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pour le

DIPLÔME D'ÉTAT DE DOCTEUR EN MÉDECINE

Qualification en Rhumatologie.

Bone Fragility in Monoclonal Gammopathy of Undetermined Significance: A Cohort Study

Fragilité osseuse et gammapathie monoclonale de signification indéterminée : Une étude de cohorte

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Sous la direction du Pr Béatrice BOUVARD

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Admis(e) dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçu (e) à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs. Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

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Liste des abréviations

K	kappa
λ	lambda
ABQ	Algorithm Based Qualitative
ASQ	Analyse Semi Quantitative de Genant
B2m	Beta 2 microglobulin
BALP	Bone alkaline phosphatase
BM	bone marrow
BMD	Bone mass density
BMI	Body mass index
CTX	C-terminal of type 1 collagen
DXA	Dual-energy X-ray absorptiometry
FLC	Free light chains
Hb	Haemoglobin
Ig	Immunoglobulin
LDH	Lactate deshydrogenase
MM	multiple myeloma
PTH	Parathyroid hormone
RR	Relative risk
SBP	Serum Binding Protein
SMM	Smouldering multiple myeloma
SWM	Smouldering Waldenström's macroglobulinemia
TBS	Trabecular Bone Score
WM	Waldenström's macroglobulinemia

RESUME

Introduction : La gammapathie monoclonale de signification indéterminée (MGUS) est une hémopathie plasmocytaire pré-maligne associée à un risque accru de fractures, comme l'ont montré des études rétrospectives. Les facteurs de risque de fragilité osseuse dans la MGUS restent mal connus. L'objectif de cette étude était d'analyser prospectivement les variations de la densité minérale osseuse (DMO), l'incidence des fractures et les paramètres biologiques chez des patients atteints de MGUS, afin d'identifier les facteurs de risque de fragilité osseuse.

Méthodes : L'étude GREMOS est une étude de cohorte prospective et monocentrique, incluant des patients récemment diagnostiqués avec une gammapathie monoclonale. Tous les patients ont eu une évaluation osseuse et hématologique (données cliniques, biologiques, radiographies du rachis, densitométrie osseuse) et ont été invités à une réévaluation à 2 ans.

Résultats : 491 patients ont été inclus (51.7 % de femmes, âge moyen de 67,5 ans). La chaîne lourde la plus fréquente était l'IgG (53,6 %), suivie de l'IgM (29,3 %) et de l'IgA (10,4 %). La chaîne légère était kappa dans 57,6 % des cas. Parmi les participants, 96,7 % étaient atteints de MGUS, 1,8 % de myélome multiple indolent (SMM) et 1,4 % de macroglobulinémie de Waldenström indolente (SWM). Lors de l'évaluation initiale, 31,8 % des patients étaient considérés comme ostéoporotiques, 10,8 % présentaient au moins une fracture vertébrale ostéoporotique et 22,2 % avaient une ostéoporose densitométrique. Après cette première évaluation, 94 patients ont reçu un traitement anti-ostéoporotique. Lors du suivi, 57 patients ont présenté un nouvel événement osseux, incluant 32 nouveaux cas d'ostéoporose densitométrique et 30 fractures ostéoporotiques majeures, dont 24 fractures vertébrales. Les patients ayant développé de nouveaux événements osseux étaient significativement plus âgés et avaient plus souvent un antécédent de fracture vertébrale.

L'âge (OR 1.05) et l'antécédent de fracture vertébrale (OR 3,3) étaient significativement et indépendamment associés à un nouvel événement osseux. De même, l'âge (OR 1,09) et les antécédents de fracture vertébrale (OR 2,92) étaient indépendamment associés à la survenue d'une nouvelle fracture vertébrale ostéoporotique.

Conclusion : Aucune caractéristique de la MGUS n'a été retrouvée associée à la survenue de nouvelles fractures vertébrales ostéoporotiques. L'âge et les antécédents de fracture vertébrale étaient les principaux facteurs de risque indépendants de fracture vertébrale incidente chez les patients atteints de MGUS.

ABSTRACT

Introduction: Monoclonal gammopathy of undetermined significance (MGUS) is a premalignant plasma cell disorder that has been associated with an increased risk of fractures in retrospective studies. However, the risk factors for bone fragility in MGUS remain poorly understood. The aim of our study was to prospectively analyse changes in bone mineral density (BMD), fracture incidence, and biochemical parameters in MGUS patients and to identify risk factors for bone fragility.

Methods: The GREMOS study is a prospective, single-center cohort study of patients newly diagnosed with monoclonal gammopathy. All participants underwent a bone and haematological assessment (clinical and biological data, spinal radiography, dual-energy X-ray absorptiometry) and were invited to a reassessment after two years.

Results: 491 patients were included, 51.7% female, mean age 67.52 years. The most common heavy chain was IgG (53.6%), followed by IgM (29.3%) and IgA (10.4%). The light chain was kappa in 57.6% of cases. 96.7% were diagnosed with MGUS, 1.8% with smouldering multiple myeloma (SMM), and 1.4% with smouldering Waldenström's macroglobulinemia (SWM). At baseline, 31.8% of patients were classified as osteoporotic, 10.8% had at least one osteoporotic vertebral fracture, and 22.2% had densitometric osteoporosis. After the initial assessment, 94 patients received anti-osteoporotic treatment. At follow-up, 57 patients had a new bone event, 32 had a new densitometric osteoporosis, and 30 had a new major osteoporotic fracture including a vertebral fracture in 24 of them. Patients who developed new bone events were significantly older and more likely to have a history of vertebral fractures. Age and previous vertebral fracture (OR 3.3) were significantly and independently associated with a new bone event. Similarly, age (OR 1.09) and previous

vertebral fractures (OR 2.92) were independently associated with new osteoporotic vertebral fractures.

Conclusion: No specific MGUS characteristics were found to be associated with the occurrence of new osteoporotic vertebral fractures. Age and previous vertebral fractures were the main and independent risk factors for vertebral fractures in MGUS patients.

INTRODUCTION

Monoclonal gammopathy of undetermined significance (MGUS) is an asymptomatic pre-malignant plasma cell disorder. It affects 3.2% of the population over the age of 50 and increases with age to 8.3 % over the age of 80 (1). MGUS is defined by a monoclonal immunoglobulin less than 30g/L, a bone marrow (BM) plasma cell percentage less than 10% and the absence of symptoms associated with multiple myeloma (MM) (lytic lesion, hypercalcemia, anemia, renal failure), Waldenström's macroglobulinemia (WM) or any other disorder associated with monoclonal gammopathy (amyloidosis, peripheral neuropathy, …) (2). MGUS consistently precedes MM (3) ; the risk of progression to MM or related disease is ~1% per year, 10% at 10 years, and 18% at 20 years (4,5).

The pathophysiology of the bone complication of MM is well understood; it is caused by a decoupling of bone turnover with an increase in osteoclast activity leading to an increased bone resorption and a decrease in bone formation resulting in the osteolytic lesions, bone mineral loss and skeletal-related events (6).

Studies have shown an increased risk of fractures, particularly vertebral fractures, and a lower bone mineral density (BMD) (7), as early as the MGUS stage, suggesting early bone alterations. In their retrospective cohort study, Melton et al (8) found an increased risk of osteoporotic fracture (SIR, 2.5; 95% CI, 2.1–2.9) explained by an excess of vertebral fractures (SIR, 6.3; 95% CI, 5.2–7.5). In the Swedish registry (9), MGUS patients had an increased risk of any fracture at 5 years of 1.74 and an increased risk of vertebral/pelvic fracture of 2.37. These findings challenge the term « undetermined significance » and lead experts to recommend an initial bone assessment using a dual-energy X-ray absorptiometry (DXA) scan to assess BMD in MGUS (10). MM and MGUS are more common in patients referred to an osteoporosis clinic than expected in the background population, justifying

systematic screening for monoclonal gammopathy in patients with osteoporosis and fragility fractures (11,12).

We know the risk factors for the progression of MGUS to hematological malignancies (serum monoclonal protein >15g/l, IgM or IgA vs IgG, abnormal free light chains (FLC) ratio, low concentration of uninvolved immunoglobulins) (13,14). Osteoporosis at the time of diagnosis of MGUS would not increase the risk of progression to MM (9,15). Otherwise, the risk factors for bone fragility associated with MGUS are less well understood. Conflicting results have been reported regarding the possible involvement of the lambda (λ) (16) or kappa (κ) light chains (8,17), the concentration of the monoclonal protein depending on the heavy chain isotypes (17) on fracture risk.

Our study aimed to prospectively analyse changes in BMD, fracture incidence and biochemical parameters in a population with MGUS and to identify risk factors for bone fragility.

MÉTHODES

1. Patients

The GREMOS (Gammapathie monoclonale et REModelage OSseux) study was a prospective, monocentric study carried out by the Rheumatology Department of the University Hospital of Angers. Since January 2008, patients with a monoclonal gammopathy have been referred to the Rheumatology Department by their general practitioner or another specialist for a simultaneous assessment of gammopathy and osteoporosis, regardless of the context of discovery of the gammopathy (assessment of asthenia, osteoporosis, anemia…).

After the initial assessment, patients with malignant haemopathy were referred to the haematology unit for management. Patients with MGUS, smoldering multiple myeloma (SMM), or smoldering Waldenström's macroglobulinemia (SWM) were followed up in the rheumatology unit and invited for a repeat bone and haematological assessment after two years.

The inclusion criteria for this follow-up study were age ≥ 40 years at the first assessment, a diagnosis of monoclonal gammopathy according to the International Myeloma Working Group criteria, SMM (2), and SWM (18).

We excluded patients who did not have two assessments, including those who did not have two DXA scans or two radiographic evaluations of the spine and those who were reassessed in less than 18 months.

At each assessment, appropriate anti-osteoporotic treatment was initiated as needed (19), including bisphosphonates and vitamin D supplementation.

The study was approved by the local ethics committee (N° CNIL 2019-024) and was conducted in accordance with the principles of the Declaration of Helsinki.

2. Methods

One patient had all tests performed on the same day. During both assessments, the following data were collected for each patient.

2.1. Clinical data

Clinical data included weight, height, body mass index (BMI), clinical signs of neuropathy, skin lesions, medical and surgical history, current treatments, lifestyle, and risk factors for osteoporosis : ethnicity, sex, age, age at onset of menopause, hormone replacement therapy, personal history of falls and fractures and the condition in which they occurred, family history of fragility fractures, corticosteroid therapy, hormone therapy for cancer, hyperthyroidism, dietary calcium intake, vitamin D supplementation, smoking and alcohol consumption.

2.2. Spinal radiography evaluation

Each patient had pelvic, anteroposterior, and lateral X-rays of the thoracic and lumbar spine. Two trained rheumatologists independently analysed the radiographs. The patient was classified as having a vertebral fracture if both readers independently found a definite fracture. First, each vertebral fracture was classified as benign or malignant based on classic radiographic signs (destruction of the cortical rim or not, posterior convexity or not). The diagnosis of osteoporotic vertebral fracture was then made first using the qualitative analyse (ABQ = Algorithm Based Qualitative) of Jiang (20) defined as: osteoporotic fracture (depressed vertebral plateau), deformity not related to osteoporosis "short vertebral height without fracture" (reduction ≥ 15% of vertebral height without vertebral plateau fracture) and normal vertebrae, and secondly using the semi-quantitative criteria according to the apparent degree of vertebral height decrease by visual estimation on the Genant scale (21) (***figure 1***): mild or grade 1 for a reduction of 20-25% in anterior, middle and/or posterior

height, moderate or grade 2 for a reduction of 26-40% in any height and severe or grade 3 for a reduction > 40% in any height. The diagnosis of osteoporotic vertebral fracture was definitively accepted in the absence of a history of vertebral trauma.

2.3. Bone mineral density

BMD was measured at the femoral neck, total hip and lumbar spine, using dual-energy X-rays absorptiometry (DXA) operating in fan-beam mode (Hologic QRD 4500A densitometer, Hologic inc, Waltham, MA, USA). Lumbar BMD was assessed from L1 to L4, in the postero-anterior, view incidence, and fractured vertebrae were excluded from the analysis. As usual, the results were expressed in absolute values (g/cm^2) and using T- and Z-scores. T- and Z-scores were calculated using manufacturers references.

All scans were interpreted according to the International Society of Clinical Densitometry. Densitometric osteoporosis was defined as a T-score ≤ -2.5.

A variation of at least 0.03 g/cm^2 between two examinations was considered significant.

2.4. Trabecular Bone Score (TBS)

From January 2019, TBS measurements were obtained from lumbar spine DXA images using TBS iNsight software version 3.0 (Medimaps, Merignac, France). The TBS values were categorised as low (TBS ≤ 1.23), intermediate (1.23 < TBS ≤ 1.31) or normal (TBS > 1.31) based on meta-analysis and population studies (22). The TBS analysis method involves the evaluation of local pixel variations in the densitometric image, which are hypothesised to reflect the trabecular microarchitecture and are associated with osteoporotic fractures. A low TBS value is associated with poorer bone architecture; conversely, a high TBS value is correlated with a better bone structure.

2.5. Biological data

Laboratory tests were performed on fasting subjects at 08:00 hours without freezing to confirm and quantify gammopathy and to assess parameters of mineral metabolism and bone turnover: serum protein electrophoresis to obtain the monoclonal protein level, serum and urinary immunoelectrophoresis, free light chains κ and λ, cells blood count, haemoglobin, β2 microglobulin (B2m), lactate dehydrogenase (LDH), creatinine, serum calcium, phosphate, albumin, 25-hydroxyvitamin D, parathyroid hormone (PTH), bone-alkaline phosphatase (BALP), C-terminal telopeptide of type I collagen serum (CTX), LH, FSH, Serum Binding Protein (SBP), for women E2 and progesterone, for men total testosterone. Anti-MAG and anti-gangliosides antibodies were measured in the case of IgM gammopathy with clinical signs of neuropathy.

A bone marrow biopsy for plasmacytosis or lymphoplasmocytosis assessment was carried out at the 1st or second assessment in the following situations: IgG > 10 g/L, IgA or IgM.

2.6. Statistical analyses

Statistical analyses were performed using the software Statistical Package for the Social Sciences (SPSS V15.01, SPSS Inc., IBM Corporation, Chicago, IL, USA). Initial characteristics and characteristics at the second assessment were expressed as mean +/- s.d. for continuous variables and n (%) for categorical variables. The comparison of groups was performed by analysis of variance (ANOVA) for continuous variables and by the Pearson Chi2 test for binary variables. The evolution of the different parameters was evaluated by T-test for paired sample. Logistic regression was used to analyse factors associated with osteoporosis. We distinguished a group called "densitometric osteoporosis", which included patients with a BMD T-score ≤ -2.5, regardless fracture history, and a group called "osteoporosis", which included patients with osteoporosis because of a fragility fracture and/or because of a BMD T-score ≤-2.5. We looked for factors associated with "densitometric

osteoporosis", factors associated with osteoporotic fractures and factors associated with osteoporosis, including BMD T-score and history of fractures.

Multivariate analyses included only parameters that were significant in univariate analysis.

As the IgM MGUS population and the non-IgM MGUS (IgA MGUS + IgG MGUS) differ, these two populations were analysed separately in logistic regression. Light-chain MGUS and MGUS with two heavy chain isotypes were included in the population but excluded from the statistical analyses due to their small numbers. Results were considered significant at $p<0.05$.

RÉSULTATS

1. Characteristics of the population at the first assessment

The characteristics of the population are detailed in Table 1 and Table 2.

We included 491 patients, 254 (51.7%) women and 237 (48.3%) men. The mean age was 67.5 +/- 11.1 years.

Their first assessment was between June 2008 and February 2022, and their second was between November 2010 and March 2024.

At the first visit, 475 (96.7%) patients were diagnosed with a MGUS, 8 (1.6%) with a SMM, 7 (1.4%) with a SWM. The most common heavy chain was IgG in 53.6% of patients, and the most common light chain was kappa in 282 patients (57.4%).

Fifty-three (10.8%) patients were diagnosed with an osteoporotic vertebral fracture. Nine (1.8%) had a hip fracture, twenty-eight (5.7%) a wrist fracture, seven (1.4%) a humerus fracture, and one had a pelvic fracture. In total, 81 patients (16.5%) had at least one osteoporotic fracture.

One hundred and nine (22.2%) had at least one BMD T-score ≤ -2.5 on the three measurable sites.

In total, one hundred and six (31.8%) patients were considered to have osteoporosis with a fragility fracture and/or a densitometric osteoporosis.

After the initial assessment, 94 patients received an anti-osteoporotic treatment: 18 received an oral bisphosphonate, and 76 received an intravenous bisphosphonate.

2. Factors associated with a new bone event at the second evaluation

The mean time to the second visit was 31.9 +/- 10.6 months. At the second assessment, 24 patients had a new vertebral fracture, three had a hip fracture, 2 had a humerus fracture, and 1 had a pelvic fracture. In addition, 32 new patients had a BMD T-score ≤ -2.5. A total of 57 patients had a new bone event (a new fracture and/or a new densitometric osteoporosis).

Patients with a new bone event were significantly older (72.98 *vs* 66.81 years; p <0.001) and more likely to have a history of vertebral fracture (35.9% *vs* 10.9%; p = 0.001) (**Table 3**).

In univariate analysis, age (OR 1.06 per year; 95% CI 1.03 – 10.87), vertebral fracture at first assessment (OR 3.3; 95% CI 1.66 – 6.55), number of vertebral fractures at first assessment (OR 1.42 per additional vertebral fracture; 95% CI 1.12 – 1.8) were associated with the occurrence of a new bone event (**Table 4**).

In multivariate analysis, age and prevalent vertebral fracture remained significantly associated with the occurrence of a new bone event (**Table 4**).

No characteristic of the gammopathy was associated with the occurrence of a new bone event.

3. Factors associated with new vertebral fracture

At the second assessment, patients with a new vertebral fracture were significantly older (80.2 *vs* 69.7 years; p<0.001) and had a significantly lower BMD at the total hip and femoral neck (**Table 5**).

In univariate analysis, age (OR 1.12 per year; 95% CI 1.06 – 1.18), vertebral fracture at first assessment (OR 5.77; 95% CI 2.39 – 13.95), number of vertebral fractures at first assessment (OR 1.61 per additional vertebral fracture; 95% CI 1.24 – 2.09), densitometric

osteoporosis at first assessment (OR 3.81; 95% CI 1.66 – 8.76) were associated with a new vertebral fracture (**Table 6**).

In multivariate analysis, age (OR 1.09; 95% CI 1.04 – 1.16) and a prevalent vertebral fracture (OR 2.92; 95% CI 1.04-1.16) remained significantly associated with a new vertebral fracture (**Table 6**).

No characteristic of the gammopathy was associated with the occurrence of a new vertebral fracture.

4. Evolution of bone mineral density

Patients treated with bisphosphonates had a significant increase in BMD at the total hip, femoral neck and lumbar spine. In contrast, there were no significant changes in untreated patients (**Table 7**).

Among the patients not receiving bisphosphonates, those with heavy IgM chains lost significant bone mass at the femoral neck between the two assessments. There were no significant changes in the non-IgM patients (**Table 8**).

5. Evolution of the gammopathy

At the second visit, three cases of MGUS progressed to SMM, two cases of MGUS progressed to SWM, two cases of MGUS progressed to MM, and one case of SWM progressed to WM.

DISCUSSION

The present study involved the prospective follow-up of 491 patients diagnosed with MGUS who underwent two consecutive comprehensive bone and haematological assessments.

To our knowledge, this is the first study to prospectively analyse osteoporosis risk factors in a MGUS population.

No characteristics of the MGUS were associated with the occurrence of a new osteoporotic vertebral fracture. In the literature, the results of the retrospective studies were contradictory regarding the effect of gammopathy characteristics on fracture risk. The fracture risk in the Swedish cohort (9) did not differ by isotype or monoclonal protein level at diagnosis. Melton et al. (8) found that patients with a lambda serum light chain had a lower risk of fracture, IgA and IgM were associated with a higher risk of fracture than IgG, and monoclonal protein level was not predictive of axial fractures. The Danish study (17) found an increased risk of fracture with high IgA concentrations, in IgG MGUS the IgG concentration had no effect on fracture risk, and in IgM MGUS the relative risk of IgM concentration suggested a decreasing risk with increasing IgM concentration.

In our study, the age and a previous vertebral fracture were the only factors independently associated with the occurrence of a new vertebral fracture. This reinforces the importance of the history of fracture in the prediction of new vertebral fractures.

In our study, we found 24 new vertebral fractures in 491 patients, representing an annual rate of about 1.6% with no significant gender difference. In a large European prospective cohort study including 6788 patients (23), the annual vertebral fracture rate was 0.57% in men and 1.07% in women.

In a cohort study in Iceland (24) of 5305 individuals including 269 MGUS and 243 Light chains MGUS, there was no difference in BMD between subjects with MGUS and others in the

spine or total hip, the risk of fractures was not significantly increased in individuals with MGUS but men with MGUS had a significantly increased fracture risk compared with other men (HR, 1.46; 95% CI, 1.03-2.08).

In our study, 19.14% of patients had bisphosphonates after the first assessment. In treated patients, there was a significant increase in BMD at all 3 sites: 2.2% at the total hip, 3.5% at the femoral neck and 5.8% at the lumbar spine. In contrast, there was no significant variation in untreated patients. The BMD of treated patients remained lower than that of untreated patients and their risk of fracture was still higher. In an open label single arm study, Berenson et al. (25) showed that the administration of 3 doses of zoledronic acid 4mg at 6 month intervals in 54 MGUS (sex ratio of 1) was associated with a significant average gain of 15% in the lumbar spine and a non-significant increase of 6% in the total hip at 13 month, they did not record any new fractures during follow-up. Pepe et al. (26) have treated 50 MGUS with osteoporotic fracture or densitometric osteoporosis with Alendronate 70mg weekly plus calcium and cholecalciferol during 18 months; the mean BMD of the lumbar spine and total femur had increased significantly by 6.1 % and 1.5 %. There are no studies with a control group of MGUS without osteoporosis.

In our study, patients with IgM MGUS experienced a significant decrease in BMD at the femoral neck during follow-up, in contrast to those with non-IgM MGUS. However, it should be noted that these patients were older than those with non-IgM MGUS.

In our population, the distribution of the light and heavy chains was similar to that already described in the Western France (16,27) with more IgM gammopathies (29.3%) than in North America (1) or in Swedish cohorts (14). We found a lower risk of progression than described in previous studies, 1.4% progression for an average follow-up time of 31.87

months, which may be explained by a lower mean monoclonal peak. It is also possible that some patients have progressed between the two assessments and have not been reassessed.

There are several limitations to this study. First, the number of fractures was low, which reduces the power of the study. Second, the follow-up time was probably too short to answer the question of the effect of gammopathy characteristics on the development of bone fragility. Third, the mean concentration of monoclonal gammopathy was low and we did not have enough patients with a peak concentration above 10 g/l or higher to prove that immunoglobulin concentration had no effect on bone fragility.

Despite these limitations, this is the first prospective study to follow up patients diagnosed with MGUS who underwent two consecutive comprehensive bone and haematological assessments to study risk factors for osteoporotic vertebral fracture, and to show that in this population

- No features of MGUS were associated with the occurrence of new osteoporotic vertebral fractures.
- Age and prevalent vertebral fracture were independently associated with the incidence of vertebral fracture.
- Patients treated with bisphosphonates after the first assessment had a significant increase in BMD, whereas there was no significant change in untreated patients.

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LISTE DES FIGURES

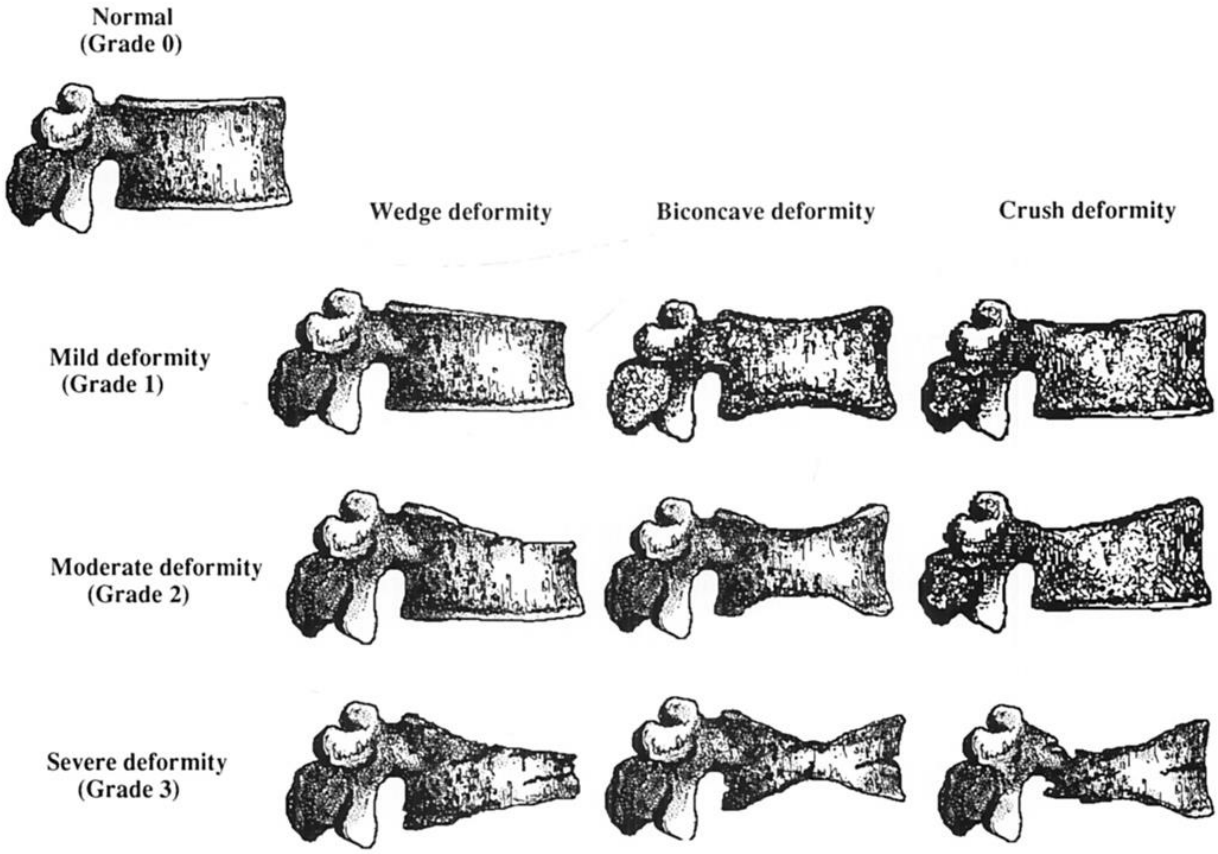

Figure 1 : Semi-quantitative visual grading of vertebral deformitie (21)

LISTE DES TABLEAUX

Tableau 1. Characteristic of the population at the first assessment

Characteristics	**mean value +/- s.d.**
age (years)	67.52 +/- 11.1
men (%)	237 (48,3%)
BMI (kg/m2)	26.53 +/- 4.55
Hb (g/dl)	13.78 +/- 1.32
monoclonal protein (g/l)	5.71 +/- 4.65
albumine (g/l)	42.08 +/- 4.32
Creatinine (µmol/l)	72.67 +/- 17.31
Calcemia (mmol/l)	2.32 +/- 0.10
PTH (pg/ml)	29.05 +/- 18.27
25OH vitamin D (nmol/l)	60.78 +/- 28.16
LDH (UI/l)	216.70 +/- 70.16
Beta 2 microglobulin (mg/l)	2.09 +/- 0.94
CRP (mg/l)	6.56 +/- 16.28
BALP (UI/l)	12.78 +/- 7.81
CTX (ng/l)	0.52 +/- 0.88
Gammaglobulins (g/l)	12.02 +/- 3.87
Kappa (mg/l)	37.17 +/- 70.19
Lambda (mg/l)	26.32 +/- 63.86
BMD total hip (g/cm2)	0.891 +/- 0.164
T-score total hip (s.d.)	-0.69 +/- 1.07
BMD femoral neck (g/cm2)	0.730 +/- 0.143
T-score total femoral neck (s.d.)	-1.25 +/- 1.23
BMD lumbar spine (g/cm2)	0.959 +/- 0.178
T-score lumbar spine (s.d.)	-0.852 +/- 0.178
TBS	1.268 +/- 0.113

Abbreviations : BMI, Body Mass Index; Hb, haemoglobin; PTH, Parathormone; LDH, Lactate Dehydrogenase; BALP, Bone-specific Alkaline Phosphatase; CTX, C-terminal Telopeptide of type I collage serum; BMD, Bone Mass Density; TBS, Trabecular Bone Score

Tableau 2. Characteristics of the population for categorial variables at the first assessment

Characteristics	**Total = 491 patients**
Heavy chain	
IgA	51 (10.4%)
IgG	263 (53.6%)
IgM	146 (29.3%)
bi-clonal or more	31 (6.3%)
Light chain	
Kappa	282 (57.6%)
Lambda	173 (35.3%)
bi-clonal	35 (7.1%)
Diagnostic	
MGUS	475 (96.7%)
SMM	8 (1.6%)
SMW	7 (1.4%)
MM	0
MW	0
Ig repression (n= 376)	
0	293 (77.9%)
1	66 (17.6%)
2	17 (4.5%)
Osteoporosis	
osteoporotic vertebral fracture (ABQ)	53 (10.8%)
osteoporotic major fracture	81 (16.5%)
densitometric osteoporosis	109 (22.2%)
total osteoporosis	156 (31.8%)
known osteoporosis	61 (12.4%)
anterior anti osteoporotic treatment	19 (3.9%)
Treatment	
introduction of antiosteoporotic treatment	94 (19.14%)
oral bisphosphonate	18 (3.7%)
IV bisphosphonate	76 (15.5%)

Abbreviations: IgA, Immunoglobulin A; IgG, Immunoglobulin G ; IgM, Immunoglobulin M ; MGUS, Monoclonal gammopathy of undetermined significance; SMM, Smoldering multiple myeloma; SMW, Smoldering Waldenström's Macroglobulinemia; MM, Multiple myeloma; MW, Waldenström's Macroglobulinemia ; Ig, Immunoglobulin

Tableau 3. Characteristics of the population with a new bone event

Characteristics	new bone event (57 patients)	no bone event (437 patients)	P-value
Age (years)	**72.98 +/- 10.01**	**66.81 +/- 11.01**	**<0.001**
BMI (kg/m2)	26.73 +/- 4.33	26.50 +/- 4.58	0.733
Hb (g/dl)	13.77 +/- 1.33	13.79 +/- 1.32	0.945
monoclonal protein (g/l)	5.56 +/- 3.89	5.74 +/- 4.74	0.790
Créatinine (µmol/l)	71.34 +/- 18.08	72.84 +/- 17.22	0.542
Calcemia (mmol/l)	2.31 +/- 0.10	2.38 +/- 1.11	0.205
CTX (ng/l)	0.51 +/- 0.28	0.52 +/- 0.92	0.941
Kappa (mg/l)	40.33 +/- 56.67	36.75 +/- 71.88	0.754
Lambda (mg/l)	19.89 +/- 15.88	27.18 +/- 67.73	0.483
BMD total hip (g/cm2)	**0.799 +/- 0.135**	**0.903 +/- 0.164**	**<0.001**
BMD femoral neck (g/cm2)	**0.652 +/- 0.119**	**0.737 +/- 0.149**	**<0.001**
BMD lumbar spine (g/cm2)	**0.841 +/- 0.169**	**0.968 +/- 0.185**	**<0.001**
SBP (nmol/l)	**67.14 +/- 31.86**	**55.57 +/- 26.84**	**0.005**
IgM/non IgM	14/39 (26.4%/73.6%)	132/286 (31.6%/ 68.4%)	0.529
osteoporotic vertebral fracture	**14/39 (35.9%)**	**43/395 (10.9%)**	**0.001**
Sexe M/W	27/30 (47.4%/52.6%)	210/224 (48.4%/51.6%)	1.000
Light chain Kappa/Lambda	31/21 (59.6%/40.4%)	251/152 (62.3%/37.7%)	0.762

Abbreviations: BMI, Body Mass Index; Hb, haemoglobin; CTX, C-terminal Telopeptide of type I collage serum; BMD, Bone Mass Density; IgM, Immunoglobulin M

Tableau 4. Factors associated with a new bone event

Characteristics	Odds Ratio	95% confidence interval	P-value
Univariate analysis			
Age	**1.06**	**1.03 – 10.90**	**<0.001**
Sexe, W vs M	1.04	0.60 – 1.81	0.885
BMI	1.01	0.95 – 1.07	0.732
Vertebral fracture	**3.30**	**1.66 – 6.56**	**0.001**
Number of vertebral fractures	**1.42**	**1.12 – 1.80**	**0.004**
Heavy chain, IgM vs non IgM	0.78	0.41 – 1.48	0.445
Light chain, Kappa vs Lambda	1.12	0.62 – 2.02	0.709
monoclonal protein (per gram)	1.00	0.93 – 1.08	0.914
Ig Repression	1.00	0.56 – 1.80	0.992
Multivariate analysis			
Age	**1.05**	**1.020 – 1.080**	**0.001**
osteoporotic vertebral fracture	**2.43**	**1.19 – 4.95**	**0.015**

Abbreviations: BMI, Body Mass Index; Ig, Immunoglobulin

Tableau 5 Characteristics of the population according to the occurrence of a new vertebral fracture

Characteristics	vertebral fracture (n = 24)	no vertebral fracture (n = 467)	P-value
Age (years)	**80.21 +/- 7.03**	**69.72 +/- 11.06**	**<0.001**
BMI (kg/m2)	26.44 +/- 3.71	26.86 +/- 4.59	0.671
Hb (g/dl)	13.25 +/- 1.41	13.61 +/- 1.41	0.218
monoclonal protein (g/l)	6.65 +/- 4.03	6.27 +/- 5.08	0.719
TBS	1.12 +/- 0.21	1.21 +/- 0.23	0.289
BMD total hip (g/cm2)	**0.789 +/- 0.136**	**0.893 +/- 0.157**	**0.002**
BMD femoral neck (g/cm2)	**0.656 +/- 0.119**	**0.727 +/- 0.142**	**0.018**
BMD lumbar spine (g/cm2)	0.901 +/- 0.220	0.975 +/- 0.179	0.183
Sexe M/W	243/224	11/13	0.554
IgM/non IgM	10/13	136/312	0.185
Light chain Kappa/Lambda	11/13	233/233	0.764

Abbreviations: BMI, Body Mass Index; Hb, haemoglobin; BMD, Bone Mass Density; IgM, Immunoglobulin M; TBS, trabecular bone score

Tableau 6. Factors associated with new vertebral fracture

Characteristics	Odds Ratio	95% confidence interval	P-value
Univariate analysis			
Age	**1.12**	**1.06 – 1.18**	**<0.001**
Sexe, W vs M	0.78	0.34 – 1.78	0.554
BMI	1.01	0.92 – 1.10	0.969
Vertebral fracture	**5.77**	**2.39 – 13.95**	**<0.001**
Number of vertebral fractures	**1.61**	**1.24 – 2.09**	**<0.001**
Densitometric osteoporosis	**3.81**	**1.66 – 8.76**	**0.002**
Heavy chain, IgM vs non IgM	1.76	0.76 – 4.12	0.19
Light chain, Kappa vs Lambda	0.76	0.46 – 1.77	0.902
monoclonal protein (per gram)	0.97	0.87 – 1.09	0.597
Ig Repression	0.94	0.40 – 2.24	0.941
Multivariate analysis			
Age	**1.09**	**1.038 – 1.155**	**0.001**
Prevalent Vertebral fracture	**2.92**	**1.038-1.155**	**0.03**
Densitometric osteoporosis	1.80	0.716 – 4.552	0.21

Abbreviations: BMI, Body Mass Index; Ig, Immunoglobulin

Tableau 7. Evolution of bone mineral density according to treatment status

	First assessment	Second assessment	Mean variation	P-value
Untreated patients				
BMD total hip (g/cm2) (n= 393)	0.926 +/- 0.155	0.919 +/- 0.150	- 0.007 +/- 0.750	0.066
BMD femoral neck (g/cm2) (n=392)	0.759 +/- 0.137	0.749 +/- 0.140	- 0.010 +/- 0.103	0.620
BMD lumbar spine (g/cm2) (n=329)	0.987 +/- 0.180	0.994 +/- 0.176	+ 0.008 +/- 0.109	0.197
Treated patients				
BMD total hip (g/cm2) (n= 92)	**0.743 +/- 0.111**	**0.760 +/-0.12**	**+ 0.017 +/- 0.060**	**0.009**
BMD femoral neck (g/cm2) (n=92)	**0.593 +/- 0.115**	**0.614 +/- 0.091**	**+ 0.021 +/- 0.072**	**0.005**
BMD lumbar spine (g/cm2) (n=59)	**0.797 +/- 0.123**	**0.844 +/- 0.143**	**+ 0.047 +/- 0.067**	**<0.001**

Abbreviation s: BMD, Bone Mass Density

Tableau 8 Evolution of bone mineral density according to the heavy chain (patients treated with bisphosphonates were excluded)

	First assessment	Second assessment	Mean variation	P-value
Non-IgM				
BMD total hip (g/cm2) (n= 266)	0.921 +/- 0.157	0.915 +/- 0.151	- 0.005 +/- 0.780	0.275
BMD femoral neck (g/cm2) (n=266)	0.758 +/- 0.136	0.756 +/- 0.140	+ 0.02 +/- 0.090	0.689
BMD lumbar spine (g/cm2) (n=228)	0.984 +/- 0.173	0.983 +/- 0.179	+ 0.002 +/- 0.060	0.952
IgM patients				
BMD total hip (g/cm2) (n= 114)	0.936+/- 0.149	0.925 +/-0.146	- 0.011 +/- 0.064	0.062
BMD femoral neck (g/cm2) (n=113)	**0.757 +/- 0.140**	**0.731 +/- 0.139**	**- 0.026 +/- 0.111**	**0.014**
BMD lumbar spine (g/cm2) (n=90)	1.000 +/- 0.184	1.019 +/- 0.165	+ 0.019 +/- 0.148	0.223

Abbreviation s: BMD, Bone Mass Density; IgM, Immunoglobulin M

TABLE DES MATIERES

BORDIER Gabriel

Fragilité osseuse et gammapathie monoclonale de signification indéterminée : Une étude de cohorte

RÉSUMÉ

Introduction : La gammapathie monoclonale de signification indéterminée (MGUS) est une hémopathie plasmocytaire pré-maligne associée à un risque accru de fractures, comme l'ont montré des études rétrospectives. Les facteurs de risque de fragilité osseuse dans la MGUS restent mal connus. L'objectif de cette étude était d'analyser prospectivement les variations de la densité minérale osseuse (DMO), l'incidence des fractures et les paramètres biologiques chez des patients atteints de MGUS, afin d'identifier les facteurs de risque de fragilité osseuse.

Méthodes : L'étude GREMOS est une étude de cohorte prospective et monocentrique, incluant des patients récemment diagnostiqués avec une gammapathie monoclonale. Tous les patients ont euune évaluation osseuse et hématologique (données cliniques, biologiques, radiographies du rachis, densitométrie osseuse) et ont été invités à une réévaluation à 2 ans.

Résultats : 491 patients ont été inclus (51.7 % de femmes, âge moyen de 67,5 ans). La chaîne lourde la plus fréquente était l'IgG (53,6 %), suivie de l'IgM (29,3 %) et de l'IgA (10,4 %). La chaîne légère était kappa dans 57,6 % des cas. Parmi les participants, 96,7 % étaient atteints de MGUS, 1,8 % de myélome multiple indolent (SMM) et 1,4 % de macroglobulinémie de Waldenström indolente (SWM). Lors de l'évaluation initiale, 31,8 % des patients étaient considérés comme ostéoporotiques, 10,8 % présentaient au moins une fracture vertébrale ostéoporotique et 22,2 % avaient une ostéoporose densitométrique. Après cette première évaluation, 94 patients ont reçu un traitement anti-ostéoporotique. Lors du suivi, 57 patients ont présenté un nouvel événement osseux, incluant 32 nouveaux cas d'ostéoporose densitométrique et 30 fractures ostéoporotiques majeures, dont 24 fractures vertébrales. Les patients ayant développé de nouveaux événements osseux étaient significativement plus âgés et avaient plus souvent un antécédent de fracture vertébrale. L'âge (OR 1.05) et l'antécédent de fracture vertébrale (OR 3,3) étaient significativement et indépendamment associés à un nouvel événement osseux. De même, l'âge (OR 1,09) et les antécédents de fracture vertébrale (OR 2,92) étaient indépendamment associés à la survenue d'une nouvelle fracture vertébrale ostéoporotique.

Conclusion : Aucune caractéristique de la MGUS n'a été retrouvée associée à la survenue de nouvelles fractures vertébrales ostéoporotiques. L'âge et les antécédents de fracture vertébrale étaient les principaux facteurs de risque indépendants de fracture vertébrale incidente chez les patients atteints de MGUS.

Mots-clés : « Adulte », « Humains », « 40 ans et plus », « Gammapathie monoclonale de signification indéterminée », « Ostéoporose », « prévalence », « incidence », « études prospectives », « radiographie », « fracture vertébrale », « densité minérale osseuse »

FACULTÉ DE SANTÉ
UNIVERSITÉ D'ANGERS

Bone Fragility in Monoclonal Gammopathy of Undetermined Significance: A Cohort Study

ABSTRACT

Introduction: Monoclonal gammopathy of undetermined significance (MGUS) is a premalignant plasma cell disorder that has been associated with an increased risk of fractures in retrospective studies. However, the risk factors for bone fragility in MGUS remain poorly understood. The aim of our study was to prospectively analyse changes in bone mineral density (BMD), fracture incidence, and biochemical parameters in MGUS patients and to identify risk factors for bone fragility.

Methods: The GREMOS study is a prospective, single-center cohort study of patients newly diagnosed with monoclonal gammopathy. All participants underwent a bone and haematological assessment (clinical and biological data, spinal radiography, dual-energy X-ray absorptiometry) and were invited to a reassessment after two years.

Results: 491 patients were included, 51.7% female, mean age 67.52 years. The most common heavy chain was IgG (53.6%), followed by IgM (29.3%) and IgA (10.4%). The light chain was kappa in 57.6% of cases. 96.7% were diagnosed with MGUS, 1.8% with smouldering multiple myeloma (SMM), and 1.4% with smouldering Waldenström's macroglobulinemia (SWM). At baseline, 31.8% of patients were classified as osteoporotic, 10.8% had at least one osteoporotic vertebral fracture, and 22.2% had densitometric osteoporosis. After the initial assessment, 94 patients received anti-osteoporotic treatment. At follow-up, 57 patients had a new bone event, 32 had a new densitometric osteoporosis, and 30 had a new major osteoporotic fracture including a vertebral fracture in 24 of them. Patients who developed new bone events were significantly older and more likely to have a history of vertebral fractures. Age and previous vertebral fracture (OR 3.3) were significantly and independently associated with a new bone event. Similarly, age (OR 1.09) and previous vertebral fractures (OR 2.92) were independently associated with new osteoporotic vertebral fractures.

Conclusion: No specific MGUS characteristics were found to be associated with the occurrence of new osteoporotic vertebral fractures. Age and previous vertebral fractures were the main and independent risk factors for vertebral fractures in MGUS patients.

Keywords : "Adult", "Humans" "aged, 40 and over", "Monoclonal Gammopathy of Undetermined Significance", "Osteoporosis", "prevalence", incidence", "prospective studies", "radiography", "vertebral fracture", "bone mineral density"