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Unveiling Skeletal Fragility in Patients Diagnosed with MGUS: No Longer a Condition of Undetermined Significance?

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Abstract

Monoclonal gammopathy of undetermined significance (MGUS) is a common finding in clinical practice, affecting greater than 3% of adults aged 50 years and older. As originally described, the term MGUS reflected the inherent clinical uncertainty of distinguishing patients with a benign stable monoclonal plasma cell disorder from subjects destined to progress to malignancy. There is now clear epidemiologic evidence, however, that patients with MGUS suffer from a significantly increased fracture risk, and that the prevalence of MGUS is increased in patients with osteoporosis. Despite this relationship, no clinical care guidelines exist for the routine evaluation or treatment of the skeletal health of patients with MGUS. Recent work has demonstrated that circulating levels of at least two cytokines (CCL3/MIP-1 α and DKK1) with well-recognized roles in bone disease in the related monoclonal gammopathy multiple myeloma are also increased in patients with MGUS. Further, recent imaging studies using high resolution peripheral quantitative CT have documented that patients with MGUS have substantial skeletal microarchitectural deterioration and deficits in biomechanical bone strength that likely underlie the increased skeletal fragility in these patients. Accordingly, this Perspective provides evidence that the ‘undetermined significance’ portion of the MGUS acronym may be best replaced in favor of the term ‘monoclonal gammopathy of skeletal significance’ (MGSS) in order to more accurately reflect the enhanced skeletal risks inherent in this condition.

Keywords

MGUS; osteoporosis; fracture; DXA; HRpQCT

Age-related bone loss and fractures are a burgeoning public health problem that will only worsen with our growing elderly population (1,2). Indeed, the United States (US) National Osteoporosis Foundation estimates that an overwhelming proportion (~60%) of Americans aged 50 yrs will suffer osteoporotic-related fragility fractures (3). Sadly, comparable rates of bone loss and fractures are well-documented in other populations, and are similarly expected to increase as the worldwide population ages at an unprecedented rate (4). Consequently, fractures impose enormous healthcare costs and burdens on society.

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Although pharmacologic prophylaxis in patients with prior fragility fractures, osteopenia and additional clinical risk factors, or osteoporosis as defined by the World Health Organization (WHO) (dual-energy X-ray absorptiometry [DXA] areal bone mineral density [aBMD] T-score <-2.5) is efficacious (5), it comes with risks of side effects (6) and treating the entire aging population is unaffordable. Therefore, identifying individuals at greatest risk for fragility fractures, who remain incompletely characterized by established fracture prediction tools (i.e., aBMD T-score or the WHO Fracture Risk Algorithm [FRAX[®]] score), is of critical importance.

Multiple risk factors for low BMD and fragility fractures have been identified and incorporated into FRAX. These include both commonly recognized risk factors (e.g., age, sex, history of personal or parental fragility fracture, and tobacco, alcohol, or glucocorticoid use), and risk factors for the development of secondary osteoporosis. As acknowledged by the FRAX algorithm authors, however, the current models of risk factors for predicting the development of low BMD and fragility fractures remain imperfect (7); thus, greater efforts are needed to establish the extent to which fracture prediction can be improved in subsets of patients beyond that provided by BMD or FRAX.

Emerging evidence suggests that one such population may include patients with a monoclonal gammopathy, a spectrum of closely related plasma cell disorders comprised of monoclonal gammopathy of undetermined significance (MGUS), smoldering multiple myeloma, and multiple myeloma. It is noteworthy that the age-associated increased risk in fractures is paralleled by the age-associated increased risk for developing these disorders. In each, monoclonal plasma cell proliferation within the bone marrow (BM) cavity is associated with the production of abnormal levels of a single monoclonal (M) protein. Among the monoclonal gammopathies, MGUS is by far the most common, and is defined by a serum monoclonal protein level of <3.0 g/dL, $<10\%$ bone marrow plasma cells, and the absence of plasma cell proliferation-related complications which would indicate myeloma such as lytic bone lesions, hypercalcemia, pathologic fractures, anemia, or renal insufficiency (8). In the intermediate condition of smoldering multiple myeloma, end-organ damage is also absent, but subjects have a circulating monoclonal protein level of <3.0 g/dL or 10% or more plasma cells in the BM (9).

At the far end of the monoclonal gammopathy spectrum is multiple myeloma, in which malignant clonal plasma cell expansion results in end-organ damage. Multiple myeloma is a severely debilitating and near uniformly fatal neoplastic disease of B-cell origin diagnosed annually in nearly 20,000 US patients (10). It is characterized by an overproduction of monoclonal protein and an imbalance in bone remodeling (i.e., bone resorption outweighs formation) that consequently leads to osteolytic lesions and diffuse bone loss (11). Importantly, MGUS is a pre-malignant condition with an annual rate of progression to multiple myeloma of approximately 1% (12), but whether MGUS is associated with disruption of skeletal health or bone metabolism in humans was not well understood for many years.

MGUS is a common finding in clinical practice, with epidemiologic evidence demonstrating that the prevalence of MGUS in a largely Caucasian population was approximately 3.2% in

persons 50 years of age or older (12). An age-related increase in the prevalence of MGUS occurs in both sexes, such that 8.9% of men and 7.0% of women are affected by age 85 (12). Further, MGUS appears to be 2-3 fold more common in African-Americans than in Caucasians (13,14). Thus, US Census Bureau population estimates (based on July 2013 data) indicate that of 106 million residents aged 50 or greater, approximately 3.4 million Americans have MGUS. Further, given the aging US population, the number of Americans with MGUS is expected to grow (15). Although world prevalence estimates are unknown, rates appear to be similar in other Caucasian populations, perhaps slightly lower in Asians, and higher in persons of African ancestry (16). Because MGUS produces no overt symptoms and is frequently identified during the course of routine medical care or during evaluation of an unrelated disorder (17), >50% patients have had MGUS for >10 yrs, and ~30% for >20 yrs prior to clinical recognition (18). As annual risk for progression from MGUS to myeloma is not affected by either age or MGUS duration (15), patients with MGUS - the vast majority of whom are elderly - are much more likely to die of causes unrelated to their plasma cell disorder. Therefore, avoiding events associated with significant morbidity and mortality, such as fractures, is important for quality of life in patients with MGUS.

As originally coined by Robert Kyle of the Mayo Clinic over 35 years ago (19), the term 'MGUS' was used to describe the hematologic clinical condition in which laboratory and physical examination findings were of 'undetermined significance' for distinguishing patients with a benign stable monoclonal plasma cell disorder from those subjects who progress to malignancy. Despite this original functional characterization of a condition of 'undetermined significance', however, there is now clear epidemiologic evidence that patients with MGUS have a significantly increased fracture risk (20–27), and that the prevalence of MGUS is increased in patients with osteoporosis (23,24,28). Thus, concordant data from both America and Europe in largely Caucasian populations suggest that overall fracture rates are increased approximately 1.7-fold, and site-specific fractures (vertebral) are increased up to approximately 6.3-fold in MGUS subjects when compared to the general population (20,21), although whether fracture rates are similar in non-Caucasian populations is at present unknown. Further, previously unrecognized MGUS is a relatively common finding in patients with fractures, as evidenced by a recent study which demonstrated that 6% of otherwise healthy subjects aged 50 years and older who sustained a hip fracture had MGUS (26). Notably, current National Osteoporosis Foundation guidelines do not recommend screening for monoclonal gammopathies in patients with low bone mass, nor is MGUS included as a potential risk factor in FRAX. Perhaps most alarmingly, even in patients in whom MGUS has been identified, no current recommendations exist for the routine evaluation or treatment of skeletal health in patients with MGUS (29–36). Given this current widespread apathy towards the skeletal health of patients with MGUS and the potential for the use of the 'undetermined significance' portion of the MGUS acronym to lull both care providers and affected patients into a false sense of security, the time has perhaps come to adopt the term 'monoclonal gammopathy of SKELETAL significance' (MGSS) to more clearly articulate the enhanced skeletal risks associated with this condition. Evidence to support this proposed change is provided below.

To date, comparatively little effort has been made to understand the basis for the increased fracture risk in MGUS. In contrast, much work has now clarified that bone disease in the related monoclonal gammopathy multiple myeloma results from an uncoupling of the normal bone remodeling sequence, such that osteoclast-mediated bone resorption is increased while osteoblast numbers and activity are simultaneously decreased (11,37,38). In myeloma, these effects on bone cells not only lead to the development of the well-recognized complication of osteolytic lesions, but also to significant systemic bone loss and a markedly increased risk of osteoporotic fractures (39) (40,41). This has led to the hypothesis that local cytokines produced either by myeloma cells, or by resident cells within the bone marrow microenvironment in response to multiple myeloma cell invasion, are responsible for the focal increased bone resorption and suppressed bone formation of myeloma that result in osteolytic lesion development. In contrast, the generalized osteoporosis found in multiple myeloma suggests that circulating factors may also be important mediators of the systemic bone loss that occurs.

Multiple factors which either increase osteoclast-mediated bone loss or suppress osteoblast-mediated bone formation and function in multiple myeloma have been described (42). Among identified osteoclast-activating factors are Receptor Activator for Nuclear Factor κ B Ligand (RANKL) (43), chemokine (C-C) ligand motif 3 (CCL3)/macrophage inflammatory protein (MIP)-1 α (44), and multiple interleukins; likewise, identified osteoblast suppressive factors in multiple myeloma include the Wnt signaling antagonists Dickkopf-related protein 1 (DKK1) (45), soluble frizzled related proteins 2 and 3 (46–48), and sclerostin (49,50). These same Wnt pathway inhibitors are also present in peripheral blood, where they inhibit mesenchymal stromal cell (MSC) to osteoblast differentiation *in vitro* (45–47, 49,51–53). Such findings suggest that systemic suppression of osteoblast function is likely of clinical significance and may contribute to the increased risk of osteoporotic (i.e. not due local osteolysis) fractures in multiple myeloma (39), and that disruption of the mesenchymal stromal cell (MSC) to osteoblast transition may begin at an early (i.e. MGUS) rather than a late (i.e. myeloma) stage of the monoclonal gammopathy disease spectrum (41,42,54). Such data may also explain the histomorphometric evidence of imbalanced bone remodeling that has been reported in patients with MGUS (55). Finally, recent data suggest that osteocyte dysfunction may also play an integral role in impaired bone cell activity in myeloma bone disease (56), although whether bone loss in MGUS results from similar alterations in osteocyte function is unknown.

To determine whether similar alterations in cytokine levels occur in patients with MGUS, we recently assessed circulating levels of several factors with well-established roles in myeloma bone disease. Whereas serum levels of the Wnt inhibitor sclerostin were not different between patients with MGUS and matched control subjects, circulating levels of the osteoclast-activating factor CCL3/MIP-1 α (57) were increased nearly 6-fold, and circulating levels of the osteoblast-suppressive factor DKK1 (45) were increased approximately 2-fold in MGUS patients compared to healthy age-, sex-, and body mass index (BMI)-matched control subjects (58). Collectively, these data strongly suggest that circulating biochemical factors implicated in multiple myeloma-associated bone disease manifest in MGUS. Given the long lead time preceding the diagnosis of MGUS in most

patients, it is conceivable that these increases in circulating cytokine levels may impact skeletal metabolism. Although >20 other factors which either increase osteoclast activity or suppress osteoblast function have been identified in multiple myeloma, very few have been examined in MGUS. Whether similar mechanisms underlie skeletal disease across the monoclonal gammopathy spectrum is currently unclear, but represents an intriguing and scientifically testable hypothesis.

Although MGUS is associated with increased fracture risk and circulating levels of at least some cytokines in patients with MGUS, whether these patients have altered bone turnover has also been unclear (59). Whereas some studies have reported that biochemical markers of bone turnover are increased in MGUS (60,61), other groups including our own (24,58,62), have not found significant differences in markers of either bone resorption or formation. Reasons for these differences are unclear, as are explanations for the apparent discrepancy between the elevated cytokine levels found in patients with MGUS and the absence (at least in some studies) of differences in circulating bone turnover marker levels. One potential explanation is that bone turnover is modestly different in patients with MGUS when compared to unaffected subjects of the same age group, but that given the significant variability in bone turnover marker levels seen even in individuals without MGUS, small variances are not evident. An alternative, but not mutually exclusive, explanation for this lack of difference may reflect the relative insensitivity of circulating bone turnover markers to detect alterations in bone metabolism occurring within the bone marrow microenvironment. Given the prolonged length of time which typically precedes formal diagnosis, however, it is plausible that even slight perturbations to the normal bone balance via effects on bone resorption and/or formation may lead to clinically meaningful skeletal deficits over time.

Finally, it is also of note that despite higher monoclonal protein levels correlating with risk for MGUS progression to multiple myeloma, no association between monoclonal protein levels and fracture risk has been found (20–22). Thus, neither standard bone turnover markers nor monoclonal protein levels obtained during routine clinical care are likely to be of value in the prediction of bone loss or fractures in patients with MGUS. Whether measurement of circulating cytokine levels might be predictive is also unclear, but the provocative findings noted above with CCL3/MIP-1 α and DKK1 levels suggest the need for future studies to definitively test their potential clinical utility. Additional deficits to our current understanding of bone disease in MGUS include both the absence of knowledge regarding the genes and pathways altered within each type of bone cell (osteoblasts, osteoclasts, and osteocytes) that contribute to the skeletal phenotype, and the absence of an appropriate animal model of disease, thereby increasing the relevance of human studies.

Although fracture incidence is increased in MGUS (20, 22–24), several studies which used DXA imaging have provided conflicting results as to whether MGUS subjects have decreased bone mass (23,24). While DXA is a safe and widely available clinical tool for monitoring overall skeletal health and it can accurately determine areal BMD (aBMD), it has several limitations including the extrapolation of a two-dimensional (areal) measurement of bone mineral content to derive a three-dimensional volumetric density, as well as the inability to accurately assess bone structure and to differentiate between cortical and

trabecular bone compartments. Collectively, these constraints limit the ability of DXA to estimate bone strength, and do not allow DXA to provide microstructural information which can be used to assess bone quality.

In order to address whether bone strength and microarchitecture are altered in patients with MGUS, we recently examined volumetric BMD and bone microarchitecture by high-resolution peripheral quantitative computed tomography (HRpQCT), and bone strength by micro-finite element (μ FE) analysis in a cohort of fifty patients with MGUS and one hundred age-, sex-, and BMI-matched control subjects (58,63). Relative to controls, the MGUS cohort showed only a significant decrease in DXA-derived aBMD at the total femur (-5.0% ; $P=0.044$), with no differences in femoral neck, lumbar spine, total body, or radial aBMD. In contrast, HRpQCT imaging of the distal radius showed significant decreases in total vBMD (-10.4% ; $P=0.005$), cortical vBMD (-4.7% ; $P=0.001$), and cortical thickness (-9.5% ; $P=0.029$), as well as a significant increase in cortical porosity ($+16.8\%$; $P=0.048$). Interestingly, trabecular number and separation did not differ between the groups, but MGUS subjects did have a significant decrease in trabecular thickness (-8.1% ; $P=0.004$). These microarchitectural alterations contributed toward reduced biomechanical strength in the MGUS patients, as determined by μ FE analysis, with apparent modulus reduced by -8.9% ($P=0.04$). Notably, both failure load and stiffness were lower in MGUS patients relative to controls (by -4.0% and -4.6% , respectively), although these deficits did not reach statistical significance, likely because of a compensatory increase in radial bone size resulting from progressive periosteal bone apposition with concomitant increases in endocortical resorption, ultimately leading to a thinner cortex. While this net outward cortical displacement increases resistance to bending stresses, it only provides a partial biomechanical adaptation to limit the overall loss of bone strength due to the decrease in cortical thickness (64). Collectively, these findings represent the first demonstration of compromised bone microarchitecture and strength in patients with MGUS, and strongly suggest the skeleton needs to be recognized as a tissue of significance in this disease.

Given that the greatest fracture increase in patients with MGUS occurs at axial sites, it will be important to determine whether the skeletal abnormalities at the radius of MGUS patients are also present at the axial skeleton. Indeed, because DXA cannot accurately distinguish bone compartments (i.e., cortical versus trabecular) and biomechanically relevant structures (e.g. trabecular connectivity and cortical porosity), it is not well suited for this purpose. This likely explains why DXA was unable to accurately detect the marked microarchitectural deterioration and loss of bone strength which occur in MGUS. Thus, more advanced tools and applications in skeletal imaging analysis will be needed. One approach to address this might involve vertebral assessment of DXA images by trabecular bone score (TBS), although TBS itself is not without limitations (65). Alternative future approaches might include dedicated studies using three-dimensional quantitative CT imaging at the spine and hip, and/or studies of peripheral sites (distal radius and a biomechanically loaded site – the tibia) with even higher resolution as now allowed with the most recent version of the HRpQCT imager which allows for a resolution of $61\ \mu\text{m}$ (versus $82\ \text{mm}$ with the earlier model). Finally, given that only cross-sectional data currently exist, there is a critical need to prospectively study large cohorts of MGUS patients using novel imaging techniques in order

to determine whether deficits in bone microarchitecture and strength are accelerated in patients with MGUS.

Conclusion

Despite clear epidemiologic evidence of a significantly increased risk for fracture (21,66), skeletal changes go undetected and untreated in current clinical practice as patients diagnosed with MGUS are followed expectantly due to the 'undetermined significance' of their disease.(67) As described above, however, emerging data now strongly suggest that alterations in circulating cytokines central to myeloma bone disease may manifest and play an important role in the skeletal health of patients with MGUS, leading to deficits in bone microarchitecture and biomechanical bone strength, and ultimately increasing fracture risk. Accordingly, the 'skeletal significance' of this disease is becoming increasingly evident. Nonetheless, fundamental questions such as whether bone loss is accelerated in patients with MGSS compared to control subjects, and whether circulating levels of candidate biomarkers can be used to identify MGSS patients at greatest risk for bone loss, microarchitectural deterioration, and reduced bone strength, remain unanswered. It is with this goal in mind that care providers need to shift the paradigm from one in which MGUS is viewed as a disorder of 'undetermined significance', to one which is recognized as a disease of 'skeletal significance' in order to ultimately limit skeletal deterioration and fractures in this high-risk population. Therefore, to more accurately reflect the enhanced skeletal risks inherent in this population, the term monoclonal gammopathy of skeletal significance (MGSS) is warranted and needs to be adopted.

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