Summary

Little information is available on the risk of fractures in patients with monoclonal gammopathy of undetermined significance (MGUS). We identified 1535 patients with MGUS between 1978 and 2003 in North Jutland County, Denmark. The population control group consisted of 15 350 persons selected from the Danish Central Population Registry, matched by age and sex. Data on fractures in the two groups were obtained from the regional Hospital Discharge Registry. In the MGUS cohort, 187 first-time fractures were identified during 9754 person-years of follow-up, corresponding to an incidence rate of 19/1000 person-years. The adjusted relative risk for fractures among MGUS patients compared with population controls was 1.4 [95% confidence interval (CI), 1.2–1.6]. After 5 years of follow-up, the risk difference was 1.8% (95% CI, 0.5–3.0). Six of the 187 MGUS patients with fractures were later diagnosed with malignant transformation. Relative risks for fractures were increased in IgG-type MGUS [1.3 (95% CI, 1.1–1.6)], IgM-type MGUS [1.6 (95% CI, 1.1–2.2)] and MGUS with kappa light chain [1.4 (95% CI, 1.1–1.7)]. MGUS patients had an increased risk of fractures, which could not be explained by comorbidity, advanced age, gender or malignant transformation.

Keywords: Benign monoclonal gammopathies, fractures, population-based study, risk, multiple myeloma.

Monoclonal gammopathy of undetermined significance (MGUS) is the most common immunoglobulin disorder, with an estimated prevalence of 5% in persons above 70 years of age (Kyle et al, 2006). MGUS confers an increased risk of malignant transformation to symptomatic malignant monoclonal gammopathy, most often to multiple myeloma (MM) and less frequently other malignant lymphoproliferative disorders (Kyle et al, 2002).

Pathological fractures as a result of osteolytic lesions are well-known complications of MM (Hernandez et al, 2004; Melton et al, 2005). Excessive osteoclastic-mediated bone resorption in the vicinity of myeloma cells represents an early stage of bone involvement in myeloma and creates an imbalance between bone resorption and formation (Bataille et al, 1989). In later stages of the disease, inhibition of bone formation is also seen (Bataille et al, 1991). In recent years, bisphosphonates have assumed an important role in reducing skeletal complications of MM by inhibiting osteoclastic activity (Rosen et al, 2003).

In contrast to MM, data from studies on bone involvement in MGUS are conflicting. Some studies, using non-invasive markers of bone turnover or bone histomorphometry, have found that bone resorption markers in MGUS patients display values intermediate between those of MM patients and healthy individuals (Pecherstorfer et al, 1997; Vejlgaard et al, 1997; Hernandez et al, 2004). Others have found normal bone resorption markers in MGUS patients (Laroche et al, 1996; Diamond et al, 2001).

Excess bone resorption markers have been documented in some MGUS patients who later became unstable or progressed to MM. Consequently, an excess of bone resorption markers might be regarded as an early sign of malignancy (Bataille et al, 1996). At the same time, another study found increased resorption marker values in seven MGUS patients who remained stable without any sign of MM (Laroche et al, 1998). The question has been raised whether, in certain MGUS cases, in situ stimulation of bone cells by monoclonal plasma cells could occur without transformation to active myeloma.
Fracture Risk in MGUS

(Laroche et al, 1998). Studies of bone histomorphometry and non-invasive markers of bone turnover have not clarified whether MGUS, as a premalignant condition, carries the same fracture risk as MM. One previous study that addressed this issue showed an increased risk of fractures among MGUS patients (Melton et al, 2004).

Using a large population-based cohort design, we compared the risk of fractures among patients with MGUS in Denmark with that of a population control group.

**Design and methods**

The study was conducted in North Jutland County, Denmark, which has 490 800 inhabitants (approximately 9% of the total Danish population). Every citizen in Denmark is assigned a personal identification number (ID number) at birth, which enables linkage between demographic and medical registries (Frank, 2000).

**MGUS classification**

For 26 years (1978–2003), the Department of Clinical Biochemistry, Aalborg Hospital, has maintained a registry of all the patients in North Jutland County that have an identified serum M-component. The registry’s records contain patient name, ID number, date of detection, type of serum M-component and concentration of immunoglobulins. Electrophoresis was requested by hospital doctors or family doctors in the county and the analyses were conducted either at Aalborg or Aarhus Hospital. All sera with a suspected M-component were subsequently examined at Aalborg Hospital by immunofixation using monospecific antibodies from Dakopatts A/S, Copenhagen, Denmark. The immunoglobulins were quantified by nephelometry.

During the study period, data from 3489 patients with M-components were entered into the registry. All cohort members were linked by ID number to the Central Population Registry to verify the ID number and to obtain dates of death or emigration. In addition, they were linked by ID number to the Danish Cancer Registry. Diagnoses in the cancer registry are coded according to a Danish version of the International Classification of Diseases, seventh revision (ICD-7), and the registry’s completeness and validity have been estimated to be 95–98% (Storm et al, 1997). We obtained information on cancer diagnosis, if any, and date of diagnosis. Persons with an M-component were classified as having MGUS if they were not diagnosed with MM (ICD-7 203.0–203.2), Waldenström macroglobulinaemia (203.3), non-Hodgkin lymphoma (200, 202, 198, 740.1–799.9), or chronic lymphocytic leukaemia (204.0) previously or within the year following detection of the M-component. In order to exclude cases of asymptomatic myeloma, levels of IgA, IgG and IgM had to be less than 30 g/l. Between 1978 and 2003, 1535 cases of MGUS were identified. The MGUS cohort has been described in detail previously (Gregersen et al, 2000).

Malignant transformation was defined as development of MM, Waldenström macroglobulinaemia, non-Hodgkin lymphoma, or chronic lymphocytic leukaemia. This condition was determined by a link to the Danish Cancer Registry using the ICD-7 codes. Hypogammaglobulinaemia was diagnosed when at least one non-monoclonal immunoglobulin was reduced. Reference intervals were 0–8–3.3 g/l for IgA, 8.0–18.0 g/l for IgG and 0–7–3.0 g/l (females 0–3–2.2 g/l) for IgM.

**Population control group**

For each MGUS patient, ten controls resident in North Jutland County were selected from the Danish Central Population Registry, and frequency matched by age and sex.

**Fractures**

Data on fracture risk among cases and controls were obtained from the regional Hospital Discharge Registry (HDR) (Nickelsen, 2002). Since its establishment in 1977, this registry has collected information on all patients admitted to hospitals in North Jutland County. From 1995, outpatient data, including emergency room records, was also collected. In the HDR, diagnoses were coded according to the International Classification of Diseases, eighth revision (ICD-8) until 1994 and thereafter the tenth revision (ICD-10) was used. The validity of orthopaedic data in this registry was over 80% (Nickelsen, 2002).

The study focused on fractures of vertebrae, ribs and pelvis (ICD-8: 805.09–805.11, 805.19, 808.08, 808.09 and ICD-10: S12.0–S12.9, S22.0, S22.1, S32.0–S32.8), femur (ICD-8: 820.00–820.09, 821.09–821.99 and ICD-10: S72.0–S72.9), and distal forearm (ICD-8: 813.20–813.29 and ICD-10: S52.5–S52.6).

**Comorbidity**

Comorbidity was classified according to the Charlson Comorbidity Index (Charlson et al, 1987). The index was computed based on ICD codes for all discharge diagnoses in the Danish National Health Registry for patients and controls since 1977. Weights were assigned to defined categories of comorbid diseases and the index was the sum of these weights. Three levels of comorbidity were defined: 0 (‘low’), for individuals with no recorded underlying diseases included in the Charlson index; 1 (‘moderate’); and 2 (‘high’).

Alcohol-related diseases were defined as ICD-8 codes 303.xx, 570.xx, 571.00, 571.10, 573.00, 573.01, 577.10, 979.xx, 980.xx, and as ICD-10 codes F10.0–F10.9, T51.0, Z72.1, R78.0, K70.x, K71.1–K71.8, K86.x.

**Statistical analysis**

The follow-up period began 1 year after detection of the M-component and ended at the date of first fracture, malignant
transformation, death, or December 31, 2003. The cumulative risk of fracture was estimated using the Kaplan–Meier method.

We used Cox proportional regression analysis to compute hazard ratios as a measure of relative risk. The following variables were considered dichotomous in the analysis: patient status (MGUS or control); gender (female or male); hypogammaglobulinaemia (present or absent); and comorbidity (level 0, 1/2). Immunoglobulin concentration (IgA, IgG, or IgM), and age were treated as continuous variables. Controls, females and absence of hypogammaglobulinaemia served as the references. The proportionality assumptions for the model, which were assessed graphically, were fulfilled.

The study was approved by the Danish Data Protection Agency (No. 2004-41-4011).

Results

The MGUS cohort included 785 males and 750 females. Mean follow-up time was 63 years (range, 0–25 years), totalling 9754 person-years at risk (54.5% prior to 1995). Mean age at time of MGUS detection was 68.3 years. In 156 cases (10.1%), the serum M-component was IgA, compared with IgG in 997 cases (65.0%), IgM in 299 cases (19.5%), biclonal in 53 cases (3.5%) and exclusively light chain in 30 cases (2.0%). In IgA-type MGUS, the mean level of IgA was 97 g/l (range, 1.2–29.3 g/l); in IgG-type MGUS, the mean level of IgG was 15.5 g/l (2.5–29.9 g/l); and in IgM-type MGUS the mean level of IgM was 7.9 g/l (0.4–29.5 g/l). Hypogammaglobulinaemia was present in 409 patients (26.6%).

During follow-up, 187 first-time fractures were recorded, corresponding to an incidence rate of 19 fractures/1000 person-years. The fractures were distributed as follows: 16 in vertebrae, pelvis or ribs, 155 in the femur, and 41 in the distal forearm. For the seven patients for whom more than one fracture was recorded on the same day, only the primary diagnosis was used for study purposes. Follow up of cohort members ceased for the following reasons: fractures in 187 patients, malignant transformation in 77 cases, death in 793 cases, and end of study in 478 following reasons: fractures in 187 patients, malignant transformation, after a median of 3 years of follow-up (range 0–9.6 years).

Because of the limited number of fractures at specific skeletal sites, we based our analyses on the total number of fractures. Kaplan–Meier curves for risk of fractures in MGUS patients and controls are shown in Fig 1.

A Cox regression model was used to analyse the impact of case status, age, sex, comorbidity and alcohol-related disease on fracture risk (Table I). In this model, the relative risk for MGUS was 1.4 (95% CI, 1.2–1.6). When hypogammaglobulinaemia was added to the model, the relative risk of this parameter was 1.0 (95% CI, 0.9–1.1) and it did not change the hazard ratio for MGUS. After 5 years of follow-up, the risk difference was 1.8% (95% CI, 0.5–3.0). Alcohol-related diagnoses were recorded in 49 (3.2%) of the MGUS patients and 247 (16%) of the population controls.

The analysis was stratified by M-component type. Patients with IgG-type MGUS and IgM-type MGUS had increased relative risks of fractures: 1.3 (95% CI, 1.1–1.6) and 1.6 (95% CI, 1.1–2.2) respectively. For IgA-type, biclonal, and light chain MGUS, the hazard ratios were normal. When stratified by light chain type, regardless of heavy chain type, fracture risk increased in patients with kappa light chain [relative risk = 1.4 (95% CI, 1.1–1.7)], as well as in patients with lambda light chain, although this was less marked [relative risk = 1.2 (95% CI, 0.9–1.5)]. Adjusting for hypogammaglobulinaemia did not change any of these estimates.
For patients with IgA-type, IgG-type and IgM-type MGUS, the concentration of the immunoglobulin comprising the M-component in g/L was included in subgroup analyses as a continuous variable. For IgA-type MGUS, the relative risk for IgA concentration was 1.03 (95% CI, 1.0–1.1), indicating an increased risk of fractures with higher IgA concentrations. For IgG-type MGUS, IgG concentration did not affect fracture risk. For IgM-type MGUS, the relative risk of IgM concentration was 0.97 (95% CI, 0.95–0.99), suggesting decreased risk with increasing IgM concentrations.

Discussion

We found an increased risk of fractures in MGUS patients compared with age- and gender-matched controls after adjusting for comorbidity. This finding is in accordance with the only previous study of fracture risk among MGUS patients that reported the follow-up of 488 MGUS patients in Olmsted County, Minnesota (Melton et al, 2004). In the Olmsted County study, 385 fractures were detected in 200 patients during a median 7.2 year follow-up period, yielding a standardised incidence ratio of 2.7 (95% CI, 2.3–3.1) for any axial fracture. The risk of limb fractures among MGUS patients was not elevated.

The fracture risk found in our study was substantially lower than that reported in the Olmsted Country study (Melton et al, 2004), particularly considering the larger size of our cohort. There are several possible explanations for this discrepancy. The mean age of the patients in our study was lower. Data from emergency units were not included until 1995, which implies that for approximately half of the observation period registration relied solely on hospital diagnoses. In our study, limb fractures were restricted to the femur and the distal forearm whereas the Olmsted County study included all types of limb fractures.

Pathological fractures due to lytic bone lesions, especially of the axial skeleton, are common in patients with MM. The fractures cluster around the time of MM diagnosis, probably as a result of the bone pain that brings patients to clinical attention (Melton et al, 2005). Also, pathological fractures are a criterion for diagnosis of this malignancy (International Myeloma Working Group, 2003). In contrast, osteoporotic fractures seem to be less of a problem; MM patients are only at a two-fold increased risk compared with the general population (Melton et al, 2005).

A key question is whether the increased risk of fractures in MGUS found in the two studies is attributable to cases of MM, either misclassified as MGUS or arising from malignant transformation of MGUS during follow-up. The study from Olmsted County did not account for the number of patients with fractures who subsequently developed MM (Melton et al, 2004). In our study, only a minority of MGUS patients with fractures was later found to have malignant transformation, so the increased risk of fractures could not be explained by symptomatic malignant gammopathy. The criteria applied in creating the MGUS cohort do confer a risk of including asymptomatic myeloma or indolent lymphoma patients. However, it is noteworthy that in our study the risk of malignant transformation expressed in terms of cumulative risk was lower than reported in most other studies (Gregersen et al, 2000). Thus, it is likely that the impact of asymptomatic myeloma on the cohort was comparable with that of other studies.

In a previous study of this cohort, increased mortality was found in MGUS patients because of various comorbid conditions, including non-haematological cancers (Gregersen et al, 2001). Many co-existing clinical conditions and diseases have been reported in MGUS patients, including chronic infections, autoimmune diseases, and neurological disorders (Colls & Lorier, 1975; Kyle et al, 2004). For most of these conditions, it is uncertain whether the prevalence is higher in MGUS patients than in the general population. It is also uncertain whether reported associations reflect a causal association or confounding by indication – implying that serum protein electrophoresis is performed on selected groups of patients (Gregersen et al, 2001; Kyle et al, 2004). The effect of comorbidity on fracture risk is complex and involves factors such as the impact of comorbid conditions, physical inactivity, risk of falling and use of drugs associated with risk of bone loss. The Charlson Comorbidity Index is a valid tool for estimating risk of death from comorbid diseases in longitudinal studies (Charlson et al, 1987). However, the index has not been validated in the context of fracture risk. It is possible that part of the increased fracture risk might be explained by a residual impact of comorbidity, not fully accounted for in our statistical analysis.

Although data regarding alcohol-related diseases was available, these diagnoses probably pertain only to patients with the highest alcohol intake. We were unable to obtain information regarding more moderate intake. We did find that presence of alcohol-related diseases were associated with MGUS. However, this may be explained by intensity of care factors. The diagnosis of MGUS may lead to a thorough examination that detects alcohol-related disease that otherwise would be overlooked. Conversely, patients in contact with the healthcare system for an alcohol-related disease may be more likely to be diagnosed with MGUS. Nevertheless, adjusting for alcohol-related diseases did not affect our risk estimates. Although we cannot rule out some residual confounding from alcohol-related diseases, it does not seem to explain the increased fracture risk among MGUS patients.

In our study, MGUS patients with lambda light chain were found to be only at a slightly increased risk of fractures, while those with kappa light chain were at significantly increased risk. The same pattern was noticed by Melton et al (2005). We are unable to explain these results, as there are no data to suggest an increased risk of fractures associated with kappa light chain in MM patients and there is no obvious pathophysiological explanation for this finding in MGUS patients. As Kappa light chains constitute approximately two-
thirds of light chains in MGUS, it is possible that the higher number of patients with kappa light chain underlies the statistical significance of their increased risk.

Our study design did not permit an evaluation of the causes of increased fracture risk in MGUS patients. In some cases monoclonal plasma cells may secrete factors that stimulate bone resorption, resulting in osteoporosis. A study of patients referred to an osteoporosis clinic detected MGUS in 3.6% of patients with subsequently confirmed osteoporosis, but in only 2% of patients for whom osteoporosis was ruled out (Abrahamsen et al., 2005).

In asymptomatic myeloma, prophylactic treatment with bisphosphonates may slow the development of skeletal complications without affecting the time to disease progression (Musto et al., 2003). Bisphosphonates have never been used as part of the treatment regimen for MGUS. Our study suggests that prophylactic treatment with bisphosphonates is required for many person-years in order to prevent just one serious hospital-treated fracture. However, there might be a preventive effect on the less serious fractures and a formal risk/benefit analysis is needed before moving forward with aggressive treatment of all MGUS patients. In addition, it is necessary to take into account potential side effects, such as osteonecrosis of the jaw, which is associated with prolonged bisphosphonate treatment (Marx et al., 2005).

The main strengths of our study were the precision of its estimates, conferred by the large size of the MGUS cohort, and use of data from the regional Hospital Discharge Registry, with its complete countywide registration of fractures. A study limitation is the risk of coding errors leading to misclassification of fractures. This risk was not likely to differ between the MGUS patients and the controls, and was therefore not likely to affect relative estimates of fracture risk. At the same time, it is well known that MGUS has a potential for malignant transformation, which may lead to increased diagnostic work-up and a higher likelihood of detecting fractures in MGUS patients, particularly vertebral fractures. This surveillance bias would lead to an overestimation of fracture risk in MGUS. It also should be noted that we lacked information on potential risk factors for fractures, such as body mass index, smoking status, alcohol intake, use of corticosteroids and specific medical conditions associated with osteoporosis.

In conclusion, we found an increased risk of fractures in MGUS patients that could not be explained by age, sex, comorbidity, or subsequent malignant transformation. While the absolute risk seems low, further studies are warranted to investigate the cause of the increased relative risk.

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References


