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Par

Jean-Maxime PIOT

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LE RISQUE D'OSTEOPOROSE AU COURS DES GAMMAPATHIES MONOCLONALES DE SIGNIFICATION INDETERMINEE : ETUDE PROSPECTIVE PORTANT SUR 201 PATIENTS

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LISTE DES ABREVIATIONS

MGUS	----------	monoclonal gammopathy of undetermined significance
MM	----------	multiple myeloma
WM	----------	Waldenström's macroglobulinemia
Ig	----------	immunoglobulin
BMI	----------	body mass index
CRP	----------	C-reactive protein
LDH	----------	lactate dehydrogenase
PTH	----------	parathyroid hormone
CTX	----------	C-terminal telopeptide of type I collagen
BALP	----------	bone alkalyne phosphatase
BMD	----------	Bone mineral density
DS/SD	----------	deviation standard/standard deviation
DXA	----------	Dual-energy X-ray absorptiometry
ANOVA	----------	analysis of variance
RANK	----------	receptor activator of nuclear factor kappa B
RANKL	----------	receptor activator of nuclear factor kappa B ligand
OPG	----------	osteoprotegerin
AL amyloidosis	----------	-Amyloid light-chain amyloidosis
POEMS	----------	Polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes syndrome
MIP1-α	----------	Macrophage inflammatory protein 1-α
DKK-1	----------	Dickkopf-1
sFRP	----------	soluble Frizzled-related proteins
κ	----------	kappa
λ	----------	lambda

PLAN

RÉSUMÉ

Introduction : Les gammapathies monoclonales de signification indéterminée (MGUS) sont définies par une absence d'atteinte osseuse. Néanmoins, plusieurs études rétrospectives tendent à montrer une augmentation du risque d'ostéoporose fracturaire ou densitométrique dans cette population. L'objectif de notre étude était de décrire le statut osseux des patients porteurs d'une MGUS et d'en déterminer les facteurs associés. Patients et Méthodes : Au cours d'une étude prospective réalisée entre 2008 et 2013, les patients porteurs d'une gammapathie monoclonale de découverte fortuite sans antécédent fracturaire ou ostéoporotique connu ont tous bénéficiés des examens suivants : recueil des facteurs de risque d'ostéoporose, radiographies du rachis thoraco-lombaire, dosage des paramètres phosphocalciques et hématologiques, densitométrie osseuse par absorbtiométrie biphotonique à rayons X sur le site lombaire, col fémoral et extrémité supérieure du fémur, typage de la MGUS, prélèvement médullaire si le contingent monoclonal le justifiait. Ceux chez qui les résultats concluaient au diagnostic de maladie de Waldenström asymptomatique ou symptomatique ou de myélome multiple asymptomatique ou symptomatique ont été exclus. Résultats : 201 patients porteurs d'une MGUS ont été analysés : âge moyen 66,63 ± 12,49 ans; 48,3% de femmes, 104 IgG (51,7%), 67 IgM (33,3%), 21 IgA (10,4%), 9 double isotype (4,5%). 127 patients (63,2%) avaient une chaîne légère kappa, 63 (31,3%) une chaîne légère lambda et 9 (4,5%) un double contingent de chaînes légères. Le pic monoclonal moyen était de 5,98 g/l et la plasmocytose moyenne de 3,3%. 59 (29,4%) patients étaient ostéoporotiques (fracture vertébrale et/ou T-Score ≤ -2.5 DS), dont 37 (18,4%) présentaient une ou plusieurs fractures vertébrales thoraco-lombaires ostéoporotiques. Les patients fracturés étaient significativement plus âgés, avaient une densitométrie significativement plus basse aux 3 sites et étaient plus fréquemment d'isotype de chaîne légère lambda. Le risque relatif de fracture vertébrale chez les MGUS avec isotype lambda comparé à l'isotype kappa était de 2,5 (IC 95 % 1,21-5,24). En analyse multivariée en tenant compte de l'âge, du sexe et de la densité osseuse, le risque de fracture associé à la chaîne lambda restait significatif ($p<0,01$). Discussion : nous ne retrouvons pas dans cette étude de lien entre l'isotype de la chaine lourde et le risque de fracture vertébrale mais une augmentation du risque associée à la présence de la chaîne légère lambda. Ce lien n'a jamais été décrit dans la littérature et le mécanisme physiopathologique est inconnu. Ce résultat nécessite d'être confirmé sur une plus large cohorte. Conclusion : dans cette cohorte de patients porteurs d'une MGUS, nous décrivons pour la première fois une augmentation du risque de fracture vertébrale ostéoporotique associée à la chaîne légère lambda.

ABSTRACT

Introduction: Monoclonal gammopathy of undetermined significance (MGUS) is defined by the absence of bone involvement. However, several retrospective studies suggest an increased risk of fracture or BMD osteoporosis in this population. The aim of our study was to describe the bone status of MGUS patients and to determine the associated factors with osteoporosis in MGUS. Patients and Methods: In a prospective study between 2008 and 2013, the holders of a monoclonal gammopathy of fortuitous discovery, without a history of fracture or osteoporosis, benefited all of the following tests: a collection of risk factors for osteoporosis, radiographs of the thoracolumbar spine, dosage of calcium, phosphate and haematological parameters, bone densitometry by dual-energy X-ray on lumbar site, femoral neck and total hip, typing MGUS, marrow sampling if warranted by the monoclonal quota. Patients diagnosed with smoldering or symptomatic Waldenstrom or smoldering or symptomatic multiple myeloma were excluded. Results: 201 holders of MGUS patients were analyzed: mean age 66.63 ± 12.49 years, 48.3 % women, 104 IgG (51.7%), 67 IgM (33.3%), 21 IgA (10.4%), 9 dual heavy chain isotype (4.5%). 127 patients had a kappa light chain (63.2 %), 63 had a lambda light chain (31.3%), 9 dual light chain isotype (4.5%). The average monoclonal peak was 5.98 g/l and the average plasma cells was 3.3%. 59 (29.4 %) patients had osteoporosis (vertebral fracture and/or T- score ≤ -2.5 SD), 37 (18.4%) had one or more osteoporotic vertebral fracture. Fractured patients were significantly older, had a significantly lower densitometry on the three sites and were more frequently lambda light chain isotype. The relative risk of vertebral fracture in MGUS with isotype lambda compared to isotype kappa was 2.52 (95% CI 1.21 to 5.24). In multivariate analysis taking into account age, sex, and bone density, the risk of fracture associated with the lambda light chain remained significant ($p < 0.01$). Discussion : We did not find in this study link between heavy chain isotype and vertebral fracture risk but an increased risk associated with the presence of the lambda light chain isotype. This link has never been described in the literature and the pathophysiologic mechanism is unknown. This result needs to be confirmed on a larger cohort. Conclusion : In this cohort of MGUS patients, we described for the first time an increased risk of osteoporotic vertebral fracture associated with lambda light chain.

INTRODUCTION

Monoclonal gammopathy of undetermined significance (MGUS) is an asymptomatic plasma cells disorder occuring in 3.2% of adults > 50 years of age and 8% of adults > 85 years (1). In most cases, MGUS is not moving towards a malignant B-cell disorder. The risk of transformation to multiple myeloma (MM) is estimated at 1% per year, 15% in 10 years (2) and the risk of transformation to Waldenström's macroglobulinemia (WM) is estimated at 1.5% per year and 24% in 15 years (3). MGUS is often accidentally discovered and is detected by the electrophoresis of serum or urine protein, confirmed and typed by immunoelectrophoresis or immunofixation of serum and/or urine protein. It is defined by a monoclonal immunoglobulin concentration in serum of 3 g/dl or less; the absence of lytic bone lesions, anemia, hypercalcemia, and renal insufficiency related to the proliferation of monoclonal plasma cells; and a proportion of plasma cells in the bone marrow less than 10 % (4).

Although the consequences of MM on bone due to the decoupled bone turnover are well known (5), the effects of MGUS, considered as an asymptomatic condition, on bone remodeling remains uncertain. The only consensus about MGUS published until now (6) recommends a bone survey with a Dual-energy X-ray absorptiometry (DXA) scan to assess bone mineral density (BMD) at the initial evaluation. Indeed, some histological, laboratory and mainly clinical evidence have already shown that MGUS is a true risk factor of fracture and particularly to osteoporotic vertebral fractures. According to retrospective studies, comparing large groups of MGUS to matched individuals, MGUS is associated with a risk of fracture at any site from 1.4 to 2.5 times greater than in control populations and a rate of vertebral fracture up to 6 times greater in MGUS groups (7-8). However, these studies are retrospective and do not distinguish traumatic fractures of osteoporotic vertebral fractures; furthermore, the lack of systematic radiographic evaluation probably underestimates the number of vertebral fractures. After 50 years old, nearly 50% of vertebral fractures are asymptomatic and occur in women with a T-score > -2.5 standard deviation (SD). Detection of asymptomatic vertebral fracture is important because of the high recurrence risk of fracture (9-10) and its impact on the quality of life. The aim of our study was to evaluate prospectively the bone and hematologic status of patients with MGUS, to estimate the rate of bone events in a prospective followed MGUS cohort and to identify risk factors for osteoporosis and/or vertebral fracture.

PATIENTS AND METHODS

Patients

This prospective and descriptive study was conducted in the department of rheumatology of the University Hospital of Angers, France, from July 2008 to June 2013. Patients were referred by the department of blood diseases of the Hospital of Angers, by general practitioners and hospital or liberal rheumatologists.

To be included, patients had to be adults and to have a monoclonal gammopathy confirmed by immunoelectrophoresis of serum or urine protein. Monoclonal gammopathy should be accidentally discovered. Patients with monoclonal gammopathy discovered during osteoporosis or fracture assessment or patients with previous known and treated osteoporosis were excluded. At the end of bone and haematological assessment, patients for whom a diagnosis of hematologic malignancy was raised were also excluded (i.e. symptomatic or asymptomatic MM (defined by a bone marrow plasma cell infiltration ≥10% with or without an organ damage(4)), symptomatic or asymptomatic WM (defined by a bone marrow infiltration by small lymphocytes showing plasmacytoid/ plasma-cell differentiation ≥10% with or without IgM related symptoms and/or tumor infiltration symptoms (11)) or other hematologic malignancies).

Methods

For each patient data collected were as follows:

- 1/ Interrogation and clinical examination to collect the following information:

age, weight, height, comorbidities, age at onset of menopause with or without hormone therapy, family history of fractures, personal history of fractures and fracture incidence condition, ongoing treatment, calcium dietary intake.

- 2/ Plain radiographs of the pelvis, anteroposterior/lateral thoracic and lumbar spine radiographs in search of vertebral fracture(s). Two trained investigators who were unaware of the patient BMD status analyzed radiographs independently. A 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. If a vertebral fracture was detected, it was characterized by the semi-quantitative classification of Genant (12) defined as such:

- normal if there is no reduction in any height,
- 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.

- 3/ 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 posteroanterior view incidence and fractured vertebrae were excluded from analysis. Total hip BMD was 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 [Standard deviation (SD)]. The T-scores were calculated using manufacturer's references and expressed the difference between the subject value and mean value of healthy young women. The World Health Organization has defined normal BMD as a T-score > -1 in the lumbar spine and total hip, low bone density as a T-score between -2.5 and -1, osteoporosis as a T-score < 2.5.
- 4/ Laboratory tests performed on fasting individuals at 8 am without freezing: to confirm and quantify gammopathy: serum protein electrophoresis, serum and urinary immunoelectrophoresis (PLC Hydrasis Sebia), cells blood count (Sysmex PLC), β2 microglobulin (Immunoturbidimetry), LDH (pyruvate substrate DGKC), creatinine (Roche Modular PLC), bone marrow by sternal puncture in patients with IgG or IgA isotype whose peak value in serum protein electrophoresis was greater than 10 g/l, bone marrow biopsy in patients with IgM isotype having a visible protein electrophoresis peak. Parameters of mineral metabolism and bone turnover: serum calcium, phosphate, albumin (PLC Modular Roche), 25-OH vitamin D (RIA) and parathyroid hormone (PTH) (Electrochimieluminescence), bone-alkaline phosphatase (BALP) (CLIA Liaison), C-terminal telopeptide of type I collagen serum (CTX) (EIA Osteometer).

Statistical analysis:

Statistical analysis was performed using the software Statistical Package for the Social Sciences (SPSS Version 15.0). All results were expressed as mean ± standard deviation. Baseline characteristics of patients were expressed in mean ± one standard deviation. The comparison of groups was performed for continuous variables by analysis of variance (ANOVA) and for binary variables by the Pearson Chi2. Differences were considered significant when $p < 0.05$. Logistic regression was performed to analyse factors associated with osteoporosis and vertebral fracture.

RESULTS

Characteristics of the population:

Flow chart of the study was detailed in ***figure 1***. Characteristics of the population were detailed in ***table 1***. Briefly, 201 patients were included, 97 women (48.3 %) and 104 men (51.3 %). The average age was 66.63 ± 12.49 years (range: 30-89 years), mean BMI 26.73 ± 5.10 kg/m^2. One hundred and ninety-five patients (97%) were of Caucasian ethnicity. The distribution of heavy chain isotypes was: 104 IgG (51.7%), 67 IgM (33.3%), 21 IgA (10.4%), and 9 dual isotype (4.5%). The light chains were distributed as follows: 127 κ light chains (63.2%), 63 λ light chains (31.3%), 9 κ + λ associations (4.5%), two light chains were not known (1%). The average monoclonal peak was 5.98 ± 4.87 g/l (range: 0-21.3 g/l) and the mean plasma cells in bone marrow of 3.3 ± 2.33% (range 0-9%). Thirty-six patients (17.9 %) had a BMD T-score < -2.5 in at least one of the three measured sites. Thirty-seven patients (18.4%) had at least one vertebral fracture at the thoracic or lumbar spine. Seventy-one vertebral fractures were detected, 19 grade 1, 37 grade 2, 14 grade 3. Eighteen patients had one vertebral fracture, 6 patients had 2 vertebral fractures, 5 patients had 3 vertebral fractures and 5 patients had 4 or more vertebral fractures. Considering BMD results and vertebral fracture status, a total of 59 (29.4%) patients had osteoporosis.

Factors associated with vertebral fracture (***Table 2***)

Thirty-seven patients (18.4%) of our cohort had one or more vertebral fracture(s). Patients with vertebral fracture(s) were significantly older than non-fractured (73.54 years *vs*. 65.07 years; $p < 0.001$) and had a significantly lower T-score and BMD regardless of the studied site. There was no significant difference in sex ratio, BMI, calcium and phosphate parameters or distribution of heavy chain isotypes between groups. Patients with λ isotype light-chain had

significantly more vertebral fracture than patients with κ isotype light-chain (48.65 % *vs* 27.33%, p = 0.013). We compared characteristics of patients with and without vertebral fractures among patients with λ isotype light-chain: patients with vertebral fracture (29.03%) were significantly older than patients without fracture (71.39 *vs* 62.16 years; p=0.011) and had a lower BMD at the femoral neck and the total hip (respectively for BMD: 0.63 *vs* 0.77 g/cm² and 0.79 *vs* 0.93 g/cm²) *(data not shown)*

In univariate and multivariate analysis, age, low BMD and λ isotype light-chain were associated with a significant increased risk of vertebral fracture (***Table 3***). Compared to patients with κ light-chain, the relative risk to be fractured for patients with λ light-chain was 2.52 (95 % CI 1.21-5.24; p=0.013).

We analyzed factors associated with severe osteoporosis characterized by ≥ 2 vertebral fractures (***Table 4***). In univariate analysis, age, low BMD and λ isotype light-chain were associated with a significant risk of ≥ 2 vertebral fractures. In multivariate analysis, low BMD and λ isotype light-chain remained significantly associated with the risk of ≥ 2 vertebral fractures. A high BMI was also associated with the presence of ≥ 2 vertebral fractures

Factors associated with BMD T-score < -2.5

Thirty-six patients (17.9 %) had a BMD T-score < -2.5 in at least one of the three measured sites. Patients with densitometric osteoporosis were significantly older than the others (***Table 5***). In univariate and multivariate analysis, age was associated with a significant increased risk of osteoporosis. A higher BMI was a protective factor of osteoporosis (***Table 6***).

DISCUSSION

The population of this study is representative of a MGUS population, with a sex ratio close to 1 (48.3% women), an isotype distribution of heavy and light chains (IgG 51.7% - 33.3% IgM - 10.4% IgA - biclonal 4.5%, κ chain 63.2% - λ chain 31.3%) similar to what is usually described in MGUS cohort studies (13) albeit with a greater percentage of IgM compared to registry studies (8). This cohort is homogeneous involving only patients with MGUS excluding asymptomatic and symptomatic MM and WM. Subjects of our cohort have no known osteoporosis or vertebral fracture history. All patients had spinal radiographs which are the most reliable means to detect vertebral fracture especially asymptomatic ones. Spinal radiographs have been read by two investigators to be sure to detect all vertebral fractures and to eliminate simple vertebral deformity which sometimes can be confused with mild vertebral fractures. The number of prevalent vertebral fractures in our study (18.4%) is higher than the prevalence typically found in standard population studies close to 12% (14). This result has to

be confirmed with a comparison to a control population. Patients with vertebral fracture in our study were significantly older and had a lower BMD on the three sites than patients without fractures, which are two known risk factors for osteoporotic fractures. Nevertheless, it was shown, for the first time in this study, a significant association between the presence of the λ light chain isotype and the presence of osteoporotic fractures with a relative risk of fracture of 2.52 (95 % CI 1.21-5.24; p=0.013) in the λ group compared with the κ group. The association between vertebral fracture and λ light chain remains significant in multivariate analysis after adjustment on BMD, age, sex and BMI. The association between λ light chain and vertebral fractures remains also significant when we analyzed patients with severe osteoporosis characterized by ≥ 2 vertebral fractures.

The λ light chain is a minority in humans (1/3 of immunoglobulins, in agreement with the distribution of the light chains in our study population) because the synthesis of light chains starts with the rearrangement of the κ light chains on chromosome 2 and continues to the synthesis of a λ light chain (locus 22q11) only if the rearrangement does not encode a functional κ chain. The κ and λ light chains have different chemical properties and despite the number of potential combinations of light chain due to the genetic rearrangement, some subtypes are more frequently associated with deposit diseases (15). The AL amyloidosis is most commonly linked with λ light chains (16) while MM with renal involvement is more common in the presence of κ light chains (17). The POEMS syndrome is almost exclusively associated with a λ light chain without any evidence of a direct pathogenic role of the λ light chain itself (18). Our study seems to go in the direction of another λ light chain-associated disease.

The risk of densitometric osteoporosis increases with age and as previously described, a high BMI is associated with a lower risk of densitometric osteoporosis; nevertheless we show in our study that a higher BMI is associated with an increased risk of multiple vertebral fractures. On the contrary to the general osteoporotic population in which females are more concerned; the risk of densitometric osteoporosis or vertebral fracture in our study is the same in male and female.

The presence, the severity and the number of osteoporotic vertebral fractures are important predictors of further vertebral and non-vertebral fracture risk. Subjects with a prevalent vertebral fracture have a fivefold increased risk of further vertebral fracture and a threefold risk of hip fracture than those without an incident vertebral fracture (19). Moreover, although osteoporosis is a benign condition, osteoporotic fractures are associated with reduced quality of life and with an increased risk of dying (20), particularly in the first few years after an event (19). Previous studies have shown that the incidence of vertebral fractures is higher in

MGUS than in the rest of the population but with contradictory results concerning the influence of isotypes on fracture risk (21-22-23) The higher fracture risk associated with the λ light chain isotype had never been previously found and may be due to a different methodology of our study with a systematic spinal radiographic evaluation. MGUS represent a potentially pre-neoplastic condition that may progress to malignant B-cell disorders, such as MM. In MM, bone lesions are due to the secretion of many cytokines by plasma cells, bone marrow stromal cells, osteoblasts and osteoclasts (24), leading to an uncoupling bone remodeling with an increased bone resorption (mainly due to osteoclast hyperactivation by uncontrolled synthesis of Receptor activator of NFκB ligand (RANKL)(25) and Macrophage inflammatory protein (MIP1-α)(26)) contrasting with a reduction in bone formation (with an inhibition of the osteoblastic differentiation Wnt/β-catenin signalling pathway through increased secretion of Dickkopf-1 (DKK-1) (27), sclerostin(28) and soluble Frizzled-related proteins 2 and 3 (sFRP2-3) (29)). Some studies have shown a similar cytokine profile in MGUS with an increased DKK-1 and MIP-1α serum levels (30) and an increased RANKL/OPG ratio in patients MGUS with (23) and without (31) osteoporotic vertebral fractures. Bone turnover in monoclonal IgM gammopathy seems to be related to a different mechanism with an increased microresorption due to a population of mononuclear osteoclasts (32). In our study IgM is not associated with an increased risk of osteoporosis or vertebral fracture even if there is a trend in the association between IgM and vertebral fracture.

The main limit of our study is the absence of a control group without MGUS matched for age and sex to determine if λ light-chain increases the risk of vertebral fracture or if κ light-chain is a factor of protection of vertebral fracture. Despite this limit, our prospective study on a large cohort of MGUS followed prospectively allows reliable assessment of haematological and bone parameters. Even if MGUS is considered as a frequently benign condition, and particularly low risk MGUS (IgG heavy chain, normal free light chain ratio, peak value < 15g/l) (33), our study shows that all newly-diagnosed MGUS patients need a full bone assessment to identify bone status and prevalent fracture. This assessment should interest all the patients whatever their sex. Particular attention should be given to older patients and patients with a λ light-chain. Because of the large number of asymptomatic vertebral fractures, systematically spinal X-rays assessment is essential to diagnose all vertebral fractures. In case of osteoporosis, anti resorptives treatment such as bisphosphonates could be proposed to the patients (34).

CONCLUSION

We show in this study a high prevalence of vertebral fractures among male and female patients with MGUS. Particular attention should be paid to MGUS with λ isotype in which fracture risk is significantly increased compared with κ isotype, demonstrated for the first time in our study. The mechanism is currently unknown. Given the potential severity of osteoporosis and its consequences, it seems appropriate to propose a systematic complete hematologic and bone evaluation in newly-diagnosed MGUS even if most of them will never progress to a malignant B-cell disorder.

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TABLES & FIGURES

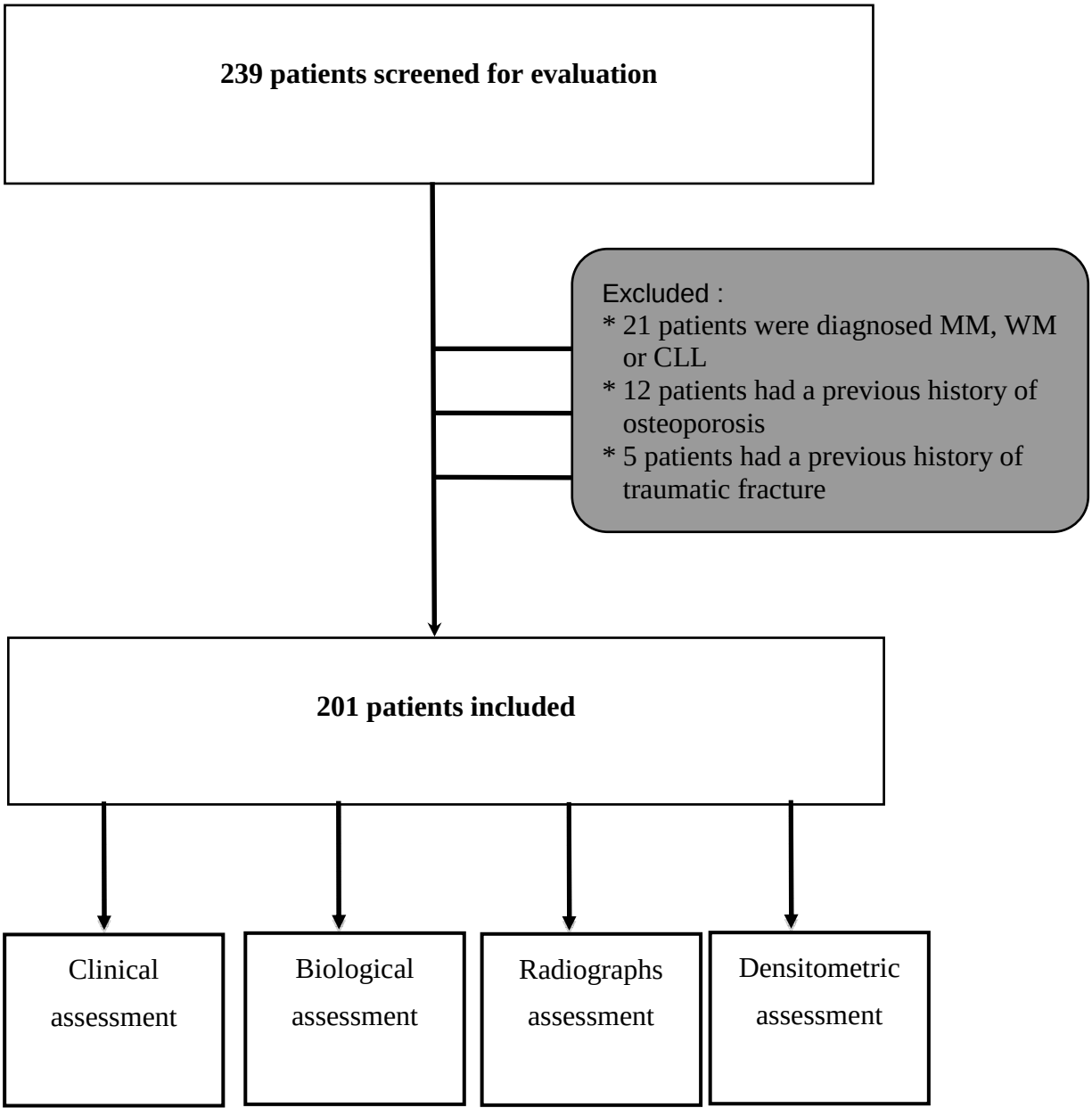

Figure 1. Flow Chart

Abbreviations: MM: multiple myeloma, WM: Waldenström's macroglobulinemia, CLL: chronic lymphocytic leukemia

	Mean value	Standard deviation
Age (years)	66.63	12.49
Weight (kilograms)	72.35	14.54
Height (centimeters)	164.06	9.13
BMI (kilograms/m^2)	26.73	5.1
BMD total hip (g/cm^2)	0.897	0.154
T-Score total hip (SD)	-0.72	1.01
BMD femoral neck (g/cm^2)	0.738	0.14
T-Score femoral neck (SD)	-1.30	1.05
BMD lower spine (g/cm^2)	0.958	0.163
T-Score lower spine (SD)	-1.09	1.45
Albumin (g/l)	42.36	5.01
Calcium (mmol/l)	2.33	0.11
Creatinine (µmol/l)	77.31	24.79
25 hydroxy-vitamine D (nmol/l)	55.47	28.48
PTH (pg/ml)	38.06	24.08
B2 microglobulin (mg/l)	2.22	0.98
LDH (UI/l)	278.51	108.75
CTX (ng/ml)	0.64	1.31
BALP (UI/l)	13.75	8.89
Marrow plasma cells (%)	3.3	2.33
Peak value (g/l)	5.98	4.87
Binary variables		
Women	97 (48.3%)	
α heavy chain	21 (10.4%)	
γ heavy chain	104 (51.7%)	
µ heavy chain	67 (33.3%)	
Double heavy chain isotype	9 (4.5%)	
κ light chain	127 (63.2%)	
λ light chain	63 (31.3%)	
Double light chain isotype	9 (4.5%)	

Abbreviations: SD : standard deviation, BMI: body mass index, BMD: bone mineral density, PTH: parathormone; LDH: lactate dehydrogenase, CTX: C-terminal telopeptid of collagen-1, BALP: Bone-alkaline phosphatase.

Table I. Characteristics of the population

	Fractured (N= 37)		Not fractured (N=163)		
	Mean	SD	Mean	SD	p
Age (years)	73.54	±10.28	65.07	±12.47	<0.001
BMI (kilograms/m^2)	27.27	±4.73	26.75	±4.75	0.558
BMD total hip (g/cm^2)	0.789	±0.114	0.920	±0.152	<0.001
T-Score total hip (DS)	-1.40	±0.76	-0.56	±0.99	<0.001
BMD femoral neck (g/cm^2)	0.636	±0.094	0.759	±0.139	<0.001
T-Score femoral neck (DS)	-1.96	±0.75	-1.14	±1.04	<0.001
BMD lower spine (g/cm^2)	0.851	±0.121	0.974	±0.161	0.005
T-Score lower spine (DS)	-2.09	±1.10	-0.92	±1.43	0.001
Albumin (g/l)	40.74	±5.07	42.75	±4.94	0.027
Calcium (mmol/l)	2.33	±0.12	2.33	±0.10	0.964
Creatinine (µmol/l)	80.19	±27.49	76.66	±24.26	0.437
25 hydroxy-vitamine D (nmol/l)	61.89	±34.67	54.22	±26.93	0.150
PTH (pg/ml)	36.89	±27.06	38.36	±23.52	0.745
B2 microglobulin (mg/l)	2.49	±0.89	2.16	±0.99	0.075
LDH (UI/l)	287.54	±104.57	276.56	±110.21	0.591
Marrow plasma cells (%)	3.13	±2.16	3.34	±2.37	0.752
Peak value (g/l)	6.95	±5.32	5.75	±4.78	0.180
Binary variables					
Sexe (femme)	20 (54.05%)		83 (50.92%)		0.73
γ heavy chain (IgG)	16 (43.24%)		87 (53.37%)		
µ heavy chain (IgM)	17 (45.94%)		50 (30.67%)		0.27
α heavy chain (IgA)	2 (5.41%)		19 (11.66%)		
Double isotype heavy chain	2 (5.41%)		7 (4.29%)		
κ light chain	16 (43.24%)		111 (68.94%)		
λ light chain	18 (48.65%)		44 (27.33%)		*0.013*
Double isotype light chain	3 (8.11%)		6 (3.73%)		

Abbreviations: SD : standard deviation, BMI: body mass index, BMD: bone mineral density, PTH: parathormone; LDH: lactate dehydrogenase, CTX: C-terminal telopeptid of collagen-1

Table II. Characteristics of the population according to whether or not fractured.

	Hazard Ratio	Confidence interval 95%	p
	Univariate analysis		
Age	1.07	1.03-1.11	*0.001*
Sex	1.13	0.55-2.32	0.73
BMI	1.02	0.95-1.10	0.56
Low BMD	4.19	1.85-9.50	*0.001*
IgM *vs* IgG and IgA	1.92	0.93-3.97	0.078
IgG *vs* IgM and IgA	0.67	0.32-1.37	0.27
IgA *vs* IgG and IgM	0.43	0.10-1.95	0.27
Lambda *vs* kappa	2.52	1.21-5.24	*0.013*
	Multivariate analysis		
Age	1.07	1.03-1.12	*0.002*
Sex	1.17	0.48-2.82	0.73
BMI	1.04	0.95-1.14	0.39
Low BMD	4.02	1.55-10.44	*0.004*
Heavy chain isotype	1.69	0.88-3.23	0.11
Lambda *vs* kappa	4.48	1.80-11.16	*0.001*

Abbreviations : BMI : body mass index, Ig : immunoglobulin, BMD : bone mineral density

Table III. Logistic regression of variables associated with osteoporotic vertebral fracture

	Hazard Ratio	Confidence interval 95%	p
	Univariate analysis		
Age	1.05	1.00-1.10	0.033
Sex	1.06	0.39-2.88	0.90
BMI	1.11	1.01-1.23	0.026
Low BMD	3.57	1.25-10.19	0.017
IgM *vs* IgG and IgA	1.87	0.68-5.09	0.22
IgG *vs* IgM and IgA	0.48	0.17-1.36	0.17
IgA *vs* IgG and IgM	1.15	0.24-5.42	0.86
Lambda *vs* kappa	4.67	1.64-13.30	0.004
	Multivariate analysis		
Age	1.05	0.29-3.13	0.086
Sex	0.95	0.30-4.41	0.93
BMI	1.16	1.03-1.30	0.011
Low BMD	4.73	1.31-17.06	0.017
Heavy chain isotype	1.59	0.63-4.00	0.32
Lambda *vs* kappa	6.40	1.85-22.12	0.003

Abbreviations : BMI : body mass index, Ig : immunoglobulin, BMD : bone mineral density

Table IV. Logistic regression of variables associated with ≥ 2 vertebral fractures.

	BMD Osteoporosis (T score ≤ -2.5) (N= 36)		No BMD Osteoporosis (T score > -2.5) (N=153)		
	Mean	SD	Mean	SD	p
Age (years)	71.11	±11.02	64.98	±12.29	0.007
BMI (kilograms/m^2)	25.65	±4.80	27.18	±4.68	0.083
Albumin (g/l)	40.07	±6.34	42.98	±4.50	*0.002*
Calcium (mmol/l)	2.32	±0.11	2.33	±0.09	0.800
Creatinine (µmol/l)	80.11	±27.39	77.19	±24.45	0.530
25 hydroxy-vitamine D (nmol/l)	48.14	±23.21	57.6	±29.07	0.074
PTH (pg/ml)	38.49	±30.39	38.16	±23.19	0.943
B2 microglobulin (mg/l)	2.34	±0.90	2.18	±1.01	0.391
LDH (UI/l)	238.40	±97.11	285.72	±107.01	*0.018*
Marrow plasma cells (%)	3.67	±3.01	3.28	±2.13	0.518
Peak value (g/l)	6.76	±4.52	5.91	±4.99	0.359
Binary variables					
Sexe (femme)	15 (41.67%)		83 (54.24%)		0.174
γ heavy chain (IgG)	19 (52.78%)		79 (51.63%)		
µ heavy chain (IgM)	14 (38.89%)		48 (31.37%)		0.585
α heavy chain (IgA)	2 (5.55%)		18 (11.76%)		
Double isotype heavy chain	1 (2.78%)		8 (5.23%)		
κ light chain	21 (58.33%)		98 (64.47%)		
λ light chain	13 (36.11%)		48 (31.58%)		0.765
Double isotype light chain	2 (5.55%)		6 (3.95%)		

Abbreviations: SD : standard deviation, BMI: body mass index, BMD: bone mineral density, PTH: parathormone; LDH: lactate dehydrogenase, CTX: C-terminal telopeptid of collagen-1, BALP: Bone-alkaline phosphatase.

Table V. Characteristics of the population according to their Bone Mineral Density (BMD) status

	Hazard Ratio	Confidence interval 95%	p
	Univariate analysis		
Age	1.05	1.01-1.08	*0.008*
Sex	0.60	0.29-1.26	0.18
BMI	0.93	0.85-1.01	0.084
IgM *vs* IgG and IgA	1.39	0.66-2.95	0.39
IgG *vs* IgM and IgA	1.05	0.51-2.17	0.90
IgA *vs* IgG and IgM	0.44	0.10-1.99	0.29
Lambda *vs* kappa	1.22	0.57-2.62	0.60
	Multivariate analysis		
Age	1.06	1.02-1.09	*0.003*
Sex	0.56	0.25-1.22	0.14
BMI	0.90	0.82-0.99	0.03
Heavy chain isotype	1.06	0.61-1.85	0.84
Lambda *vs* kappa	1.51	0.66-3.45	0.33

Abbreviations : BMI : body mass index, Ig : immunoglobulin

Table VI. Logistic regression of variables associated with densitometric osteoporosis

TABLE DES MATIERES