UNIVERSITE D'ANGERS

FACULTE DE MEDECINE

Année 2015 **N°…….**

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Qualification en : RHUMATOLOGIE

Par

Alexis MARGOTTIN

Né le 03 octobre 1987 à Saumur

Présentée et soutenue publiquement le : 01 octobre 2015

GAMMAPATHIE MONCLONALE DE SIGNIFICATION INDÉTERMINÉE ET RETENTISSEMENT OSSEUX : UN SUIVI PROSPECTIF DE 2 ANS DE 99 PATIENTS

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LISTE DES ABREVIATIONS

MGUS	Monoclonal gammopathy of undetermined significance
BMD	Bone mineral density
IEP	Immunoelectrophoresis
BMI	Body mass index
DXA	Dual energy X-ray absorptiometry
BALP	Bone alkaline phosphatase
CTX	C-terminal telopeptide of type I collagen serum
ANOVA	Analysis of variance
LSC	Least significant change
DKK-1	Dickkopf-1

SUMMARY

RÉSUMÉ

Introduction. La gammapathie monoclonale de signification indéterminée (MGUS) est considérée comme un facteur de risque d'ostéoporose et de fractures non traumatiques. Le principal objectif de notre étude était d'évaluer la densité minérale osseuse, l'évolution et l'incidence des fractures chez les patients avec une MGUS en parallèle du statut hématologique.

Patients et méthodes. Il s'agit d'une cohorte de patients avec une MGUS, vus au CHU d'ANGERS, avec un suivi prospectif, de juillet 2008 à avril 2015. Une évaluation osseuse (densité minérale osseuse au col fémoral, à la hanche totale, au rachis lombaire, recherche de fracture vertébrale) et une évaluation biologique phospho-calcique étaient réalisées en parallèle de l'évaluation hématologique, à l'inclusion des patients dans la cohorte et renouvelées 2 ans plus tard.

Résultats. Quatre-vingt-neuf patients ont eu deux évaluations. Neuf (9,1%) patients avaient des fractures vertébrales à l'inclusion et 3 ont eu une fracture majeure au cours des deux années de suivi. La DMO a diminué de manière significative chez 36,8% des patients non traités par bisphosphonates pour au moins un des 3 sites étudiés. Les patients avec une chaîne légère lambda avaient une diminution significative de la DMO du col du fémur. Le taux de la protéine monoclonale n'a pas varié de manière significative au cours du suivi. Trois patients ont progressé vers une maladie hématologique.

Conclusion. Un tiers des patients atteints de MGUS avait une diminution significative de la DMO après 2 ans de suivi. Les patients avec une chaîne légère lambda avaient une diminution significative de la DMO du col fémoral.

ABSTRACT

Introduction : Monoclonal gammopathy of undetermined significance (MGUS) is considered as a risk factor for osteoporosis and non-traumatic fractures, but no study has assessed prospectively the evolution of bone parameters in patients with MGUS. The main objective of our study was to assess bone mineral density (BMD) evolution and fracture incidence in patients with MGUS in parallel of hematologic disorder evolution. **Patients and methods :** It is a prospective and monocentric cohort conducted from July 2008 to April 2015 including patients with MGUS. A bone assessment with the measure of bone mineral density, the detection of vertebral fracture and a biological evaluation was performed in parallel of the MGUS assessment at the time of the discovery of the hematologic disorder. A second bone assessment was performed 2 years later. Bone evolution was analysed on the whole population and according to the type of gammopathy. **Results :** Ninety-nine patients had two evaluations. Among them, nine (9,1 %) patients had vertebral fractures at the first evaluation and 3 patients had a major fracture during the two-years follow-up. Taking into account the smallest detectable difference in bone density, BMD decreased significantly in 36.8 % of the patients not treated by bisphosphonates. Only patients with lambda light chain had a significant BMD decrease in femoral neck. The monoclonal protein value did not change significantly during the 2 years of follow-up. 3 patients had a bad evolution of their hematologic disorder : 1 to multiple myeloma, 1 to Waldenstrom's disease, 1 to low grade lymphoma. **Conclusion :** One-third of patients with MGUS had a significant BMD decrease after 2 years of follow-up. Patients with lambda light chain had a significant decrease in femoral neck BMD.

INTRODUCTION

Monoclonal gammopathy of undetermined significance (MGUS) and osteoporosis frequently affect people older than 50 years. Prevalence of MGUS was established at 3.2 % in persons older than 50 years, 5.3 % in persons older than 70 years, and in 8.9 % in persons older than 85 years (1). MGUS are more common in osteoporotic patients, 4.9 % in a Danish study compared to 2,2 % in a controlled population (2). Patients with MGUS have an increased risk of non-traumatic fractures (2–8). Matthew Drake recently proposed to replace the term "monoclonal gammopathy of undetermined significance" in favor of the term "monoclonal gammopathy of skeletal significance" in order to more accurately reflect the enhanced skeletal risks inherent in this condition (9). However european guidance for the diagnosis and management of osteoporosis in postmenopausal women (10) doesn't recommend systematically test for monoclonal bands in serum, and neither the recommendations of the National Osteoporosis Foundation (11). Guidelines for the management of MGUS from the European Myeloma.

Network underline the link between osteoporosis and MGUS through induction of alterations in the bone marrow microenvironment and recommend the performance of absorptiometry in MGUS patients (12). There is no prospective study evaluating in parallel both the bone status and the gammopathy, and data concerning osteoporosis in MGUS patients are from transversal studies.

The main objective of our study was to assess bone mineral density (BMD), evolution and fracture incidence in patients with MGUS in parallel of hematologic disorder evolution.

PATIENTS AND METHODS

Patients

This prospective and descriptive study was conducted by both the department of rheumatology and the department of blood diseases of the University Hospital of Angers, France, from January 1, 2008 to April 1, 2015.

Patients included were adults and had a monoclonal gammopathy confirmed by immunoelectrophoresis (IEP) of serum or urine protein. Monoclonal gammopathy had to be discovered in other situations than osteoporosis assessment. Patients with monoclonal gammopathy discovered during osteoporosis or fracture assessment, patients with previous known and treated osteoporosis and patients known to have a previous history of traumatic vertebral fractures were excluded from this study. Mostly the electrophoresis was made in the medical check-up of asthenia or inflammatory syndrome or arthralgia. General practitioners mainly referred patients. After the initial bone and hematological assessment, patients with a diagnosis of hematologic malignancy were also excluded (symptomatic or asymptomatic multiple myeloma or Waldenström Macroglobulinemia, chronic lymphocytic leukemia). Finally, we included only patients with MGUS defined as International Myeloma Working Group criteria by (a) a serum monoclonal immunoglobulin concentration below 3 g/dl, (b) the absence of lytic bone lesions or pathological fractures, (c) the absence of anemia, hypercalcemia or renal insufficiency and (d) a proportion of plasma cells in the bone marrow below 10 % (12).

Every patient who had a first evaluation was invited to have a second evaluation 2 years after the first one.

The study was carried out in accordance with the ethical standards set by the Declaration of Helsinki. The local Ethical Committee approved the entire study protocol. Patients underwent informed consent.

Methods

All the following data were collected for each patient. All the exams were performed the same day for one patient at the time of the discovery of the MGUS and 2 years later.

Clinical data

Interrogation and clinical data examination were performed for each patient to collect the following information : age, weight, height, body mass index (BMI), comorbidities, age at onset of menopause, hormonal replacement therapy, family history of fractures, personal history of fractures and their incidence condition, current treatment, calcium dietary intake.

Spinal radiographs and vertebral fracture assessment

Each patient had antero-posterior and lateral thoracic and lumbar spine radiographs. Two trained investigators who were unaware of the patient BMD status, analysed radiographs independently in three steps: (a) detect vertebral fracture, (b) determine benign or malignant origin, (c) classify the fracture as mild, moderate or severe.

The patient was classified as having a vertebral fracture if both readers independently found a definite fracture. He was classified as normal if both readers independently found that the films were normal. When the readers disagreed, the films were reviewed in conference by both investigators. Each vertebral fracture was classified as benign or malignant using classical radiographic signs (destruction of the cortical margin or not, posterior convexity or not). The benign vertebral fractures were characterized by the semi-quantitative classification of Genant and defined as such : *mild* or *grade 1* for a reduction of 20-25 % of anterior, middle, and/or posterior height, *moderate* or *grade 2* for a reduction of 26-40 % in any height, *severe* or *grade 3* for a reduction > 40 % in any height.

Bone Mineral Density

BMD was measured using dual energy X-ray absorptiometry (DXA) operating in fan-beam mode (Hologic® QDR 4500A densitometer, Hologic Inc., Waltham, MA). Quality control scans were carried out daily, using the manufacturer-supplied anthropomorphometric spine

phantom ; the long-term (> 1 year) coefficient of variation was 0.40 %. Lumbar BMD was assessed from L2 to L4, in the postero-anterior view incidence, and fractured vertebrae were excluded from the analysis. Total hip BMD and femoral neck BMD were measured at upper left femur. The mean precision error of DXA measurement is < 1.5 % for the lumbar spine and < 2 % for hip BMD. As usually, the results were expressed in absolute values (g/cm^2) and using the T-score. The T-scores were calculated using manufacturer's references and expressed the difference between the subject value and the mean value of healthy young adults. The World Health Organization has defined normal BMD as a T-score > -1, low bone density as a T-score between -2.5 and -1, and osteoporosis as a T-score < -2.5. All BMD were assessed on the same DXA and by the same operator at first and second evaluation. The least significant change (LSC) is the smallest difference between successive measurements of BMD that can be considered to be a real change and not attributable to chance. The smallest detectable difference in bone density on our DXA was 0.022326 g/cm^2 on lumbar spine, 0.026675 g/cm^2 on total hip, 0.28808 g/cm^2 on femoral neck.

Biological data

Laboratory tests were performed on fasting subjects at 8 am without freezing to confirm and quantify gammopathy and to assess parameters of mineral metabolism and bone turnover:

- at the first evaluation : serum protein electrophoresis to obtain the monoclonal protein level, serum and urinary IEP, cells blood count, β2 microglobulin, lactate dehydrogenase, creatinine, bone marrow by sternal puncture in patients with IgG or IgA isotype, bone marrow biopsy in patients with IgM isotype having a visible protein electrophoresis peak, serum calcium, phosphate, albumin, 25-hydroxy vitamin D, parathyroid hormone, bone alkaline phosphatase (BALP), and C-terminal telopeptide of type I collagen serum (CTX).
- at the second evaluation : serum protein electrophoresis to obtain the monoclonal protein level, cells blood count, β2 microglobulin, lactate dehydrogenase, creatinine,

serum calcium, phosphate, albumin, 25-hydroxy vitamin D, parathyroid hormone, BALP and CTX.

Statistical Analyses

Statistical analysis was performed using the software Statistical Package for the Social Sciences (SPSS V. 15.0.1, SPSS Inc, IBM Corporation, Chicago, IL, USA). Baseline characteristics of patients were expressed in mean ± one standard deviation 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 the student's T-test for paired sample for continuous variables and by McNemar's test for binary variables. Logistic regression was performed to analyse factors associated with BMD decrease. Differences were considered significant when $p < 0.05$.

RESULTS

Evolution of the characteristics of the population

The flow chart is represented in **figure 1.** The ongoing cohort included 237 patients with a MGUS, among them 99 had two evaluations from July 2008 to April 2015. 48 (47.5 %) were women, and mean age at the second evaluation was 63.8 ± 11.5 years. Characteristics of the population at the first and second evaluation are detailed in **table 1**. The second evaluation occurred 26.5 ± 7.0 months after the first one. Twelve patients started a treatment with bisphosphonates after the first bone evaluation because of low-traumatic fracture history or T-score < -2.5 (five had an oral bisphosphonate, seven had an intravenous bisphosphonate). Vitamin D supplementation was systematically proposed in patients with 25-hydroxy vitamin D concentration < 75 nmol/L at the first evaluation.

The distribution of heavy chain in patients was 11 IgA (11.1 %), 53 IgG (53.5 %), 30 IgM (30.3 %), 5 dual isotype (5.1 %) and no light chain MGUS. The light chains were distributed as follows: 67 kappa light chains (67.7 %), 29 lambda light chain (29.3 %), and 3 kappa + lambda association.

Evolution of bone status parameters

Incident fractures

At the first evaluation, 14 non-traumatic vertebral fractures were found in nine patients (9.1 %) : four grades 1, eight grades 2, and two grades 3. Two patients had minor fractures : one had a wrist fracture and one a costal fracture.

At the second evaluation, 3 new major non-traumatic fractures were reported in three patients : two vertebral fractures (grade 1, T12 and L5) and one pelvic fracture. Characteristics of these three patients are reported in annexe 1. One patient had a previous fracture ; none of them had a T-score < -2.5.

BMD evolution

At first evaluation, 8 patients (8.1 %) had at least one T-score < -2.5, at the second evaluation 2 new patients had a T-score < -2.5.

After excluding patients who received bisphosphonates after the first bone evaluation because of non traumatic fracture or T-score < -2.5 (n = 12), we analysed the evolution of BMD in the 87 other patients. Taking into account the least significant change, 32 from 87 patients (36.8 %) had a decrease in BMD in at least one site between the first and the second evaluation. 14 patients (16 %) had a significant BMD decrease in total hip but none of them had a T-score < -2.5 at the second evaluation. Seventeen patients (19.5 %) had a significant decrease in femoral neck BMD, two of them had a T-Score < -2.5 at femoral neck at the second evaluation. Seventeen patients (19.5 %) had a significant decrease in lumbar spine

BMD, and one had a T-score < -2.5 at the second evaluation but had already a T-score < -2.5 at the first evaluation. In logistic regression, only gender was significantly associated with a significant BMD decrease, with an OR for female *vs* male = 3.8 (CI9 5% 1.5-9.4, p = 0.002). None of the characteristics of the gammopathy (type of heavy or light chain, monoclonal protein value) was significantly associated with a BMD decrease whatever the site of the BMD measure.

Then we analysed BMD evolution at each site for each heavy chain and each light chain (**Table 2**). Only patients with lambda light chain had a significantly decrease in BMD femoral neck. In logistic regression, light chain was not associated with significant BMD decrease.

Biological parameters

CTX and BALP significantly decreased in patients treated or not by bisphosphonates. At inclusion 10 patients had a 25-hydroxy vitamin D concentration < 25 nmol/L, at the second evaluation 3 patients still had vitamin D deficiency. A quarter of patients had an optimal concentration > 75 nmol/L at the first and second evaluation.

MGUS biological parameters evolution

At the second evaluation, one patient had progressed to a Waldenström's disease, one patient had progressed to asymptomatic multiple myeloma (concentration of monoclonal protein increased from 12 to 24.5 g/L and plasma cells to 11 %), one patient had progressed to low-grade lymphoma. Characteristics of these three patients are reported in **annexe 2**.

First, we analysed monoclonal protein value evolution according to the type of gammopathy. Monoclonal protein value did not change significantly whatever the type of heavy or light

chain. Only three patients had an increase of monoclonal protein value above 5 g/L, including the patient who progressed to asymptomatic MM.

Then, we analysed monoclonal protein evolution according to BMD evolution (**Table 3**). Patients who had a significant BMD decrease had also a significant increase in monoclonal protein value (not significant, $p = 0.051$). Bisphosphonate treatment and previous fracture had no influence in monoclonal protein value evolution.

DISCUSSION

In this study, we conducted a 2-years prospective and parallel evaluation of bone and hematological status in 99 men and women with MGUS. The population of this study is representative of a MGUS population, with a sex ratio close to 1 (47.5 % women), an isotype distribution of heavy and light chains (IgG 53.5 %, 30.3 % IgM, 11.1 % IgA, biclonal 5.1 %, κ chain 67.7 %, λ chain 29.3 %) similar to what is usually described in MGUS cohort studies of western France, albeit with a greater percentage of IgM compared to north American registry studies (1,13,14).

Previous studies analysing fracture rate or BMD in MGUS patients were transversal and none of them had analysed prospectively theses parameters. To better define the evolution of bone status parameters and gammopathy, we selected patients with strict criteria, excluding patients with hematological diseases, known osteoporosis or a history of vertebral fracture. All patients had spine radiography at the first and second evaluation to detect vertebral fracture, especially asymptomatic ones. Two trained investigators have read spine radiography in this study to be sure to detect all vertebral fractures, to diagnose pathological fractures and to eliminate simple vertebral deformity, which sometimes can be confused with mild vertebral fractures. BMD was measured at the first and second evaluation on the same DXA, which is

the only way to analyse its evolution.

Two years after the first evaluation, 36.8 % of the patients not treated by bisphosphonates had a significant BMD decrease according to the smallest detectable difference. In the group of patients not treated by bisphosphonates, the mean BMD decreased by 1.25 % at the femoral neck ($p = 0.04$), by 0. 5% ($p = 0.40$) at the total hip, and by 0.2 % ($p = 0.75$) at the lumbar spine. BMD decrease was not associated with any of the characteristics of the gammopathy. Three patients had a new low-traumatic fracture; the follow up was not long enough to better analyse fracture incidence.

We had previously shown that patients with lambda light chain had more vertebral fractures than patients with kappa light chain (15). In this prospective study we found that patients with lambda light chain had a significant BMD decrease in femoral neck.

Monoclonal protein value did not change significantly, only one patient had a 50 % increase in monoclonal protein value, this is considered as worrisome in the literature (16). There was no difference in monoclonal protein value between patients treated or not with bisphosphonates.

The value of monoclonal protein was initially low and the follow-up too short to observe significant modification. Three patients progressed towards malignancy hematologic disease, an incidence of 1.5 % per year, consistent with the expected values of 1 % per year (17).

In multiple myeloma, there are two types of lesions : osteolytic lesions, due to paracrin effect of cytokin released by myeloma and environmental cells, and significant systemic bone loss, due to circulating factors, and an increased risk of osteoporotic fractures (3). Relationship between gammopathy and osteoporosis is unclear, some data suggest that circulating factors are involved in bone’s loss. It has been shown that bone resorption markers in MGUS are

higher than healthy patients but lower that in symptomatic multiple myeloma. (18). Alterations in cytokine levels occur in patients with MGUS, circulating levels of the osteoclast activating factor CCL3/MIP-1a were increased and circulating levels of the osteoblast-suppressive factor DKK-1 were increased in MGUS patients. Serum levels of the Wnt inhibitor sclerostin were not different between patients with MGUS and control subjects, (16,19)

On the histomorphometric features of transiliac bone biopsy in patients with MGUS, excessive bone resorption was significantly associated with progression to multiple myeloma and constituted an early marker for malignancy that was detectable several years before myeloma onset. (20) The enhancement of osteoclast activity and the subsequent increase in biochemical markers of bone resorption appear to represent an early sign of malignant cell behavior.

CONCLUSION

We followed up 99 patients with MGUS over 2 years. 3 patients had incident axial low-traumatic fractures, 32 had a detectable BMD decrease. BMD decrease was significantly associated with gender, with an OR female vs male = 3,8 (CI95 % 1.5-9.4, p = 0.002). Patients with lambda light chain had a significantly decrease in BMD femoral neck.

BIBLIOGRAPHY

1. Kyle RA, Therneau TM, Rajkumar SV, Larson DR, Plevak MF, Offord JR, et al. Prevalence of monoclonal gammopathy of undetermined significance. N Engl J Med 2006;354:1362-9.

2. 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;330:818.

3. Melton LJ, Rajkumar SV, Khosla S, Achenbach SJ, Oberg AL, Kyle RA. Fracture risk in monoclonal gammopathy of undetermined significance. J Bone Miner Res. 2004;19:25-30.

4. Kristinsson SY, Tang M, Pfeiffer RM, Björkholm M, Blimark C, Mellqvist U-H, et al. Monoclonal gammopathy of undetermined significance and risk of skeletal fractures: a population-based study. Blood 2010;116:2651-5.

5. Gregersen H, Jensen P, Gislum M, Jørgensen B, Sørensen HT, Nørgaard M. Fracture risk in patients with monoclonal gammopathy of undetermined significance. Br J Haematol 2006;135:62-7.

6. Golombick T, Diamond T. Prevalence of monoclonal gammopathy of undetermined significance/myeloma in patients with acute osteoporotic vertebral fractures. Acta Haematol 2008;120:87-90.

7. Pepe J, Petrucci MT, Nofroni I, Fassino V, Diacinti D, Romagnoli E, 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;134:485-90.

8. Edwards BJ, Langman CB, Bunta AD, Vicuna M, Favus M. Secondary contributors to bone loss in osteoporosis related hip fractures. Osteoporos Int 2008;19:991-9.

9. Drake MT. unveiling skeletal fragility in patients diagnosed with MGUS: no longer a condition of undetermined significance ? J Bone Miner Res 2014;29:2529-33.

10. Kanis JA, McCloskey EV, Johansson H, Cooper C, Rizzoli R, Reginster J-Y, et al. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int 2013;24:23-57.

11. Cosman F, de Beur SJ, LeBoff MS, Lewiecki EM, Tanner B, Randall S, et al. Clinician's Guide to Prevention and Treatment of Osteoporosis. Osteoporos Int 2014;25:2359-81.

12. Kyle RA, Durie BGM, Rajkumar SV, Landgren O, Blade J, Merlini G, et al. Monoclonal gammopathy of undetermined significance (MGUS) and smoldering (asymptomatic) multiple myeloma: IMWG consensus perspectives risk factors for progression and guidelines for monitoring and management. Leukemia 2010;24:1121-7.

13. Cabrera Q, Macro M, Hebert B, Cornet E, Collignon A, Troussard X. Epidemiology of Monoclonal Gammopathy of Undetermined Significance (MGUS): The experience from the specialized registry of hematologic malignancies of Basse-Normandie (France). Cancer Epidemiol 2014;38:354-6.

14. Saleun JP, Vicariot M, Deroff P, Morin JF. Monoclonal gammopathies in the adult population of Finistère, France. J Clin Pathol 1982;35:63-8.

15. Piot JM, Royer M, Schmidt-Tanguy A, Hoppé E et al. Factors associated with an increased risk of vertebral fracture in monoclonal gammopathies of undetermined significance. Blood Cancer J 2015;5:1-5

16. Berenson JR, Yellin O, Quiery A, Brady J, Patel R, Wong S-F, et al. A retrospective study to evaluate the work-up and follow-up of patients with monoclonal gammopathy of undetermined significance. Clin Lymphoma Myeloma Leuk 2011;11:336-41

16. Ng AC, Khosla S, Charatcharoenwitthaya N, Kumar SK, Achenbach SJ, Holets MF, et al. Bone microstructural changes revealed by high-resolution peripheral quantitative computed tomography imaging and elevated DKK1 and MIP-1α levels in patients with MGUS. Blood 2011;118:6529-34.

17. Kyle RA, Therneau TM, Rajkumar SV, Larson DR, Plevak MF, Melton LJ. Long-term follow-up of 241 patients with monoclonal gammopathy of undetermined significance: the original Mayo Clinic series 25 years later. Mayo Clin Proc 2004;79:859-66.

18. Politou M, Terpos E, Anagnostopoulos A, Szydlo R, Laffan M, Layton M, 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;126:686-9

19. M Roussou AT. Increased expression of macrophage inflammatory protein-1alpha on trephine biopsies correlates with extensive bone disease, increased angiogenesis and advanced stage in newly diagnosed patients with multiple myeloma. Leukemia 2009;23:2177-81.

20. Alexandre C, Bataille R, Chappard D, Dessauw P, Sany J, Riffat G. [Contribution of bone biopsy with histomorphometry in the evaluation of monoclonal gammopathy]. Rev Rhum 1987;54:717-21.

TABLES, FIGURES AND ANNEXES

Table I. Characteristics of the population (n = 99) at the first and the second evaluation

Characteristics	Mean value ± SD 1st evaluation	Mean value ± SD 2nd evaluation	P
Age, years	63.64 ± 11.30	63,8 ± 11,5	
Weight, kilograms	73.69 ± 12.42	73.72 ± 12.44	0.892
Height, centimeters	165.81 ± 8.70	165.62 ± 8.77	0.040
BMI, kilograms/m^2	26.80 ± 4.13	26.86 ± 4.10	0.450
BMD total hip, g/cm^2	0.920 ± 0.122	0.920 ± 0.127	0.656
T-Score total hip, SD	-0.56 ± 0.77	-0.54 ± 0.78	
BMD femoral neck, g/cm^2	0.762 ± 0.112	0.754 ± 0.120	0.101
T-Score femoral neck, SD	-1.09 ± 0.83	-1.11 ± 0.88	
BMD lumbar spine, g/cm^2	0.986 ± 0.142	1.001 ± 0.132	0.640
T-Score lumbar spine, SD	-0.86 ± 1.24	-0.62 ± 1.18	
Albumin, g/l (nl : 40-47)	43.37± 4.42	42.43 ± 4.13	0.024
Calcium, mmol/l (nl : 2.10-2.43)	2.32 ± 0.10	2.33 ± 0.09	0.426
Creatinine, µmol/l (nl : 64-104)	74.54 ± 14.86	77.24 ± 15.82	0.001
25 hydroxy-vitamin D, nmol/l (nl : 75-250)	59.46 ± 26.78	60.76 ± 21.46	0.528
PTH, pg/ml (nl : 15-65)	37.85 ± 14.85	25.58 ± 12.19	0.001
Beta 2 microglobulin, mg/l (nl : 1.20-2.50)	1.94 ± 0.58	2.24 ± 0.83	0.001
LDH, UI/l (nl: 125-220)	299.11 ± 91.33	204.20 ± 63.28	0.001
CTX, ng/ml (nl : 0,11-0,75)	0.50 ± 0.21	0.44 ± 0.24	0.009
BALP, UI/l (nl : 5.5-24.6)	12.19 ± 4.43	10.82 ± 3.34	0.001
Marrow plasma cells (%)	3.0 ± 2.2		
M-protein value, g/l	5.47 ± 4.61	5.64 ± 5.05	0.250
IgA	3.8 ± 3.7	4.8 ± 4.0	0.098
IgG	5.7 ± 5.3	6.1 ± 6.0	0.350
IgM	5.5 ± 3.7	5.3 ± 3.6	0.560
Double peak	3.24 ± 3.11	4.00 ± 1.83	0.460

Abbreviations : BMI, body mass index ; BMD, bone mineral density ; PTH, parathormone ; LDH, lactate dehydrogenase ; CTX, C-terminal telopeptide of collagen-1 ; BALP, bone-alkaline phosphatase ; nl, normal

Table II. BMD evolution according to the characteristics of the gammopathy

	IgG (n = 35)	p	IgM (n = 30)	p	IgA (n = 11)	p	Kappa (n = 67)	P	Lambda (n = 29)	p
BMD LS 1st, g/cm²	0.997±0.140	0.71	1.019±0.126	0.71	0.973±0.134	0.98	1.032±0.128	0.96	0.930±0.117	0.99
BMD LS 2nd, g/cm²	0.993±0.134		1.025±0.136		0.974±0.138		1.032±0.127		0.930±0.118	
BMD TH 1st, g/cm²	0.913±0.106	0.89	0.938±0.152	0.90	0.957±0.109	0.87	0.932±0.132	0.68	0.905±0.928	0.66
BMD TH 2nd, g/cm²	0.913±0.108		0.937±0.144		0.958±0.133		0.930±0.133		0.908±0.903	
BMD FN 1st, g/cm²	0.759±0.938	0.12	0.750±0.141	0.44	0.800±0.112	0.97	0.767±0.115	0.37	0.746±0.109	**0.02**
BMD FN 2nd, g/cm²	0.750±0.979		0.744±0.153		0.800±0.114		0.762±0.123		0.727±0.108	

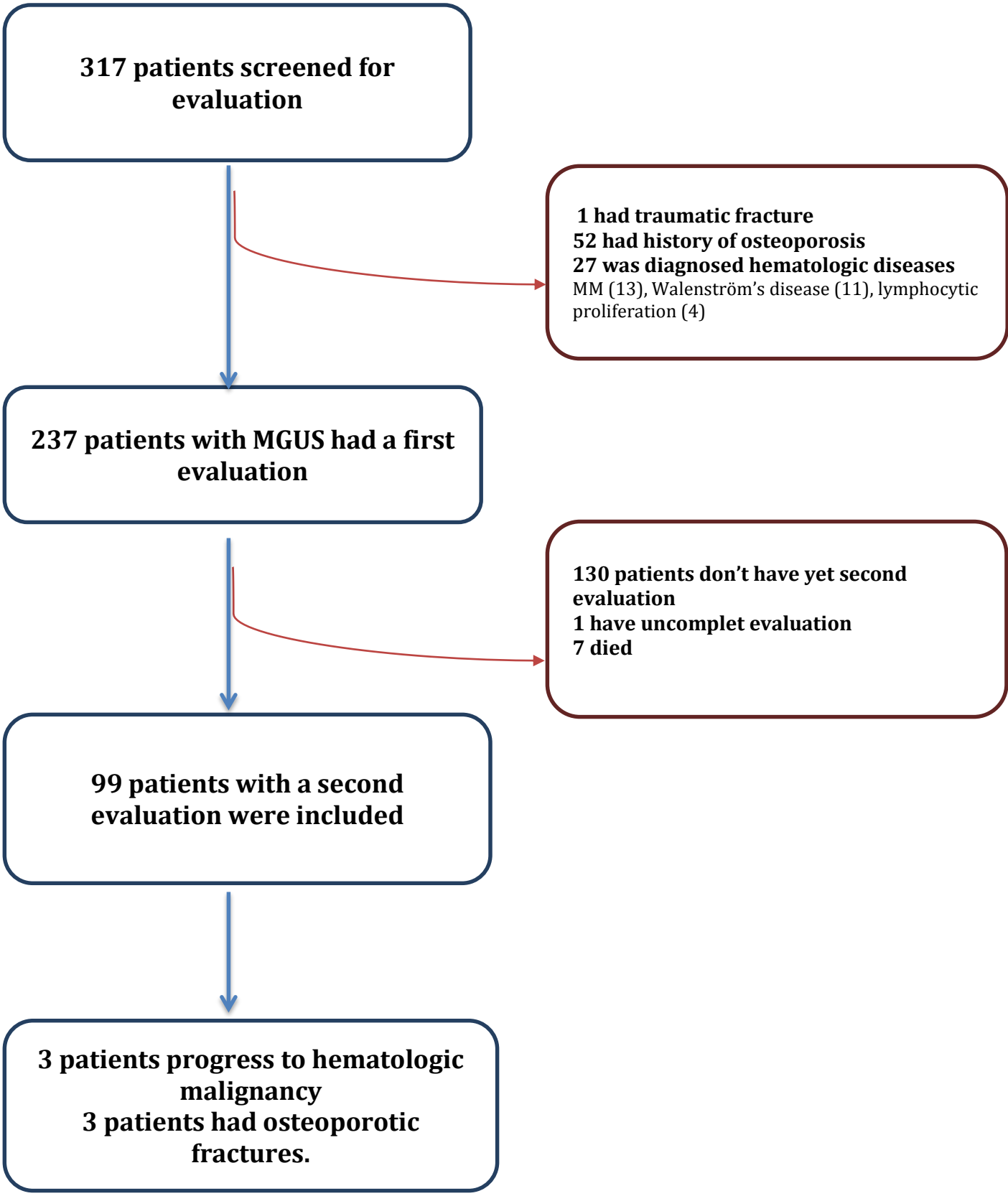
Abbreviations : BMD, bone mineral density ; LS : lumbar spine ; TH, total hip ; FN, femoral neck ; 1st, first evaluation ; 2nd, second evaluation

Table III. Gammopathy evolution according to bone status

	Stable BMD (n = 52)	p	BMD decreased (n = 35)	p	Bisphosphonate (n = 12)	p	No bisphosphonate (n = 87)	p
M-protein 1st, g/L	5.85±5.14	0.970	5.04±4.32	0.051	3.95±2.96	0.420	5.51±4.80	0.334
M-protein 2nd, g/L	5.87±5.59		5.69±4.87		4.42±2.82		5.79±5.27	

Abbreviations : BMD, bone mineral density ; M-protein, monoclonal protein value ; 1st, first evaluation ; 2nd, second evaluation

Figure – 1 Flow chart



Annexe 1 - characteristics of patients with incident fracture

	Patient 1	Patient 2	Patient 3	Norm	Unit
At the inclusion					
Gender	female	female	male		
Age	85	55	81		
History of fracture	no	T11	no		
Isotype	Ig G lambda	IgM lambda	Ig G kappa		
Risk factor for osteoporosis	0	Tobacco	0		
Calcium	2,51	2,22	2,28	2,2-2,5	mmol/L
LDH	439	276	293	210-390	UI/L
CRP	3	3	4	< 5	mg/L
Beta2 microglobulin	3,3	1,21	2,41	1,2-2,5	mg/L
M-protein value	0	5,2	3,3		g/L
PTH	45	58	31	15-65	pg/mL
25-hydroxy vitamin D	18	119	65	75-250	nmol/L
BALP	13,4	14,4	15,5	juin-30	ng/mL
CTX	0,58	0,55	0,43	0,11-0,75	ng/mL
BMD total hip	0,825	0,755	0,972		g/cm2
T-score total hip	-0,9	-1,4	-0,5		
BMD femoral neck	0,661	0,63	0,802		g/cm2
T-score femoral neck	-1,7	-1,9	-1		
BMD lumbar spine		0,915	1,108		g/cm2
T-score lumbar spine		-1,1	-0,1		
At the second evaluation					
Delay between first evaluation and fracture	18	1	36		month
Location of the new fracture	pelvis	vertebra L5	vertebra T12		
grade		1	1		
Calcium	2,39	2,18	2,2	2,2-2,5	mmol/L
LDH	292	305	211	210-390	UI/L
CRP	3	3	5	< 5	mg/L
Beta2 microglobulin	4,12	1,45	2,76	1,2-2,5	mg/L
M-protein value	0	3,1	3,1		g/L
Delta M-protein value	0	-2,1	-0,2		g/L
PTH	36	59	34,9	15-65	pg/mL
25-hydroxy vitamin D	49	89	75	75-250	nmol/L
BALP	12,1	19,8	8,5	0,11-0,75	ng/mL
CTX	0,97	0,59	0,3		
BMD total hip	0,825	0,74	0,89		g/cm2
T-score total hip	-0,9	-1,5	-1		
BMD femoral neck	0,661	0,627	0,758		g/cm2
T-score femoral neck	-1,7	-0,8	-1,3		
BMD lumbar spine	0,914	1,12			g/cm2
T-score lumbar spine	-1,1	0			

Annexe 2 - Characteristics of patients whom progress to hematologic disease

	Patient 1	Patient 2	Patient 3		
At the inclusion					
Gender	male	male	male		
Age	54	77	75		years
Isotype	Ig G kappa	IgA kappa + IgM lambda	IgM kappa		
Risk factor for osteoporosis	no	Inflammatory arthritis	no		
Albumin	36	43	43,7	35-52	g/L
Creatinine	88	99	73	65-105	micromol/L
Calcium	2,33	2,26	2,26	2,2-2,5	mmol/L
LDH	193	385	235	210-390	UI/L
CRP	3	29	3	< 5	mg/L
Beta2 microglobulin	1,68	2,94	2,61	1,2-2,5	mg/L
M-protein value	12,4	2,5	7,2		g/L
25-hydroxy vitamin D	75	80	81	75-250	nmol/L
BALP	9,9		9,7	6-30	ng/mL
CTX	0,78		0,37	0,11-0,75	ng/mL
T-score total hip	-1,4	-0,1	-1,3		
T-score femoral neck	-1,4	-0,2	-2,3		
T-score lumbar spine	-1,6	0,5	-1,5		
At the second evaluation					
Hematologic malignancy	Smoldering MM	Low grade non Hodgkin lymphoma	Waldenström's macroglobulinemia		
Diagnostic delay	24	24	24		month
New fracture	0	0	0		
Albumin	45	38	39	35-52	g/L
Creatinine	95	92	73	65-105	micromol/L
Calcium	2,26	2,39	2,36	2,2-2,5	mmol/L
LDH	143	156	136	210-390	UI/L
CRP	3	11	6	< 5	mg/L
Beta2 microglobulin	1,8	3,31	7,49	1,2-2,5	mg/L
M-protein value	25,8	3,8	7,1		g/L
Delta M-protein value	+13,4	+1,3	-0,1		
25-hydroxy vitamin D	54	48	78	75-250	nmol/L
BALP	7,2	17,8	10,6	6-30	ng/mL
CTX	0,77	1,57	0,33	0,11-0,75	ng/mL
T-score total hip	-1,5	-0,4	-1,2		
T-score femoral neck	-1,5	-0,8	-2,3		
T-score lumbar spine	-1,5	0	-1,4		

TABLE DES MATIÈRES

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EVOLUTION OF BONE STATUS IN PATIENTS WITH MGUS: NINETY-NINE PATIENTS FOLLOWED PROSPECTIVELY OVER 2 YEARS

GAMMAPATHIE MONCLONALE DE SIGNIFICATION INDÉTERMINÉE ET RETENTISSEMENT OSSEUX : UN SUIVI PROSPECTIF DE 2 ANS DE 99 PATIENTS

RESUME

Introduction. La gammapathie monoclonale de signification indéterminée (MGUS) est considérée comme un facteur de risque d'ostéoporose et de fractures non traumatiques. Le principal objectif de notre étude était d'évaluer la densité minérale osseuse (DMO), l'évolution et l'incidence des fractures chez les patients avec une MGUS en parallèle du statut hématologique.

Patients et méthodes. Il s'agit d'une cohorte de patients avec une MGUS, vus au CHU d'ANGERS, avec un suivi prospectif, de juillet 2008 à avril 2015. Une évaluation osseuse (densité minérale osseuse au col fémoral, à la hanche totale, au rachis lombaire, recherche de fracture vertébrale) et une évaluation biologique phospho-calcique étaient réalisées en parallèle de l'évaluation hématologique, à l'inclusion des patients dans la cohorte et renouvelées 2 ans plus tard.

Résultats. Quatre-vingt-neuf patients ont eu deux évaluations. Neuf (9,1%) patients avaient des fractures vertébrales à l'inclusion et 3 ont eu une fracture majeure au cours des deux années de suivi. La DMO a diminué de manière significative chez 36,8% des patients non traités par bisphosphonates pour au moins un des 3 sites étudiés. Les patients avec une chaîne légère lambda avaient une diminution significative de la DMO du col du fémur. Le taux de la protéine monoclonale n'a pas varié de manière significative au cours du suivi. Trois patients ont progressé vers une maladie hématologique.

Conclusion. Un tiers des patients atteints de MGUS avait une diminution significative de la DMO après 2 ans de suivi. Les patients avec une chaîne légère lambda avaient une diminution significative de la DMO du col fémoral.

MOTS-CLES

Gammapathie monoclonale de signification indéterminée
ostéoporose
suivi
fracture
densité minérale osseuse

FORMAT

☐ **Mémoire**
☒ **Article**[1] **:** ☒ à soumettre ☐ soumis ☐ accepté pour publication ☐ publié

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[1] statut au moment de la soutenance