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Review

Monoclonal gammopathy of undetermined significance, multiple myeloma, and osteoporosis

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ABSTRACT

The finding of monoclonal gammopathy of undetermined significance (MGUS) is not infrequent during an evaluation for osteoporosis or a fracture. In most cases, the diagnosis is MGUS, whose prevalence increases with age. Although the impact of MGUS on bone mineral density, bone remodeling, and the fracture risk remains unclear, this asymptomatic hematological disorder may constitute a risk factor for osteoporosis. Furthermore, each year, 1% of patients with MGUS progress to multiple myeloma, a disease whose pathophysiology and association with bone loss and pathological fractures are increasingly well understood. Osteoporotic fractures, although probably common in myeloma patients, are less likely to be recognized. Here, we discuss the pathophysiology of myeloma and MGUS and their impact in terms of bone mineral density, osteoporotic fractures, and bone turnover markers.

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1. Introduction

Monoclonal gammopathy of undetermined significance (MGUS) is a hematological disorder whose prevalence increases with age (Table 1) [1]. In a study conducted in Minnesota in over 21,000 Caucasian individuals older than 50 years of age, the prevalence of MGUS was 3.2% overall, 3.7% in males, and 2.9% in females [2]. In both males and females, the prevalence increased with age, reaching 8.9% in males and 7.0% in females older than 85 years of age. The most common monoclonal immunoglobulin isotype was IgG (68.9% of cases) and the most common light-chain type was kappa (62.0%). The monoclonal immunoglobulin concentration was less than 10 g/dl in 63.5% of patients [2]. Among patients with MGUS, the annual rate of progression to myeloma is 1% [3]. Studies done at the Mayo Clinic [4–6] have identified several risk factors for progression to myeloma including the monoclonal protein concentration, monoclonal immunoglobulin isotype, and serum free light-chain ratio. MGUS characterized by an abnormal serum free light-chain ratio, a non-IgG monoclonal protein, and a monoclonal protein concentration of 15 g/L or more is associated with a 58% risk of progression to myeloma within 20 years, compared to only 5% in MGUS with none of these three risk factors.

Myeloma causes osteolytic lesions that may manifest as fractures of the spine, ribs, and appendicular bones. Advances in

molecular biology have shed some light on the mechanisms underlying osteolysis related to bone invasion by myeloma cells. Osteoporotic fractures in myeloma patients, in contrast, are less well understood, although they are probably common. The impact of MGUS on bone mineral density, bone turnover, and the occurrence of fractures is unclear. More specifically, whether this asymptomatic hematological disorder is a risk factor for osteoporosis or a cause of osteoporosis remains unknown.

2. Impact of myeloma on bone

2.1. Pathophysiology of bone lesions in myeloma

The main feature of myeloma-related bone lesions is uncoupling of bone resorption, which is increased as a result of osteoclast stimulation from bone formation, which is diminished by osteoblast inhibition (Fig. 1).

2.1.1. Mechanisms leading to excessive bone resorption

Invasion of the marrow spaces by the myeloma cells causes an imbalance in the RANK/RANK-Ligand/osteoprotegerin (OPG) system. Myeloma cells increase RANK-Ligand expression by the stromal cells via direct cell-to-cell contact and an interaction between myeloma-cell VLA4 integrin and stromal-cell VCAM1. By interacting with CD44, myeloma cells also stimulate the endothelial cells to express RANK-Ligand. The locally produced RANK-Ligand interacts with its RANK receptor at the surface of osteoclast progenitors, which differentiate to osteoclasts. Furthermore, myeloma

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Table 1
Diagnostic criteria for monoclonal gammopathies [1].

	Organ/tissue damage	Laboratory data
MGUS	None	Serum monoclonal protein < 30 g/L And marrow plasma cells < 10%
Asymptomatic (smoldering) myeloma	None	Serum monoclonal protein ≥ 30 g/L And/or marrow plasma cells ≥ 10%
Symptomatic myeloma	Hypercalcemia (> 2.75 mmol/L) Or renal failure (serum creatinine > 173 μmol/L) Or anemia (Hb < 10 g/dl) Or bone lesions Or symptomatic hyperviscosity Or amyloidosis Or recurrent bacterial infections	Monoclonal protein in serum or urine and marrow plasma cells ≥ 10%

MGUS: monoclonal gammopathy of undetermined significance.

cells suppress OPG gene transcription in the osteoblasts and stromal cells. In addition, syndecan-1 (CD138) released by the myeloma cells binds to OPG and mediates its internalization and lysosomal degradation. This combination of effects increases the soluble RANK-Ligand/OPG ratio, which correlates with bone resorption markers [7].

MIP-1α and MIP-1β belong to the RANTES family of chemokines and activate monocytes, thereby contributing to increase osteoclast

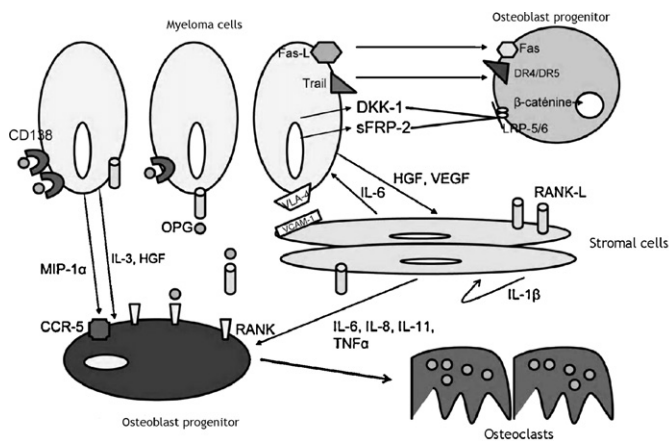


Fig. 1. Pathophysiology of bone involvement in multiple myeloma. Myeloma-related bone disease is characterized by uncoupling of bone formation and bone resorption. The main mechanisms underlying the excessive bone resorption in myeloma involve disturbances in the RANK/RANK-Ligand/osteoprotegerin (OPG) system. Interaction of myeloma-cell VLA4 integrin with stromal-cell VCAM1 leads to upregulation of RANK-Ligand expression by stromal cells. Locally produced RANK-Ligand binds to its RANK receptor on the surface of osteoclast progenitors, which then differentiate to osteoclasts. Myeloma cells suppress OPG gene transcription in osteoblasts and stromal cells. Syndecan-1 (CD138) is expressed by myeloma cells and also decreases the effect of OPG. MIP-1α contributes to stimulate osteoclast activity by binding to its CCR5 receptor at the surface of the osteoclast progenitors. Myriad cytokines are involved in osteoclast activation and interact with one another. Thus, IL-6, produced chiefly by the stromal cells, promotes growth not only of the myeloma-cell clone, but also of the osteoclasts via increased cell division and decreased apoptosis. IL-1β leads to paracrine stimulation of IL-6 production. IL-3 in combination with MIP-1α and RANK-Ligand promotes osteoclast formation and bone resorption. TNF-α stimulates the NF-κB bone resorption pathway and the production of IL-6. Hepatocyte growth factor (HGF) produced by the myeloma cells stimulates stromal cells to produce IL-11, which upregulates RANK-Ligand expression. Vascular endothelial growth factor (VEGF) is also expressed by myeloma cells and not only plays a key role in tumor neovascularization, but also promotes osteoclast survival and increases bone resorption. IL-8 activates osteoclast differentiation and bone resorption by directly stimulating the differentiation of human monocytes into osteoclasts. Myeloma cells suppress bone formation by blocking the Wnt/β-catenin signaling pathway and by producing the two proteins DKK-1 and sFRP-2. Osteoblast progenitors express the Fas receptor and the DR4/DR5 receptors and may be induced to undergo apoptosis via interaction with the corresponding ligands, Fas-Ligand and TRAIL, respectively, which are expressed by myeloma cells.

activity in myeloma patients [8]. Osteoclast progenitors and stromal cells express CCR5, the receptor for both MIP-1α and MIP-1β. Binding of MIP-1α to CCR5 induces the final steps of osteoclast progenitor differentiation. Furthermore, MIP-1α and MIP-1β induce RANK-Ligand expression by stromal cells, thereby promoting osteoclast formation and bone resorption. MIP-1α also promotes the growth and survival of myeloma cells, since these express CCR5 [9]. Serum MIP-1α concentrations correlate with bone resorption markers, presence of osteolytic lesions, and myeloma severity [10].

Stromal cell-derived factor-1α (SDF-1α) is a chemokine produced by stromal cells, endothelial cells, and myeloma cells. In addition to promoting myeloma cell adhesion, growth, and migration, SDF-1α is involved in osteoclast progenitor recruitment and myeloma angiogenesis [11]. Furthermore, osteoclast activation involves myriad cytokines that interact with one another [12]. IL-6 is produced chiefly by stromal cells and promotes the growth not only of myeloma cells, but also of osteoclasts via both stimulation of cell division and inhibition of apoptosis. IL-1β induces paracrine IL-6 production. IL-3 in combination with MIP-1α and RANK-Ligand increases osteoclast formation and bone resorption. TNF-α stimulates the NF-κB bone-resorption pathway and the production of IL-6. Hepatocyte growth factor (HGF) is expressed by myeloma cells and stimulates stromal cells to produce IL-11, which upregulates RANK-Ligand production. High serum HGF levels may predict low survival and unresponsiveness to chemotherapy. Vascular endothelial growth factor (VEGF), which is also expressed by myeloma cells, plays a pivotal role in tumor angiogenesis. Furthermore, VEGF promotes osteoclast survival and increases bone resorption. VEGF stimulates the stromal cells to express IL-6, which increases VEGF expression and secretion by the myeloma cells, suggesting the existence of paracrine interactions between myeloma and stromal cells. Osteopontin, a matrix protein produced by osteoblasts, osteoclasts, and myeloma cells, contributes to bone resorption in myeloma. Serum osteopontin levels are elevated in myeloma patients and correlate with disease progression and bone destruction. Adhesive interactions with myeloma cells cause osteoclasts to increase their production of IL-6 and osteopontin. IL-8 expressed by macrophages, neutrophils, T cells, endothelial cells, and various tumor cell types activates osteoclast differentiation and bone resorption via upregulation of RANK-Ligand expression by osteoblasts and via direct promotion of monocyte differentiation to osteoclasts [13]. Thus, multiple interactions between myeloma cells and osteoclasts promote tumor growth and bone resorption, leading to the release of cytokines and growth factors that, in turn, stimulate tumor growth. The result is a vicious cycle of uncontrolled tumor progression and bone destruction.

2.1.2. Insufficient bone formation

Abnormalities in osteoblast function also make a major contribution to the development of osteolytic lesions in patients with

myeloma. Thus, bisphosphonate therapy halts the bone resorption process but fails to induce the repair of bone defects, indicating that osteoblast number and function are impaired.

Several studies strongly suggest that the dickkopf (DKK) proteins, which inhibit the wingless-type (Wnt)/ β -catenin pathway, may play a pivotal role in suppressing bone formation in myeloma patients. Both the *DKK-1* gene and the DKK-1 protein were overexpressed in patients who had osteolytic lesions, DKK-1 suppressed osteoblast activity, and DKK-1 concentrations seemed correlated with the extent of osteolysis severity and the risk of relapse [14,15]. In a murine myeloma model, administration of an antibody against DKK-1 improved bone mass, increased osteocalcin levels, and decreased tumor burden [16]. Bortezomib [17] acts on the myeloma cells and on their interactions with the marrow microenvironment, diminishing the serum levels of DKK-1, RANK-Ligand, C-telopeptides of type-1 collagen (CTX), and tartrate-resistant acid phosphatase 5b (TRACP 5b). Bortezomib markedly increases bone formation and decreases bone resorption independently from the response to chemotherapy.

Myeloma cells may also block the Wnt/ β -catenin signaling pathway by producing secreted frizzled-related protein-2 (sFRP-2), another Wnt/ β -catenin inhibitor [18]. Myeloma cells inhibit the transcription factor Runx2/Cbfa1 in osteoblast progenitors either via direct cell-to-cell contact or via IL-7, whose serum levels are elevated in myeloma patients compared to healthy individuals [19]. Osteoblast progenitors express the Fas receptor and the DR4/DR5 receptors and may be induced to undergo apoptosis when they interact with the corresponding ligands (Fas-Ligand and TRAIL, respectively) expressed by the myeloma cells [20]. Finally, IL-3, which is produced by T cells, is elevated in myeloma patients and may both inhibit osteoblast differentiation and increase bone resorption [21–23].

2.2. Bone mineral density and fractures in multiple myeloma

Several studies suggest that bone mineral density (BMD) may be decreased in myeloma patients [24–28], most notably at the spine, in females, and in patients with an IgA monoclonal component. Myeloma treatment was followed by improvements in the low BMD values, and these improvements were greatest at the spine, in males, and in responders to chemotherapy [27,28].

The BMD data contribute to explain that myeloma is associated not only with pathological fractures through tumor foci, but also with a high rate of fractures at tumor-free sites. In a retrospective population-based cohort of 165 myeloma patients (including 55% of men) with a mean age of 70.7 years, the fracture risk was increased 9-fold compared to the expected risk in the general population [29]. The relative risk of fracture was 14 at the spine and two at nonspinal sites. Only two-thirds of these fractures were pathologic, indicating a high risk of fracture at tumor-free sites. After 10 years, 9% of the patients had experienced a new fracture at a tumor-free site. Predictors of the fracture risk were a history of fracture, glucocorticoid use, and chemotherapy use.

2.3. Bone turnover in multiple myeloma

Several studies of myeloma patients showed elevated levels of bone resorption markers that correlated with both the extent of bone disease and patient survival [30]. In a study of 121 patients with newly diagnosed myeloma, serum TRACP-5b levels were increased compared to controls and correlated with the extent of bone disease [31]. Myeloma patients with bone lesions by magnetic resonance imaging (MRI) but not by plain radiography had significantly elevated levels of ICTP compared to myeloma patients with normal MRI findings [32]. Data on bone forma-

tion markers are somewhat inconsistent. Although most studies found decreased levels of bone formation markers, discrepancies occurred across studies, in part as a result of differences across markers [33].

Bisphosphonate therapy is associated with decreases in the levels of bone resorption markers, which seem correlated with a decrease in the rate of pathologic fractures. Conversely, persistent elevation of bone resorption markers (e.g., CTX) after chemotherapy may indicate resistance or a relapse.

3. Bone manifestations of monoclonal gammopathy of undetermined significance

Laboratory tests done to evaluate osteoporosis often show a monoclonal peak, which usually indicates MGUS. In a retrospective cross-sectional study of 799 patients with suspected osteoporosis, 4.9% of the patients with confirmed osteoporosis had a monoclonal peak compared to only 2.2% of patients without osteoporosis [34]. A study of 157 patients with hip fractures found a 6% prevalence of MGUS [35]. These data suggest that MGUS, although usually described as an asymptomatic abnormality, may contribute to cause bone loss and multiple osteoporotic fractures.

3.1. Bone mineral density and fractures in monoclonal gammopathy of undetermined significance

Few data are available on the incidence of fractures in patients with MGUS. One study compared the fracture incidence, BMD values at the lumbar spine and proximal femur, and bone turnover markers in 65 women with MGUS (59 IgG, 5 IgA, and 1 IgM), a mean time since MGUS diagnosis of 7.4 years, a mean age of 61.3 years, and a time since menopause of 10 years and in 130 control women matched on age and time since menopause [36]. None of the women was taking medications known to affect bone tissue. Among the 65 MGUS patients, 13 had normal BMD values, 35 had osteopenia, and 17 had osteoporosis; 52% of them had at least one mild vertebral fracture, compared to 23.8% of controls. Only three patients with MGUS had a history of appendicular fracture (wrist). Compared to the MGUS patients without fractures, those with fractures were older (62.8 ± 6.1 years vs 59.7 ± 5.0 years) and had a longer time since MGUS diagnosis (8.8 ± 7.1 years vs 5.8 ± 4.1 years), a higher serum RANK-Ligand/OPG ratio, and lower BMD values at the lumbar spine (0.811 ± 0.14 vs 0.956 ± 0.12), femoral neck (0.660 ± 0.09 vs 0.747 ± 0.10), and total proximal femur (0.788 ± 0.11 vs 0.884 ± 0.11). MGUS patients with fractures had lower serum osteocalcin and higher serum CTX levels than those without fractures, but the differences were not statistically significant. A negative correlation was found between BMD and serum CTX. The BMD and laboratory test data from the controls are not reported, which precludes a comparison of the MGUS patients without fractures to the controls [36].

Both the risk of MGUS and the risk of fractures increase with age. However, if MGUS contributed to bone loss, the fracture risk would be closely dependent on the duration of the disorder. In a retrospective study of 488 patients with MGUS (52% men; mean age, 71.4 years), 385 fractures occurred in 200 (41%) patients [37]. Compared to the expected fracture rates in the general population, the risk of vertebral fractures was increased (relative risk, 2.7), whereas the risk of appendicular fractures was not (relative risk, 1.1). Predictors of fracture were older age and a history of corticosteroid use. Protective factors were greater weight, a gamma light chain, and, unexpectedly, a higher IgG level. BMD was not determined in this study [37].

3.2. Pathophysiology of bone loss in monoclonal gammopathy of undetermined significance

Available data on the mechanisms of bone loss in MGUS are chiefly descriptive and histological. The histomorphometric features of transiliac bone biopsy specimens and the clinical course were evaluated in 46 patients with benign ($n=17$) or malignant ($n=29$) monoclonal gammopathy [38]. Among the 14 patients with MGUS and normal eroded surface values, none experienced progression to malignant disease during the 40-month follow-up. In contrast, malignancies developed in all three patients with increased eroded surface areas in contact with the lymphoplasmocytic nodules (one case each of myeloma, Waldenström macroglobulinemia, and chronic lymphocytic leukemia). In the patients with myeloma at baseline, factors associated with greater eroded surface area were more extensive marrow invasion by myeloma cells and an IgA or light-chain monoclonal component. The authors suggested that eroded surface area measurement may help to establish the diagnosis and prognosis not only of myeloma, but also of MGUS [38]. Similarly, in 87 patients with IgA or IgG MGUS, excessive bone resorption was significantly associated with progression to myeloma and constituted an early marker for malignancy that was detectable several years before myeloma onset [39]. However, the excessive bone resorption was apparent only in the immediate vicinity of the plasma cells, suggesting that detection of this abnormality might be difficult in small bone biopsy samples [39]. The same group investigated cell recruitment to bone in patients with myeloma or MGUS [40]. Bone turnover was normal in the patients with MGUS and accelerated in those with early asymptomatic myeloma, who had an increase in osteoblast recruitment. The patients with symptomatic untreated myeloma had a high bone turnover rate and complete uncoupling with massive increases in both osteoclast number and bone resorption in the immediate vicinity of myeloma cells and a decrease in bone formation. These abnormalities were most marked in patients with advanced or aggressive myeloma [40].

3.3. Bisphosphonate therapy in monoclonal gammopathy of undetermined significance

Studies of myeloma patients have produced sound evidence that bisphosphonate therapy decreases bone resorption, the hypercalcemia risk, fractures at osteolytic sites, and fracture-related clinical events (e.g., pain and use of radiation therapy). However, the data from patients with asymptomatic myeloma are less compelling. Some studies of the antineoplastic effect of bisphosphonates also evaluated the effect on bone mass. A randomized controlled trial was done in 163 patients with asymptomatic myeloma, of whom 81 received zoledronic acid (4 mg intravenously monthly for 12 months) and 82 a placebo [41]. Neither the monoclonal component level nor the proportion of plasma cells in bone marrow was significantly different between the two groups. Neither was the rate of progression to myeloma significantly different (44.4% in the zoledronic acid group and 45.1% in the placebo group). The only statistically significant difference was a smaller number of skeletal events (pathologic fractures and hypercalcemia) in the zoledronic acid group. These data are consistent with earlier results from two studies of pamidronate in patients with early-stage myeloma [42–44].

Few studies evaluated the potential benefits of bisphosphonate therapy in patients with MGUS. The effect of alendronate therapy (70 mg weekly) combined with calcium and vitamin D supplements was assessed in 30 patients (23 postmenopausal women and seven men) with osteoporosis and MGUS [45]. No fractures occurred during the 18-month follow-up. BMD increased by 6.1% at the lumbar spine and 1.5% at the proximal femur and significant decreases

occurred in bone alkaline phosphatase, osteocalcin, and CTX. An open-label uncontrolled study was done in 54 patients who had MGUS (mean age, 67 years) and osteopenia or osteoporosis diagnosed by absorptiometry, to assess the BMD effects of three 4 mg zoledronic acid infusions at 6-month intervals [46]. At study completion 1 month after the last infusion, BMD was higher by 15% at the lumbar spine and 6% at the femur. No cases of fracture or jaw osteonecrosis were recorded. The monoclonal component concentration showed no significant variation. To date, there is no evidence suggesting that bisphosphonate therapy in MGUS patients may diminish the risk of subsequent progression to malignant disease.

4. Future perspectives

Despite the small number of available studies and paucity of scientific evidence, the literature suggests close links between MGUS and the occurrence of bone loss and bone insufficiency fractures after 50 years of age. In some patients with MGUS, histological studies show excessive bone resorption in contact with the lymphoplasmacytic infiltrates, which may explain the subsequent development of fractures. Of even greater concern is the possibility that this focal bone resorption may constitute a harbinger of progression to myeloma. Molecular studies of myeloma have shown that the myeloma cells and bone microenvironment interact via a cytokine network that can not only promote tumor growth, but also increase bone resorption. Data from vast studies have produced detailed information on the slow, gradual, and inconsistent progression of MGUS to aggressive hematological malignancies. Somewhat surprisingly, few prospective longitudinal studies have evaluated the baseline bone status in MGUS patients and its influence on the course of the hematological disorder. The small number of available studies show that bisphosphonate therapy in patients with MGUS or asymptomatic myeloma increases BMD values and decreases the fracture risk but fails to diminish the rate of progression to symptomatic myeloma. The impact of monoclonal gammopathies on bone probably varies with the heavy- and light-chain isotypes and with the disease stage (MGUS or asymptomatic myeloma). Longitudinal studies are needed to identify factors associated with rapid bone loss and/or fractures and to evaluate potential associations between bone manifestations and progression to symptomatic myeloma.

Conflicts of interest

The authors have no conflicts of interest to declare.

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