Monoclonal gammopathy of undetermined significance and risk of skeletal fractures: a population-based study

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Patients with multiple myeloma (MM) have an increased risk of fractures. On the basis of small numbers, patients with monoclonal gammopathy of undetermined significance (MGUS) have been reported to have an increased fracture risk. Using population-based data from Sweden, we assessed the risks of fractures in 5326 MGUS patients diagnosed from 1958 to 2006, compared with 20 161 matched controls. MGUS patients had an increased risk of any fracture at 5 (hazard ratio [HR] = 1.74; 95% confidence interval [CI], 1.58-1.92) and 10 (HR = 1.61; 95% CI, 1.49-1.74) years. The risk was significantly higher for axial (skull, vertebral/pelvis, and sternum/costae) compared with distal (arm and leg) fractures ($P < .001$). On the basis of 10 years of follow-up, there was an increased risk of vertebral/pelvic (HR = 2.37; 95% CI, 2.02-2.78), sternal/costae (HR = 1.93; 95% CI, 1.5-2.48), arm (HR = 1.23; 95% CI, 1.06-1.43), leg (HR = 1.40; 95% CI, 1.26-1.56), and other/multiple fractures (HR = 4.25; 95% CI, 3.29-5.51). Risks for fractures did not differ by isotype or M protein concentration at diagnosis. MGUS patients with (versus without) fractures had no excess risk of MM or Waldenström macroglobulinemia. Our results suggest that bone alterations are present in early myelomagenesis. Our findings may have implications for the development of better prophylaxis for bone disease in MGUS, and they provide novel clues on pathogenesis of MM bone disease. (*Blood*. 2010; 116(15):2651-2655)

Introduction

Multiple myeloma (MM) is a chronic malignant B-cell disorder characterized by plasma cell infiltration in the bone marrow and a monoclonal immunoglobulin in serum or urine or both.[1] Patients with MM have a variety of clinical signs and symptoms, with approximately 80% experiencing a pathologic fracture over the course of their disease, and 90% will have bone lesions.[2] Fractures and skeletal pain are thus a very important disease manifestation in this patient population.

According to recent studies, MM is always preceded by the precursor condition monoclonal gammopathy of undetermined significance (MGUS).[3] However, not all patients with MGUS develop MM, and the risk for transformation to MM, lymphoma, or amyloidosis has been reported to be 1% to 1.5% per year.[4] Although patients with MGUS are asymptomatic, they may have increased morbidity and mortality.[5-7]

Previous smaller studies found that patients with MGUS have an increased risk of fractures,[2,5,8,9] and that the prevalence of MGUS is high in patients with osteoporosis[9-11]; however, it is unclear whether this is associated with MM transformation or related to MGUS per se. On the basis of small numbers, patterns of fracture risk in relation to MGUS immunoglobulin (Ig) isotype and concentration of the monoclonal (M) protein concentration are inconsistent.[2,8] Furthermore, some, but not all, investigators have found abnormal bone resorption markers in patients with MGUS compared with healthy controls.[12-15]

Using high-quality population-based data from Sweden, we assessed the risk of fractures in 5326 patients with MGUS compared with 20 161 population-based matched controls. We further explored risk of fractures in relation to MGUS isotype and M protein concentration at diagnosis.

Methods

Central registries, patients, and controls

The details of the study population have been described previously.[16] In Sweden, a clinician who detects a patient with an M protein will typically consult with a hematologist at a hospital-based center and refer the patient for further work-up, to rule out a lymphoproliferative malignancy.

We established a nationwide MGUS cohort from a national hospital network that included patients with MGUS that was diagnosed between 1965 and 2005 in Sweden. When available, information on MGUS Ig isotype and concentration of the M protein at diagnosis was collected. To minimize the influence of a potentially undetected lymphoproliferative malignancy, patients with MGUS who developed a lymphoproliferative malignancy within 6 months of diagnosis were excluded from the analysis.

For each patient with MGUS, 4 population-based controls (matched by sex, year of birth, and county of residence) were chosen randomly from the Swedish Population database. All controls had to be alive and free of any preceding hematologic malignancy at the time of MGUS diagnosis for the corresponding case.

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Table 1. Characteristics of patients with MGUS and their matched controls

	Patients with MGUS	MGUS controls
Total, n	5326	20 161
Sex, N (%)		
Male	2642 (49.61)	9990 (49.55)
Female	2684 (50.39)	10 171 (50.45)
Median age at diagnosis, y (range)	71 (22-100)	71 (22-100)
Age group, y, n (%)		
Younger than 40	114 (2.14)	446 (2.21)
40-49	336 (6.31)	1310 (6.50)
50-59	765 (14.36)	2963 (14.70)
60-69	1210 (22.72)	4684 (23.33)
70-79	1779 (33.40)	6756 (33.51)
80 and older	1122 (21.07)	4002 (19.85)
MGUS subtype, n (%)		
IgG	2146 (40.29)	—
IgA	578 (10.85)	—
IgM	530 (9.95)	—
IgD	2 (0.00)	—
Missing	2070 (38.87)	—
M protein concentration, n (%)		
Less than 10.0 g/L	1732 (32.52)	—
At least 10.0 g/L	1108 (20.80)	—
Missing	2486 (46.68)	—

— indicates not applicable.

The centralized Swedish Patient Registry captures information on individual patient-based discharge diagnoses and discharge listings from inpatient (since 1964) and outpatient (since 2000) care, with a very high coverage.[17] Information on occurrence and date of fractures was obtained using the 7th, 8th, 9th, and 10th revisions of the International Classification of Diseases. All fractures were analyzed individually and grouped into 2 categories (axial and distal). Through linkage with the Cause of Death Register and the Register of Total Population, we collected information on vital status until December 31, 2006.

Approval was obtained from the Karolinska Institutional Review Board for this study. Informed consent was waived because we had no contact with study subjects. An exemption from review by the institutional review board was obtained from the National Institutes of Health Office of Human Subjects Research because we used existing data without personal identifiers.

Statistical analysis

Cox proportional hazard models (PROC PHREG; SAS Version 9.1; SAS Institute) were used to compare 5- and 10-year risks of fractures in patients with MGUS compared with controls. The proportional hazards assumption for variables used in the models was assessed by visual inspection of the hazard function and formally by including interaction terms between the covariates and time. Follow-up time for an MGUS case started at the later of either his or her diagnosis of MGUS or January 1, 1987, and for a control at the later of time of diagnosis of the matched case or January 1, 1987. The delayed entry was accommodated by the entrytime option in PROC PHREG. Follow-up ended at the time of diagnosis of a specific fracture event, or at time of censoring. Censoring events were death, emigration, or the end of the data acquisition period (December 31, 2006). For the analysis of MGUS cases and controls, persons were additionally censored at the time of diagnosis of MM or Waldenström macroglobulinemia (WM). Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated overall and separately for men and women. Adjustment variables included in the models were sex, age at diagnosis, and year of diagnosis in quartiles. In addition to sex, models were stratified by MGUS isotype and M protein concentration at diagnosis. *P* values for heterogeneity of effects by MGUS isotype were computed by including appropriate interaction terms in the models. To compute *P* values for heterogeneity for risk of axial (skull, vertebral/pelvis, and sternum/costae) versus distal (arm and leg) fractures, we duplicated the cohort and added an indicator variable with value zero for the original cohort and value one for the duplicated cohort. We then counted axial fractures as events in the original and distal in the duplicated cohort and tested for differences by including an interaction term between case-control status and the cohort indicator. Dependence between the cohorts was accommodated with the use of the sandwich variances estimate.

Results

A total of 5326 patients with MGUS and 20 161 matched controls were included in the study. Demographic and clinical characteristics of the patients and controls are shown in Table 1. The median age at diagnosis was 71 years, and 50% of patients were men.

MGUS isotype was available for 61% of patients, and was IgG, IgA, and IgM in 40%, 11%, and 10%, respectively. Data on M protein concentration at diagnosis were available for 53% of patients; of those, 60% had concentrations above 10.0 g/L and 40% below (Table 1).

Compared with controls patients with MGUS had a significantly increased risk of any fracture of 1.7-fold (95% CI, 1.6-fold to 1.9-fold) and 1.6-fold (1.5-fold to 1.7-fold) after 5 and 10 years of follow-up, respectively (Table 2). No statistical difference was observed in risk between men and women. When analyzing specific anatomic sites of fractures, patients with MGUS had a

Table 2. Relative risk of selected fractures after a diagnosis of MGUS compared with matched controls

	5-y follow-up			10-y follow-up		
Disease/grouping	MGUS (n = 5326)	Ctrl (n = 20 161)	HR* (95% CI)	MGUS	Ctrl	HR* (95% CI)
Any fracture (combined)						
All patients	569	1461	1.74 (1.58-1.92)	880	2455	1.61 (1.49-1.74)
Men	222	519	1.89 (1.61-2.21)	337	874	1.71 (1.51-1.94)
Women	347	942	1.66 (1.47-1.88)	543	1581	1.56 (1.42-1.72)
Specific fractures						
Skull fracture	15	52	1.22 (0.69-2.17)	23	81	1.20 (0.76-1.91)
Vertebral/pelvis fracture	155	255	2.67 (2.18-3.26)	231	435	2.37 (2.02-2.78)
Sternum/costae fracture	52	109	2.06 (1.48-2.87)	87	197	1.93 (1.50-2.48)
Arm fracture	130	399	1.38 (1.13-1.69)	224	777	1.23 (1.06-1.43)
Leg fracture	279	807	1.53 (1.33-1.75)	439	1394	1.40 (1.26-1.56)
Other/multiple bone fractures	78	71	4.55 (3.30-6.27)	116	115	4.25 (3.29-5.51)

HR indicates hazard ratio; CI, confidence interval; and ctrl, controls.

*Adjusted for age, sex, and calendar period.

Table 3. Relative risk of selected fractures among patients with MGUS patients (vs matched controls), stratified by MGUS subtype

	IgG/IgA subtype						IgM subtype					
	5-y follow-up			10-y follow-up			5-y follow-up			10-y follow-up		
Disease/grouping	MGUS (n = 2724)	Ctrl (n = 10 348)	HR* (95% CI)	MGUS	Ctrl	HR* (95% CI)	MGUS (n = 530)	Ctrl (n = 2017)	HR* (95% CI)	MGUS	Ctrl	HR* (95% CI)
Any fracture	276	685	1.67 (1.45-1.92)	446	1214	1.55 (1.39-1.73)	59	169	1.31 (0.97-1.76)	95	275	1.30 (1.03-1.64)
Axial fractures†	104	184	2.27 (1.79-2.89)	169	331	2.12 (1.76-2.55)	20	49	1.48 (0.88-2.50)	30	71	1.59 (1.04-2.44)
Distal fractures‡	177	532	1.36 (1.15-1.61)	298	974	1.27 (1.11-1.44)	43	126	1.28 (0.91-1.81)	70	223	1.17 (0.89-1.53)

HR indicates hazard ratio; CI, confidence interval; and ctrl, controls.
*Adjusted for age, sex, and calendar period.
†Skull, vertebral/pelvis, sternum/costae.
‡Arm, leg.

significantly increased 5- and 10-year risk of vertebral/pelvis (HR = 2.7; 95% CI, 2.2-3.2 and HR = 2.4; 95% CI, 2.0-2.8), sternum/costae (HR = 2.1; 95% CI, 1.5-2.9 and HR = 1.9; 95% CI, 1.5-2.5), arm (HR = 1.4; 95% CI, 1.1-1.7 and HR = 1.2; 95% CI, 1.1-1.4), leg (HR = 1.5; 95% CI, 1.3-1.8 and HR = 1.4; 95% CI, 1.3-1.6), and other/multiple fractures (HR = 4.6; 95% CI, 3.3-6.3 and HR = 4.3; 95% CI, 3.3-5.5).

Analyses on the basis of type of M protein are shown in Table 3. Patients with IgG or IgA MGUS had a significantly increased risk of any fracture at 5 years (HR = 1.7; 95% CI, 1.5-1.9) and 10 years (HR = 1.6; 95% CI, 1.4-1.7) of follow-up. The risk for axial (skull, vertebral/pelvis, and sternum/costae) fractures was higher compared with distal (arm and leg) fractures according to 5 years (HR = 2.3; 95% CI, 1.8-2.9 vs HR = 1.4; 95% CI, 1.2-1.6; $P < .001$) and 10 years (HR = 2.1; 95% CI, 1.8-2.6 vs HR = 1.3; 95% CI, 1.1-1.4; $P < .001$) of follow-up. Risk of any fracture among patients with IgM MGUS was increased at 10 years (HR = 1.3; 95% CI, 1.0-1.6) but not at 5 years after diagnosis. Risk of any fracture on the basis of 5 ($P = .14$) and 10 ($P = .18$) years of follow-up between IgG/IgA and IgM MGUS was not statistically different.

The risk of fractures on the basis of 5 and 10 years of follow-up in patients with MGUS with a high compared with low M protein concentration at diagnosis (above vs below 10.0 g/L) was similar (Table 4).

Within 10 years after MGUS diagnosis, 187 patients with IgG/IgA had progressed to MM. The risk of progression to MM did not differ between patients with MGUS with fracture and patients without (HR = 0.7; 95% CI, 0.4-1.4). Similarly, among patients with MGUS with an IgM isotype, the risk for WM was similar when analyzing patients with fractures compared with patients without fractures. Sensitivity analyses that excluded fractures occurring within 12 months before MM or WM diagnosis gave similar results (data not shown).

Discussion

In this large study that included more than 5000 patients with MGUS and their matched controls, we found that patients with MGUS had an increased risk of fractures. Importantly, we did not find fractures to predict for MM or WM progression. Our findings provide further support for the development of osteoporosis prophylaxis strategies in patients with MGUS and are of importance for the understanding of the underlying mechanisms for bone disease in MGUS and MM.

Available information on fracture risk in MGUS is restricted and typically based on small numbers.[2,5,8,9] In one study that included 488 patients with MGUS, an increased risk was only observed of axial but not distal fractures.[2] In a screening study from the Mayo Clinic, based on 605 patients with MGUS, a significantly increased risk was observed of vertebral, hip, and clavicle fractures, whereas there was no increase in the risk of fracture of long bones.[5] To our knowledge, these are the only 2 studies that analyzed the risk of different types of fractures in patients with MGUS. In contrast to these investigations, we observed an increased risk of many types of fractures after 5 and 10 years of follow-up, including fracture of the vertebra, pelvis, sternum, ribs, arms, and legs. When we analyzed axial and distal fractures separately, we found a higher risk of axial than distal fractures among patients with IgG/IgA MGUS; however, both were significantly higher than for controls. Taken together, these data show that patients with MGUS have an increased risk of fractures; however, the higher risk in axial sites suggests that the underlying mechanism might be related to the production of hematopoietic marrow, primarily seen in axial bones. Interestingly, studies that used more sensitive methods such as magnetic resonance imaging have detected more bone lesions than standard bone survey in patients

Table 4. Relative risk of selected fractures among patients with MGUS (vs matched controls), stratified by M protein concentration at diagnosis

	Concentration of M protein below 10 g/L						Concentration of M protein above 10 g/L					
	5-y follow-up			10-y follow-up			5-y follow-up			10-y follow-up		
Disease/grouping	MGUS (n = 1732)	Ctrl (n = 6585)	HR* (95% CI)	MGUS	Ctrl	HR* (95% CI)	MGUS (n = 1108)	Ctrl (n = 4214)	HR* (95% CI)	MGUS	Ctrl	HR* (95% CI)
Any fracture	173	448	1.61 (1.35-1.92)	278	776	1.52 (1.32-1.74)	117	303	1.55 (1.25-1.92)	184	497	1.52 (1.28-1.80)
Axial fractures†	64	113	2.28 (1.68-3.11)	100	211	1.99 (1.57-2.53)	43	88	1.86 (1.29-2.69)	68	134	2.02 (1.51-2.70)
Distal fractures‡	123	360	1.41 (1.15-1.74)	202	637	1.32 (1.13-1.55)	71	225	1.26 (0.97-1.65)	119	393	1.22 (1.00-1.50)

HR indicates hazard ratio; CI, confidence interval; and ctrl, controls.
*Adjusted for age, sex, and calendar period.
†Skull, vertebral/pelvis, sternum/costae.
‡Arm.

with MM and that they predicted survival.[18] Future studies are needed to characterize bone disease in patients with MGUS because this may have prognostic indications. Currently, international guidelines do not recommend the use of bisphosphonates in patients with MGUS.[19] However, 2 studies have evaluated the effect of bisphosphonates in patients with MGUS and have found an improvement in bone mineral density and bone loss.[20,21] Randomized clinical trials are needed to establish the role of bisphosphonates in patients with MGUS.

On the basis of small numbers, contradictory results have been reported about MGUS isotype and fracture risk. In the Danish study, including 1535 patients with MGUS, IgG and IgM MGUS was found to be associated with a higher risk,[8] whereas in the Mayo Clinic study (n = 488), IgG MGUS was found to be protective.[22] In our study, we found that among 2724 patients with IgG/IgA MGUS, there was a slightly higher risk of fractures compared with that among 530 patients with IgM MGUS; however, the difference was not significant. It is possible that this might be due to small numbers. Future studies are needed to address this issue. Similar to previous studies,[8,22] we found no association between concentration of M protein and risk of fractures. The underlying mechanisms for these findings need to be explored.

Our study adds substantially to the limited literature on fracture risk in MGUS. Earlier studies have found an abnormal bone degradation by histomorphometric studies in bone biopsies from patients with MGUS.[23] In addition, an increase in bone resorption makers has been found in some MGUS studies but not all.[12-15,24-26] Interestingly, characterization of markers such as receptor activator of nuclear factor-κB ligand has provided new insights into the pathophysiology of bone disease in MM and has also been shown to be affected in patients with MGUS.[9,27] In addition, studies have shown an increased production of the Wnt-signaling antagonist DKK1 in MM but not in patients with MGUS,[28] and that it correlates with focal bone lesions in patients with MM.[29] Because MM is consistently preceded by MGUS,[3] there may be similar subgroups of patients with MGUS who have different risks of bone disease; however, other biomarkers of bone disease may also play a role. Interestingly, the expression of DKK1 was increased in patients with MGUS compared with controls and not in advanced MM, suggesting that these inhibitors may mediate bone destruction in the early phase of MM or even in MGUS.[28]

Our study has several strengths, including its large size as well as the application of high-quality data from Sweden, its population with access to standardized medical care during the entire study period. In our study, we used a register-based cohort design, which ensured a population-based setting and generalization of our findings. As reported previously,[30] the patients with MGUS in our study had their condition diagnosed at hematology/oncology outpatient units. In accordance with clinical practice in Sweden, most patients with MGUS typically underwent a bone marrow examination as part of the clinical workup. In a recent validation study, we have reported that ascertainment and diagnostic accuracy for lymphoproliferative disorders is very high (> 90%-95%) in Sweden.[31] Limitations include the lack of information on potential confounders (although the matched design and analyses ensured adjustment for sex, age, and geography) and lack of detailed clinical data, including underlying diseases. Because our data do not come from an MGUS screening study, some of the controls might have an undiagnosed MGUS, and also the observed excess risks among patients with MGUS may partly reflect various underlying medical illnesses that lead to the medical workup and the detection of the M protein. To minimize such influences, patients with MGUS with a diagnosis of a lymphoproliferative malignancy and fractures occurring within 6 months after MGUS diagnosis were excluded from our analyses. Another limitation is the potential inaccuracy and lack of independent validation of fracture diagnosis obtained from the centralized Patient Registry. However, because we compared MGUS cases with matched controls, using data from the same registries, the ascertainment should be nondifferential, and any bias should be toward a null association.

In summary, compared with controls, we found patients with MGUS to have a significantly increased risk of several types of fractures. We did not find the occurrence of fracture to be a predictor of MM or WM progression among patients diagnosed with MGUS. Our findings are of relevance for the development of clinical studies designed to uncover pathogenesis and to prevent bone disease in early myelomagenesis. Consequently, they may have implications for the development of future MM treatment strategies that target the bone marrow microenvironment.

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Authorship

Contribution: S.Y.K., M.B., I.T., and O.L. designed the study; S.Y.K., M.B., I.T., and O.L. obtained data and initiated this work; M.T. and R.M.P. performed all statistical analyses. All the authors were involved in the interpretation of the results. S.Y.K., R.M.P., and O.L. wrote the report. All authors read, gave comments, and approved the final version of the manuscript. All authors had full access to the data in the study and take responsibility for the accuracy of the data analysis.

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References

1. Kyle RA, Rajkumar SV. Multiple myeloma. *N Engl J Med.* 2004;351(18):1860-1873.

2. Melton LJ III, Kyle RA, Achenbach SJ, Oberg AL, Rajkumar SV. Fracture risk with multiple myeloma: a population-based study. *J Bone Miner Res.* 2005; 20(3):487-493.

3. Landgren O, Kyle RA, Pfeiffer RM, et al. Monoclonal gammopathy of undetermined significance (MGUS) consistently precedes multiple myeloma: a prospective study. *Blood.* 2009;113(22):5412-5417.
4. Kyle RA, Therneau TM, Rajkumar SV, et al. A long-term study of prognosis in monoclonal gammopathy of undetermined significance. *N Engl J Med.* 2002;346(8):564-569.
5. Bida JP, Kyle RA, Therneau TM, et al. Disease associations with monoclonal gammopathy of undetermined significance: a population-based study of 17,398 patients. *Mayo Clin Proc.* 2009; 84(8):685-693.
6. Kristinsson SY, Fears TR, Gridley G, et al. Deep vein thrombosis after monoclonal gammopathy of undetermined significance and multiple myeloma. *Blood.* 2008;112(9):3582-3586.
7. Kristinsson SY, Bjorkholm M, Andersson TM, et al. Patterns of survival and causes of death following a diagnosis of monoclonal gammopathy of undetermined significance: a population-based study. *Haematologica.* 2009;94(12):1714-1720.
8. Gregersen H, Jensen P, Gislum M, Jorgensen B, Sorensen HT, Norgaard M. Fracture risk in patients with monoclonal gammopathy of undetermined significance. *Br J Haematol.* 2006;135(1): 62-67.
9. Pepe J, Petrucci MT, Nofroni I, et al. Lumbar bone mineral density as the major factor determining increased prevalence of vertebral fractures in monoclonal gammopathy of undetermined significance. *Br J Haematol.* 2006;134(5): 485-490.
10. Abrahamsen B, Andersen I, Christensen SS, Skov Madsen J, Brixen K. Utility of testing for monoclonal bands in serum of patients with suspected osteoporosis: retrospective, cross sectional study. *BMJ.* 2005;330(7495):818.
11. Golombick T, Diamond T. Prevalence of monoclonal gammopathy of undetermined significance/ myeloma in patients with acute osteoporotic vertebral fractures. *Acta Haematol.* 2008;120(2): 87-90.
12. Hernandez JM, Suquia B, Queizan JA, et al. Bone remodelation markers are useful in the management of monoclonal gammopathies. *Hematol J.* 2004;5(6):480-488.
13. Jakob C, Zavrski I, Heider U, et al. Bone resorption parameters [carboxy-terminal telopeptide of type-I collagen (ICTP), amino-terminal collagen type-I telopeptide (NTx), and deoxypyridinoline (Dpd)] in MGUS and multiple myeloma. *Eur J Haematol.* 2002;69(1):37-42.
14. Laroche M, Attal M, Dromer C. Bone remodelling in monoclonal gammopathies of uncertain significance, symptomatic and nonsymptomatic myeloma. *Clin Rheumatol.* 1996;15(4):347-352.
15. Vejlgaard T, Abildgaard N, Jans H, Nielsen JL, Heickendorff L. Abnormal bone turnover in monoclonal gammopathy of undetermined significance: analyses of type I collagen telopeptide, osteocalcin, bone-specific alkaline phosphatase and propeptides of type I and type III procollagens. *Eur J Haematol.* 1997;58(2):104-108.
16. Landgren O, Kristinsson SY, Goldin LR, et al. Risk of plasma cell and lymphoproliferative disorders among 14621 first-degree relatives of 4458 patients with monoclonal gammopathy of undetermined significance (MGUS) in Sweden. *Blood.* 2009;114(4):791-795.
17. *Patientregistret 1987-1996: Kvalitet och innehåll* (in Swedish). Stockholm, Swedem: EpC, National Board of Health and Welfare; 1998.
18. Walker WJ, Bratby MJ. Magnetic resonance imaging (MRI) analysis of fibroid location in women achieving pregnancy after uterine artery embolization. *Cardiovasc Intervent Radiol.* 2007;30(5): 876-881.
19. Terpos E, Sezer O, Croucher PI, et al. The use of bisphosphonates in multiple myeloma: recommendations of an expert panel on behalf of the European Myeloma Network. *Ann Oncol.* 2009; 20(8):1303-1317.
20. Pepe J, Petrucci MT, Mascia ML, et al. The effects of alendronate treatment in osteoporotic patients affected by monoclonal gammopathy of undetermined significance. *Calcif Tissue Int.* 2008;82(6):418-426.
21. Berenson JR, Yellin O, Boccia RV, et al. Zoledronic acid markedly improves bone mineral density for patients with monoclonal gammopathy of undetermined significance and bone loss. *Clin Cancer Res.* 2008;14(19):6289-6295.
22. Melton LJ III, Rajkumar SV, Khosla S, Achenbach SJ, Oberg AL, Kyle RA. Fracture risk in monoclonal gammopathy of undetermined significance. *J Bone Miner Res.* 2004;19(1):25-30.
23. Bataille R, Chappard D, Basle MF. Quantifiable excess of bone resorption in monoclonal gammopathy is an early symptom of malignancy: a prospective study of 87 bone biopsies. *Blood.* 1996;87(11):4762-4769.
24. Woitge HW, Horn E, Keck AV, Auler B, Seibel MJ, Pecherstorfer M. Biochemical markers of bone formation in patients with plasma cell dyscrasias and benign osteoporosis. *Clin Chem.* 2001;47(4): 686-693.
25. Diamond T, Levy S, Smith A, Day P, Manoharan A. Non-invasive markers of bone turnover and plasma cytokines differ in osteoporotic patients with multiple myeloma and monoclonal gammopathies of undetermined significance. *Intern Med J.* 2001;31(5):272-278.
26. Pecherstorfer M, Seibel MJ, Woitge HW, et al. Bone resorption in multiple myeloma and in monoclonal gammopathy of undetermined significance: quantification by urinary pyridinium crosslinks of collagen. *Blood.* 1997;90(9):3743-3750.
27. Politou M, Terpos E, Anagnostopoulos A, et al. Role of receptor activator of nuclear factor-kappa B ligand (RANKL), osteoprotegerin and macrophage protein 1-alpha (MIP-1a) in monoclonal gammopathy of undetermined significance (MGUS). *Br J Haematol.* 2004;126(5):686-689.
28. Tian E, Zhan F, Walker R, et al. The role of the Wnt-signaling antagonist DKK1 in the development of osteolytic lesions in multiple myeloma. *N Engl J Med.* 2003;349(26):2483-2494.
29. Kaiser M, Mieth M, Liebisch P, et al. Serum concentrations of DKK-1 correlate with the extent of bone disease in patients with multiple myeloma. *Eur J Haematol.* 2008;80(6):490-494.
30. Landgren O, Kristinsson SY, Goldin LR, et al. Risk of plasma cell and lymphoproliferative disorders among 14 621 first-degree relatives of 4458 patients with monoclonal gammopathy of undetermined significance in Sweden. *Blood.* 2009; 114(4):791-795.
31. Turesson I, Linet MS, Bjorkholm M, et al. Ascertainment and diagnostic accuracy for hematopoietic lymphoproliferative malignancies in Sweden 1964-2003. *Int J Cancer.* 2007;121(10):2260-2266.