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ORIGINAL ARTICLE

Bone tissue quality in patients with monoclonal gammopathy of uncertain significance

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Abstract

Introduction Monoclonal gammopathy of uncertain significance (MGUS) is highly prevalent in older adults and affects bone structure, with osteoporosis and increased risk of fractures in up to 14% of affected patients. Dual-energy X-ray absorptiometry (DXA), the standard technique for diagnosing osteoporosis, is ineffective to reveal microstructure and bone quality in this disease.

Materials and methods We conducted a cross-sectional study of patients with MGUS, recruited consecutively from the Hematology and Internal Medicine Departments of Hospital del Mar, Barcelona, between January 2011 and January 2018. Medical records, clinical results and spinal X-ray images were collected. Bone mineral density (BMD) at hip and spine was measured by DXA and Bone Material Strength index (BMSi) by impact microindentation on the tibial mid-shaft.

Results Thirty-nine patients with MGUS and 65 age-matched controls without previous fractures were included. In the MGUS group, 11 (28.2%) patients had prevalent fractures, nearly half of them vertebral ($n = 5$, 45.45%). Compared to controls, MGUS patients had significantly lower BMSi, a mean (SD) of 70.72 (9.70) vs. 78.29 (8.70), $p = 0.001$, and lower spinal BMD values (0.900 [0.159] vs. 1.003 [0.168], respectively, $p = 0.012$), but no significant differences at femoral neck and total hip. No association was observed between BMSi and DXA. Bone remodeling markers (procollagen type-1 N propeptide, bone-alkaline phosphatase and C-terminal telopeptide of type I collagen) did not differ between the two groups.

Conclusions Spinal BMD and mechanical properties of bone tissue, as measured by impact microindentation, were impaired in patients with MGUS. These changes in bone tissue mechanical resistance were independent of DXA levels.

Keywords Monoclonal gammopathy of uncertain significance · Bone quality · Bone microindentation · DXA

Introduction

Monoclonal gammopathy of uncertain significance (MGUS) is the most frequent monoclonal gammopathy [1]. Although the prevalence of MGUS is 3.2% in individuals older than 50 years and increases to 7–9% at the age of 85, only a third of cases are diagnosed [1, 2]. MGUS is defined by serum monoclonal protein (non-IgM type) < 3 g/dl, clonal bone marrow plasma cells < 10%, and absence of end-organ damage such as renal failure, hypercalcemia or anemia, as well as bone lesions or amyloidosis that can be attributed to this plasma cell proliferative disorder [3]. In patients with MGUS, osteoporosis and fracture prevalence is 14% and the risk of fracture is twice that of the general population, affecting mainly the axial skeleton (vertebral fractures) [4–9]. Bone histomorphometry has revealed a quantifiable excess

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of bone resorption in MGUS [10], as well as Wnt pathway inhibition via DKK1, alteration in MIP-1 alpha pathway and an increased RANKL/OPG ratio [8, 11–13].

The standard technique to diagnose osteoporosis is densitometry measured by dual-energy X-ray absorptiometry (DXA). However, the utility of DXA to estimate MGUS bone fragility is controversial due to its limited capacity to detect bone loss, even in patients with established osteoporotic fracture [14, 15]. DXA measures bone mineral density (BMD) but does not inform about microstructure or bone material quality, which are essential contributors to mechanical resistance to fracture [16]. Nevertheless, these diseases are associated with a considerable degradation of microstructure and resistance leading to bone fragility [8, 13, 17]. Despite having a larger bone size [13], patients with MGUS present with a more porous cortical and possibly reduced resistance, as evidenced by High-Resolution Peripheral Quantitative Computed Tomography (HRpQCT) in distal radius, compared to the general population [18, 19].

Impact microindentation (IMI), a recently developed and minimally invasive technique, directly measures the mechanical properties of bone tissue in vivo, complementing DXA and contributing new information about bone quality [20]. Microindentation has revealed deteriorated bone quality in diverse clinical situations where there is an increased risk of fracture without a proportional BMD decrease, such as glucocorticoid-induced osteoporosis [21], type 2 diabetes [22], Gaucher diseases [23], HIV [24], atypical femoral fracture [25] and acromegaly [26].

Our goal was to study bone health in MGUS patients using areal bone mineral density (aBMD) and IMI to gain a better understanding of the mechanisms of bone fragility that could support improved disease management in these patients in the future.

Materials and methods

Subjects

This cross-sectional study recruited 39 MGUS patients (mean [SD] age 69.5 [11.0] years) and 65 healthy volunteers (mean age 67.0 [10.6] years) with no history of low-energy fractures from the Hematology and Internal Medicine Clinics of Hospital del Mar in Barcelona between January 2011 and January 2018. Eligible participants with MGUS had a recorded diagnosis according to the International Myeloma Working Group (IMWG) criteria [27]. Patients with IgM MGUS were not included in the study because bone involvement in this context is not described in the literature. Eligible patients with evidence of previous or current use of a drug with a known effect on bone metabolism were excluded from participation.

In both patients and controls, medical history, blood tests, DXA (spinal and hip BMD), anteroposterior and lateral thoracolumbar spine X-ray and IMI were assessed. Fractures on record were classified as vertebral, hip, and other.

All study participants gave their informed consent according to the Declaration of Helsinki (Fortaleza, Brazil, October 2013) and the project was approved by the research ethics committee of our institution (registration number 2015/6412/i).

Blood analysis

Routine blood tests were performed in all 39 patients and 65 controls. Bone remodeling markers were measured in blood plasma extracted in the morning after at least 8 h fasting. We measured C-terminal telopeptide of type I collagen (CTX) and procollagen type 1 N propeptide (P1NP) with electrochemiluminescence immunoassay (Elecsys®, Roche Diagnostics GmbH, Mannheim, Germany), bone-alkaline phosphatase (B-ALP) and 25-hydroxy (OH) vitamin D (VitD) with chemiluminescent immunoassay (Elecsys®, Roche Diagnostics GmbH, Mannheim, Germany). Immunoglobulins and light chains were quantified.

Bone measurement by DXA

BMD was measured using DXA in lumbar spine (BMD_LS), femoral neck (BMD_FN) and total hip (BMD_TH) with Hologic QDR 4500 SL, Hologic, Inc., Bedford, MA, USA). Spinal BMD was assessed according to the International Society of Clinical Densitometry criteria (www.iscd.org/visitors/positions/OPReferences.cfm). Vertebrae showing deformity were withdrawn from analysis and L1–L4 mean BMD was recalculated over the remaining vertebrae.

Microindentation

All participants were tested by IMI, following the published protocol [28]. A portable OsteoProbe Reference Point Indenter® was used in this study (ActiveLife Scientific, Santa Bárbara, CA) to perform some microscopic indentations in the middle third of the anterior surface of the right tibia. Microindentation values are expressed as Bone Material Strength index (BMSi), equivalent to 100 times the ratio of the microindentation median distance increase in methacrylate to that inside the tibia cortex. The median distance increase was determined by performing eight indentations in methacrylate and eight indentations in the tibia mid-shaft.

The procedure was repeated by two investigators; interobserver variability coefficient was 5%.

Statistical analysis

Statistical analysis was carried out with Stata15 for Windows. Descriptive variables were compared between the groups with chi-square tests (χ^2) for categorical variables and analysis of variance (ANOVA) for quantitative variables. Mean comparisons for the densitometry-related measures were compared through general linear models (GLM) adjusted by sex, age, body mass index (BMI), glomerular filtration rate (GFR), VitD and BMD_LS value (adjustment variables defined as covariates into the models). Assumptions of normality and homogeneity of variance for the ANOVA and GLM in the use of these procedures were achieved, while Fisher exact test was used for proportion comparison when expected frequencies were $e_{ij} < 5$.

The association between variables was estimated using correlation coefficients. Due to the strong association between significance (p value) and sample size for these coefficients (low r coefficients achieve statistical significance in large sample size and high r coefficients are not significant in low sample size), only correlations in which effect size was within the mild/moderate ($|r| > 0.24$) to large/good range ($|r| > 0.37$) were considered as relevant [29].

The Finner method was used to control for Type I error due to multiple statistical comparisons, including pairwise comparisons in the post hoc analysis of the GLM models. The procedure used to correct p values is included in the familywise error rate stepwise procedures, and offers more statistical power than the classical Bonferroni correction. A complete description of this procedure is described in the Finner study [30].

Results

Characteristics of the sample

There were 27 women and 12 men in the MGUS group and 33 and 32, respectively, among the controls. Abnormal protein in gammopathy was IgG in 32 cases and IgA in 7; the light chain was *Kappa* in 24 and *Lambda* in 15 cases. Table 1 shows the characteristics of the study participants. Mean comparisons between laboratory values were adjusted by age, sex and BMI. There were no statistical differences in age between MGUS (69.5 [11.0] years) and controls (67.0 [10.6] years); $p = 0.331$). VitD levels were significantly lower in the MGUS group ($p = 0.004$).

Table 1 Descriptive data and comparison of patients and controls

	Control $n = 65$		MGUS $n = 39$		Control vs MGUS
	n	%	*n*	%	*p*
SexWomen	33	50.8%	27	69.2%	0.101
Men	32	49.2%	12	30.8%	
	Mean	SD	Mean	SD	*p*
Age (years)	67.00	10.60	69.46	10.99	0.331
Height (cm)	1.64	0.08	1.60	0.08	0.089
Weight (kg)	68.77	12.62	71.18	14.69	0.379
BMI (kg/m^2)	25.54	4.45	27.65	5.12	0.089
P1NP (ng/ml)	57.04	13.64	51.36	21.39	0.181
B-ALP (U/L)[a]	18.40	21.39	14.91	5.61	0.354
CTX (ng/ml)[a]	0.40	0.12	0.33	0.20	0.107
Vit_D (ng/ml)[a]	35.60	15.79	21.30	11.74	0.004*
LDH (U/L)[a]	N/A	N/A	332.26	64.03	N/A
B2µgl (mg/L)[a]	N/A	N/A	2.19	0.88	N/A
IgG (mg/dl)[a]	N/A	N/A	1135.36	543.38	N/A
IgA (mg/dl)[a]	N/A	N/A	241.29	291.95	N/A
MC (g/dl)[a]	N/A	N/A	0.73	0.54	N/A
κ-Light (mg/L)[a]	N/A	N/A	187.92	368.74	N/A
λ-Light (mg/L)[a]	N/A	N/A	143.89	409.87	N/A
K/L quotient[a]	N/A	N/A	7.63	19.47	N/A

BMI body mass index (kg/m^2); *SD* standard deviation; *N/A* Not available for the group *P1NP* procollagen type 1 n-terminal propeptide; *ng/ml* nanograms per milliliter; *B-ALP* bone-alkaline phosphatase; *U/L* units per liter; *CTX* C-terminal telopeptide of type I collagen; *Vit_D* vitamin D; *LDH* lactate dehydrogenase; *B2µgl* B2 microglobulin; *mg/L* milligrams per liter; *IgG* immunoglobulin G; *mg/dl* milligrams per deciliter; *IgA* immunoglobulin A; *MC* monoclonal component; *g/dl* grams per deciliter; *κ-light kappa* light chain; *λ-light lambda* light chain. *K/L* quotient *kappa/lambda*

[a]For the laboratory tests, mean estimates and comparisons are adjusted by sex, age and BMI

*Statistical differences between groups (0.05). *p* values include Finner correction

Comparison of bone parameters

Mean BMSi values adjusted by sex, age and BMI were significantly lower for cases, compared to controls: 70.72 (SD 9.70) and 78.29 (SD 8.70), respectively ($p = 0.001$) (Fig. 1). In the scatterplots, no correlation was found between BMSi and the monoclonal component type (data not shown).

In the GLM, BMD results adjusted by sex, age, BMI, VitD, and GFR showed significantly lower BMD_LS values for cases, compared to controls ($p = 0.012$). However, no differences were found for BMD_FN and BMD_TH (Table 2).

Regarding previous fragility fracture, there were five vertebral fractures, one hip fracture and five non-vertebral and non-hip fractures (two wrist, one humerus, one fibula and one metatarsus) in MGUS patients. Among the 11 patients with fractures, 8 had *Kappa* light chain. Despite

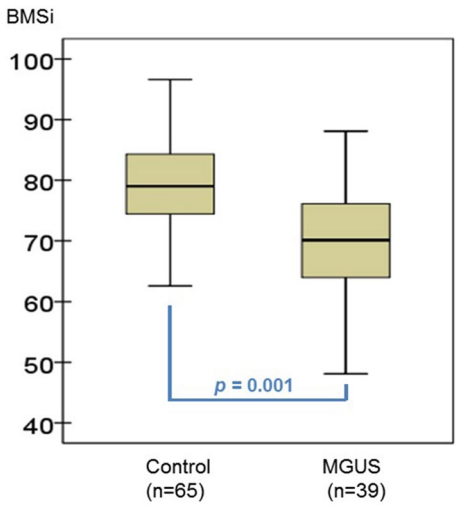

Fig. 1 Boxplot for BMS adjusted for sex, age and body mass index by ANOVA between MGUS and controls. BMS_i bone material strength index

Table 2 Comparison between groups: ANOVA

	Control $n=65$		MGUS $n=39$		
	Mean	SD	Mean	SD	*p*
BMD_LS[a]	1.003	0.168	0.900	0.159	0.012*
BMD_FN[a]	0.723	0.117	0.713	0.140	0.791
BMD_TH[a]	0.856	0.140	0.848	0.150	0.841

BMD_LS bone mineral density, lumbar spine; *BMD_FN* bone mineral density, femoral neck; *BMD_TH* bone mineral density, total hip; *SD* standard deviation

[a]Results adjusted by sex, age, body mass index, vitamin D and glomerular filtration rate

*Statistical differences between groups (0.05). *p* values include Finner correction

this observation, the difference in BMSi between fractured and unfractured participants did not reach statistical significance ($p=0.477$) and no correlation was found between the BMSi and the monoclonal type. Moreover, adjusted by sex, age and BMI, BMSi was 70.91 (SD 8.45) in the patients with previous fractures and 70.35 (SD 9.05) in patients without previous fractures ($p=0.885$).

Correlation between bone parameters

We found no significant differences in the bone turnover markers B-ALP, P1NP and CTX between patients and controls (Table 1). Table 3 displays the correlation matrix between bone densitometry values and BMSi, with the unadjusted Pearson coefficients and adjusted pairwise coefficients. No statistical association was found between BMSi and the other bone measurements (effect size for the correlation estimates were also in the null to poor range).

Safety

No local or systemic complications were observed in any individual in the case or control groups after the IMI procedure.

Discussion

To the best of our knowledge, this is the first study of microindentation use to evaluate bone material properties in vivo in patients affected by monoclonal gammopathy. The MGUS group had lower BMSi than that of controls; however, BMD was also lower in the lumbar spine and no significant BMD differences in the femoral neck and total hip were observed, compared to controls. These results are consistent with a published meta-analysis that found no significant decrease in BMD in MGUS compared to the general population [9]. As shown by the lack of correlation between BMSi and mineral density, these two techniques appear to be independent of each other in describing bone strength in patients with MGUS.

Bone strength depends on mineral density, tissue-level biomechanical properties, microarchitecture, and how these elements combine with each other [20]. Therefore, a single technique is insufficient to estimate the increase in bone fragility, as it captures only one of the contributors to skeletal strength. In addition, measurements made on fractured and unfractured bones are often superimposed without a single pattern [31]. This lack of correlation between the mineral density measured by DXA and the cortical tissue properties measured by IMI is due to differences in the bone characteristics evaluated [18, 19, 24].

Table 3 Correlation between BMSi and BMD parameters (MGUS subsample; $n=39$)

	Pearson correlation (*p* value)			Partial correlation[a] (*p* value)		
	BMD_LS	BMD_FN	BMD_TH	BMD_LS	BMD_FN	BMD_TH
BMS_i	0.101 (0.542)	− 0.030 (0.858)	− 0.094 (0.568)	0.003 (0.987)	− 0.108 (0.557)	− 0.175 (0.339)

BMD bone mineral density; *BMD_LS* bone mineral density, lumbar spine; *BMD_FN* bone mineral density, femoral neck; *BMD_TH* bone mineral density, total hip; *BMSi* bone material strength index

[a]Results adjusted by sex, age, body mass index, vitamin D, and glomerular filtration rate

High-Resolution Peripheral Quantitative Computed Tomography (HRpQCT) has provided valuable data on bone microarchitecture. By HRpQCT it is known that there are greater porosity and cortical thinning in MGUS patients suffering from fractures [18, 19]. Some disadvantages of HRpQCT include that it remains expensive with limited availability to a few specialized centers worldwide. Therefore, in addition to its portability and a short learning curve, IMI is more sensitive, as it is influenced not only by cortical porosity [32] but also by other elements of tissue quality [31].

Around 30% of patients had prevalent fractures, of which almost 45% were vertebral. This result is consistent with the high prevalence of fractures, especially axial, observed in MGUS by other authors [5–7, 9].

Another relevant issue is the significantly low levels of VitD in the patients affected by MGUS. This VitD deficiency was previously observed in patients with gammopathies [5, 33], with a greater deficiency as the disease progresses [34]. Although another study was unable to demonstrate the benefit of reducing the number of vertebral fractures after VitD supplementation [35].

Bone remodeling markers were also measured (P1NP, B-ALP, CTX). Some authors have reported increased CTX in MGUS patients [8], while other studies, including our own, detected no increase in CTX or P1NP [13]. One explanation of these conflicting results might be the uncontrollable and controllable sources of pre-analytical variability of bone markers themselves, which require specific studies on this disease [36].

Regarding the relationship between gammopathy and fracture, 15 patients in our study had a fracture, 11 of them with a *Kappa* light chain. Some groups have suggested that light chain type might be related to bone injury in gammopathy patients, and most authors have observed an association with the *Kappa* type [7, 37]. Others have linked these events with the *Lambda* type [17]. Despite the high frequency of *Kappa* light chain in our fractured patients, there was no significant difference compared to the nonfracture group. We analyzed the relationship between BMSi and the monoclonal type but found no correlation between the two parameters. Our results do not provide an explanation for this possible deleterious effect of *Kappa* light chains on bone; further research is needed in this area.

The IMI is a relatively new technique. However, several studies support its potential use, particularly in cases where increased fracture risk is not well captured by conventional DXA. Farr et al. [22] describe the 10.5% decrease of BMSi in patients with type 2 diabetes compared to controls, with no differences in BMD or microarchitecture analyzed by HRpQCT. Subsequent studies show similar results in diabetics [38, 39]. IMI detects early bone deterioration in patients under corticosteroid treatment, even at low doses of prednisone (5 mg/day). In the same study, concomitant treatment with denosumab and teriparatide elevates BMSi at 7 weeks post-onset, while there were no changes in the group treated with risedronate [21]. In HIV-infected patients, a decrease in BMSi was also observed with respect to controls ($p = 0.001$) [24], as well as in Gaucher disease [23] and acromegaly [26]. A recent IMI study on atypical femoral fracture in 15 postmenopausal patients found no difference with respect to controls, despite the higher incidence of type 2 diabetes [40]. This contrasts with the cited studies about diabetes and with two other studies on atypical and typical femoral fractures, in which a deterioration of the mechanical properties at the level of the bone tissue was found by means of indentation [25, 41, 42]. The IMI also discriminates patients with bone fragility fractures [43–46] in some studies, but not in others [47]. A study by Malgo et al. supports IMI as a good predictor of fracture risk; despite similar BMD, BMSi values were lower in patients with a fragility fracture, compared to nonfracture patients (79.9 ± 0.6 vs 82.4 ± 1 respectively $p = 0.032$) [45]. The BMSi values associated with fracture in our study were even lower (70.9); however, the sample was too small to ascertain statistical significance. In another important study, Sosa et al. [44] observed increased fracture risk with a decrease of one standard deviation in BMSi (odds ratio of 2.62). Large-scale longitudinal studies are needed to strengthen the available data on this topic.

Multiple myeloma, a further step of MGUS, is a recognized cause of secondary osteoporosis, although the reason for increased risk of fracture is not clear. Decades ago, an alteration in the balance between bone formation and resorption was suspected [10]. Since then, different mechanisms have been proposed, from the inhibition of the Wnt pathway by means of DKK1 to pathways involving MIP-1alpha [11–13] as well as the increase of RANKL/OPG [8]. The classical turnover markers did not prove to be helpful in monitoring the bone health of these patients [13]. It is now known that monoclonal component levels do not increase the risk of fracture in MGUS [12, 13] On the other hand, as mentioned above, the type of light chain [7, 17, 37] as well as the predictive capacity of VitD on vertebral fracture [5] are interesting fields for further investigation.

The mean obtained for the BMSi continued to be lower in cases compared to controls after adjusting for sex, age, VitD, BMI, GFR and BMD_LS. At the moment there is no consensus on the correlation between IMI and age. Some studies have found a negative relationship between BMSi and age [45], but these were independent variables for others [43, 44]. Still other authors argue that perhaps these changes are due more to bone tissue disease than to the patient's own chronological age [31]. To avoid this possible confounding factor, we have compared two groups of the same age.

Our study has some potential limitations. We had a relatively low number of patients, restricting the possibility to assess differences between fractured and non-fractured

patients, due to low statistical power. Future studies with larger clinical sample sizes are needed to provide greater statistical power to identify potential associations between the variables, and also to improve the external validity that facilitates the generalization of results to broader populations.

The strength of our study is its novelty. We assessed bone in a comprehensive manner, including a new method, IMI, not previously used to study monoclonal gammopathies.

In conclusion, patients with MGUS showed an alteration in the properties of bone materials, which contributed to their increased bone fragility and tendency to fracture, especially in the spine. We observed a lower BMSi value in patients with MGUS than in controls. At the same time, a decrease in VitD was observed in our patients and an increased incidence of fractures in those with *Kappa* light chains. Through microindentation, a new approach to the study of bone involvement in gammopathies, we have contributed to the knowledge about the decrease of the mechanical properties of bone materials regardless of mineral density in a pathology of high prevalence. Therefore, our results add to the previous evidence of IMI as a way to better identify high-risk patients who would benefit from therapy designed to prevent fragility fracture.

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Author contributions Study design: LM and GO. Study contact: GO and XN. Study conduct: GO, LM, XN and ADP. Data collection: EA, LM and GO. Data analysis: RG, MP, DPA, GO and ADP. Data interpretation: ADP, GO, LM and XN. Drafting manuscript: GO, LM, XN and ADP. Revising manuscript content: All authors. Approving final manuscript: All authors.

Compliance with ethical standards

Conflict of interest ADP—Board Membership: UCB, Roche, Echo-Light. Payment for lectures: Lilly, UCB, Roche, Gilead. Stocks/stock options: Active Life Sci. XN. Advisory board Amgen, Lilly. Educational talks: Amgen, Lilly, Italfarmaco, FAES. DPA—Department has received research grants from Amgen, UCB. Educational grants: J&J. His research group has received payment for speaker and consultancy services from Amgen and UCB.

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