men or women (IRR for men < 55 yrs: 1.0, 95% CI 0.4–2.3; IRR for women ≥ 55 yrs: 0.9, 95% CI 0.5–1.5; IRR for women < 55 yrs: 1.6, 95% CI 0.7–3.6).

Conclusion. Elderly male patients with GPA have a pronounced risk of developing fractures. This finding is of relevance for the clinical management of patients with GPA. (J Rheumatol First Release August 1 2015; doi:10.3899/jrheum.141566)

Key Indexing Terms:
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Granulomatosis with polyangiitis (GPA) is a vasculitic syndrome of unknown etiology characterized by granulomatous inflammation in the upper and lower airways, glomerulonephritis, and the presence of circulating antineutrophil cytoplasmic antibodies (ANCA)[1]. Treatment regimens based on cyclophosphamide and corticosteroids have improved the prognosis in GPA dramatically[2,3], but the mortality of patients with GPA remains increased[4]. Moreover, disease- and therapy-induced organ damage affects the majority of patients during longterm followup[5,6].

Previous cohort studies indicate that patients with GPA experience a substantial number of skeletal fractures. Hoffman, *et al* observed fractures in 11% of 158 patients during a mean followup period of 8 years[5]. Koldingsnes, *et al* reported fractures in 10% of 56 patients followed for 3.5 years[7], while a recent study of ANCA-associated vasculitis patients enrolled in clinical trials conducted by the European Vasculitis Society demonstrated fractures in 14% during a mean followup period of 7.3 years[6]. To our knowledge, however, the occurrence of fractures among patients with GPA has not been compared with that in the general population. It is, therefore, unknown whether the incidence rate of fractures is increased among patients with GPA. It is also unknown whether the fracture risk associated with GPA and its treatment varies between male and female patients and/or among patients of different age groups.

To answer these questions, we performed a study of the fracture risk in Danish patients with GPA. By linkage with the Danish National Hospital Register (NHR), we collected data on fractures for patients diagnosed with GPA and treated at a tertiary care center from 1995 to 2010 and for all other persons who were diagnosed with GPA and experienced a first-time hospitalization at any Danish rheumatology de-partment under a diagnosis of GPA during this calendar period. We subsequently compared the incidence rate of fractures among the patients with that among control subjects of the general population in analyses stratified according to age, sex, and calendar period of vasculitis diagnosis.

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MATERIALS AND METHODS

Monocentric GPA cohort. The monocentric cohort was established as previously described[8]. The Department of Rheumatology at Copenhagen University Hospital, Rigshospitalet, Denmark, is a tertiary care center with specialized functions in treating patients affected by inflammatory rheumatic diseases. By means of electronic hospital discharge lists, we identified all patients treated at the department under a diagnosis of GPA between 1995 and 2010 [International Classification of Diseases, 8th Revision (ICD-8) code: 446.29, ICD-10 code: M31.3]. Available medical files were reviewed, and patients who retrospectively met the classification criteria for GPA[9] were included in the cohort.

Among the identified patients, we subsequently selected those who were registered with a first-time diagnosis of GPA in the NHR from 1995 to 2010 and who were ≤ 85 years at the date of diagnosis. The NHR was founded in 1977 and contains records on admissions to nonpsychiatric hospital departments in Denmark with a coverage of > 99%[10]. Information on visits to emergency rooms and outpatient clinics has been included since 1995. Every hospital visit initiates a record that is marked by the patient's personal identification number (unique to each citizen of Denmark) and includes dates of admission and discharge, hospital and department codes, start and end dates of outpatient visits, a primary discharge diagnosis, and supplementary diagnoses. The discharge diagnoses were coded according to a Danish version of the ICD-8 until the end of 1993, and have been coded according to the ICD-10 thereafter.

Register-derived GPA cohort. A register-based GPA cohort was established by means of the NHR. In the register, we identified all persons who (1) were diagnosed with GPA from 1995 to 2010, (2) experienced a first-time hospitalization for GPA at any Danish rheumatology department during this calendar period, and (3) were not included in the above-mentioned monocentric cohort. From this population, we selected patients aged ≤ 85 years at index date (defined below).

Population controls. We constructed comparison cohorts of individually matched persons identified from the Danish Civil Registration System. This system contains a variety of data on each citizen of Denmark, including personal identification number, name, sex, date of birth, and continuously updated information on vital status[11]. For each patient with GPA, we randomly identified 7 population controls who had the same sex and date of birth as the patient, and were residing in Denmark and not diagnosed with GPA at index date.

Fractures. Information regarding hospitalizations under fracture-related ICD-10 diagnoses was extracted from the NHR [ICD-10 fracture codes: S42 (humerus, clavicle, scapula); S52 (forearm); S62 (hand); S72 (hip and femur); S82 (lower leg, patella); S92 (foot); S12.0, S12.1, S12.2, S12.7, S12.9, S22, S32, T08, M48.4, and M48.5 (spine, sternum, ribs, pelvis)]. A validity of 97% was previously reported for fracture diagnoses in the NHR[12].

Statistical analyses. The index date for the patients of the monocentric cohort was defined as the date of GPA diagnosis as registered in the NHR. The index date for the patients of the register-derived cohort was defined as date of first hospitalization for GPA at any department of rheumatology in Denmark. The index date for the control subjects was defined as index date of the patient with GPA to whom they were matched. The study outcome was time to first hospitalization under any of the fracture-related diagnoses listed above. For all study individuals, we calculated person-years of followup from index date until date of first fracture, death, emigration, loss to followup, 8 years of followup, or December 31, 2010, whichever came first.

The occurrence of fractures among the patients with GPA was compared with that among the population controls by the calculation of incidence rate ratios (IRR) with 95% CI. We used Cox regression analyses adjusted for age and sex to compare the fracture risk among control subjects with an index date between 1995 and 2002 with that among controls with an index date between 2003 and 2010. We computed Kaplan-Meier tables to construct plots to illustrate time to first fracture. SPSS version 13.0 (SPSS Inc.) was used to perform the analyses.

Ethics. The study was approved by the Danish Data Protection Agency (journal number 30-0604).

RESULTS

Characteristics of patients and controls are summarized in Table 1. The monocentric cohort was composed of 159 patients, while the register-derived cohort was composed of 402 patients. The median duration of followup in the cohorts was 5.7 years and 4.6 years, respectively. None of the patients or controls was lost to followup.

In the monocentric cohort, 18 patients experienced fractures (site of first-time fracture: 1 humerus, 3 forearms, 3 hands, 4 hips, 2 lower legs, 1 foot, 2 spines, 2 ribs) during a total of 789 person-years, corresponding to an overall IRR for fractures of 1.2 (95% CI 0.7–2.0; Figure 1A). As described in Table 2 and graphically presented in Figure 1C, we observed a 3.5 times increased risk of fractures among men aged ≥ 55 years at time of the GPA diagnosis (the median patient-age at index date) in the cohort. The risk of fractures was not significantly increased among younger men or among women (Table 2).

The patients of the register-derived GPA cohort were followed for a total of 1793 person-years. Forty-five patients were diagnosed with fractures during followup, yielding an overall IRR for fractures of 1.2 (95% CI 0.9–1.7; Figure 1B). Analyses stratified according to age and/or sex demonstrated IRR comparable with those observed in the monocentric GPA cohort. Thus, a significantly increased risk of fractures was found among men aged ≥ 55 years at index date (Table 2, Figure 1D), but not among male patients of younger age or female patients (Table 2).

We did not observe major differences in fracture IRR for patients diagnosed between 2003 and 2010 and those diagnosed between 1995 and 2002 in either cohort (Table 2). To exclude the possibility that these risk estimates were influenced by differences in fracture risk between the corresponding subgroups of controls, we investigated whether controls with index date between 2003 and 2010 and controls with index date between 1995 and 2002 differed with respect to the incidence rate of fractures. These analyses did not reveal significant differences between groups [adjusted IRR (controls for the monocentric cohort): 1.1 (95% CI 0.7–1.6); adjusted IRR (controls for the register-derived cohort): 1.2 (95% CI 0.9–1.6)].

DISCUSSION

To our knowledge, the current investigation is the first to provide age- and sex-specific risk estimates for fractures in GPA. We observed a significantly increased incidence rate of fractures among elderly male patients with GPA, but not among younger men or among women.

Inflammatory rheumatic diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) have previously been associated with an increased risk of fractures[13,14,15,16,17,18]. In these disorders, a range of risk

Table 1. Characteristics of patients treated for GPA at a Danish tertiary care center from 1995 to 2010 and of all other patients aged ≤ 85 years who were diagnosed with GPA and experienced a first-time hospitalization at any Danish rheumatology department under a diagnosis of GPA from 1995 to 2010.

Characteristics	Monocentric Cohort		Register-derived Cohort	
	Patients	Controls*	Patients	Controls*
n	159	1113	402	2814
Men, n (%)	80 (50)	560 (50)	195 (48)	1365 (48)
Age at first hospitalization for GPA, yrs, median (IQR)**	55 (43–63)	55 (43–63)	59 (46–68)	59 (46–68)
Followup, yrs, median (IQR)**	5.7 (2.1–8.0)	6.1 (2.9–8.0)	4.6 (1.7–7.9)	5.2 (2.6–8.0)
Person-yrs of followup	789	5880	1793	13.933
Deaths during followup, n	28	104	85	345
Persons with at least 1 fracture during followup, n	18	109	45	279

* Each patient was matched with 7 age- and sex-matched population controls. ** Followup began at date of first hospitalization for GPA (monocentric cohort)/date of first hospitalization for GPA at any Danish rheumatology department (register-derived cohort) and continued until first fracture, death, emigration, 8.0 years of followup, or December 31, 2010, whichever came first. GPA: granulomatosis with polyangiitis; IQR: interquartile range.

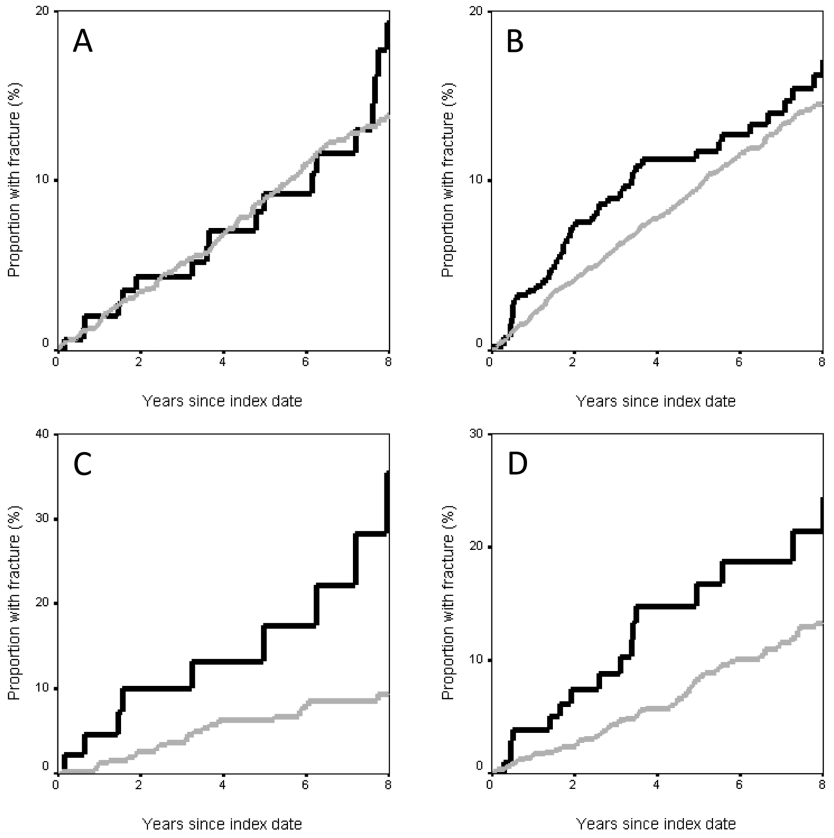

Figure 1. Proportion with fracture among patients from a monocentric GPA cohort and patients from a register-derived GPA cohort (both indicated with black lines), and among age- and sex-matched population controls (grey lines). A. Patients from the monocentric cohort versus controls. B. Patients from the register-derived cohort versus controls. C. Male patients aged ≥ 55 years from the monocentric cohort versus controls. (D) Male patients aged ≥ 55 years from the register-derived cohort versus controls. In the monocentric cohort, index date was defined as the date of first hospitalization for GPA. In the register-derived cohort, index date was defined as the date of first hospitalization for GPA at any department of rheumatology in Denmark. GPA: granulomatosis with polyangiitis.

Table 2. IRR for fractures among patients treated for GPA at a Danish tertiary care center from 1995 to 2010 and among all other patients aged ≤ 85 years who were diagnosed with GPA and experienced a first-time hospitalization at any Danish rheumatology department under a diagnosis of GPA from 1995 to 2010*. Values are IRR (95% CI).

Characteristics	Monocentric Cohort, n = 159	Register-derived Cohort, n = 402
Overall	1.2 (0.7–2.0)	1.2 (0.9–1.7)
Patients < 55 yrs at GPA diagnosis	0.5 (0.2–1.5)	1.2 (0.7–2.2)
Patients ≥ 55 yrs at GPA diagnosis	2.0 (1.1–3.6)	1.3 (0.9–1.9)
Women	0.9 (0.4–1.9)	1.0 (0.7–1.6)
Men	1.7 (0.8–3.3)	1.6 (1.0–2.5)
Women < 55 yrs at GPA diagnosis	0.7 (0.2–2.4)	1.6 (0.7–3.6)
Women ≥ 55 yrs at GPA diagnosis	1.0 (0.4–2.7)	0.9 (0.5–1.5)
Men < 55 yrs at GPA diagnosis	0.3 (0.04–2.1)	1.0 (0.4–2.3)
Men ≥ 55 yrs at GPA diagnosis	3.5 (1.6–7.6)	2.0 (1.2–3.5)
Patients diagnosed with GPA 1995–2002	0.9 (0.4–1.9)	1.2 (0.8–2.0)
Patients diagnosed with GPA 2003–2010	1.7 (0.9–3.4)	1.2 (0.8–1.9)

* The incidence of first-time fractures among the patients was compared with that among age- and sex-matched population controls (7 controls per patient). IRR: incidence rate ratios; GPA: granulomatosis with polyangiitis.

factors for fractures has been identified, including older age, prolonged disease duration, treatment with high cumulative corticosteroid doses, physical disability, and preexisting reduced bone mineral density (BMD)[13,15,16,17,19,20]. The fracture risk in GPA is also likely to be influenced by several factors. The disease processes of GPA frequently involve the peripheral nerves, lungs, and joints, and functional impairment related to such organ manifestations may lead to an increased risk of fractures secondary to falls during phases with inflammatory activity. In the current cohorts, the importance of risk factors related to active vasculitis is suggested by the early-occurring rise in fracture incidence observed among elderly male patients (Figure 1C, Figure 1D). During followup, patients with GPA affected by glomerulonephritis are at risk of developing chronic renal insufficiency, and chronic nephropathy is a risk factor for decreased bone strength and fragility fractures[21]. Moreover, a substantial proportion of patients with GPA develop irreversible damage to the cardiovascular system, lungs, and peripheral nervous system, and this may result in chronic disability and a sustained risk of fall-related fractures. Finally, prolonged corticosteroid therapy is often needed to obtain and maintain disease control in GPA[22,23,24], and longterm treatment with corticosteroids is an important determinant of osteoporotic fractures[25].

Our risk estimates for fractures differ from those reported in epidemiological studies of patients with RA and SLE[17,18]. Kim, *et al* found an increased incidence rate of fractures among 47,034 patients with RA compared with that among matched patients without RA[18]. Incidence rates were elevated across age groups and sexes with no major differences observed between subgroups. In a study of 4343 patients with SLE and 21,780 matched patients without SLE, Bultink, *et al* reported an increased risk of fractures in the SLE cohort without substantial differences in risk estimates observed across age strata[17]. Excess occurrence of fractures was found among patients of both sexes with a higher relative risk identified for men than for women. Together with our observations, these data indicate that the risk of fractures might vary among patients affected by different inflammatory rheumatic diseases.

The reasons that the significantly increased incidence of fractures occurred only among elderly male patients in the current GPA cohorts cannot be determined from our data. It could be speculated that the well-known risk of osteoporosis among postmenopausal women[26] led to more rigorous screening for osteoporosis in elderly female patients than in elderly male patients after the diagnosis of vasculitis. This could potentially have resulted in less systematic treatment of corticosteroid-induced osteoporosis among elderly men, which in turn could have contributed to the increased relative risk of fractures observed in this subgroup of patients. Of note, Boomsma, *et al* reported high prevalence of osteopenia and osteoporosis among Dutch patients with ANCA-associated vasculitis, but only male patients had BMD values below age- and sex-specific norms[27]. This observation indicates that accelerated bone loss might be an important contributing risk factor for fractures among male patients with GPA treated according to conventional immunosuppressive regimens. However, additional studies are needed to characterize the spectrum of factors predisposing to early- and late-occurring fractures among patients with GPA.

No major differences in IRR for fractures were found across calendar periods, indicating that the relative risk of fractures among Danish patients with GPA remained stable throughout the period of study. In the monocentric cohort, nonsignificantly increased overall IRR of 1.7 and 0.9 were calculated for patients diagnosed between 2003 and 2010 and those diagnosed between 1995 and 2002, respectively, but the observed difference in IRR between these subgroups must be interpreted with caution because of the limited number of patients available for the analysis.

Our study has strengths and weaknesses. The completeness of data contained within the Danish Civil Registration System enabled us to track patients and controls without loss to followup, and the high validity of fracture diagnoses contained within the NHR allowed us to collect trustworthy information regarding hospitalizations for fractures. We consider the analyses based on the register-derived GPA cohort to be a strength, even though we did not assess the validity of GPA diagnoses as registered in the NHR. In the Swedish Inpatient Register, a validity of 88% has been reported for the diagnosis of GPA[28], and there is no reason to assume that the validity of GPA diagnoses in the Danish NHR should be any higher. However, we observed IRR for fractures in the register-derived GPA cohort, which are

comparable with those found in the much smaller, monocentric cohort. Thus, the risk estimates calculated on the basis of register data add support to those calculated for patients with a validated diagnosis of GPA.

Reliable information on fractures prior to index date was not available because data on visits to emergency rooms and outpatient clinics were not reported to the NHR before 1995. Therefore, the fracture risk associated with previous fractures (an established risk factor for subsequent fractures)[29] could not be analyzed. We were unable to collect information regarding cumulative corticosteroid doses, BMD levels, bisphosphonate exposures, risk factors for falls, or chronic kidney disease stages by medical files review, and this prevented analyses of the fracture risk associated with vasculitis-induced organ damage and therapeutic interventions, respectively.

The current study demonstrates a pronounced risk of fractures among elderly male patients with GPA. From a clinical perspective, our observations indicate that screening for risk factors for fractures is of particular relevance in patients with GPA with this age and sex profile.

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