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Review Article

Monoclonal Gammopathy of Undetermined Significance And Bone Disease: A Mini Review

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Abstract

Monoclonal Gammopathy of Undetermined Significance (MGUS), is a benign disease, characterized by serum monoclonal protein (M protein) levels <3g/dl, clonal plasma cells <10% in the bone marrow, and the absence of symptoms of plasma cell disorders (e.g., hypercalcemia, renal insufficiency, anemia, and bone lesions). This review studied the association between MGUS and bone disease. A search was performed through 3 databases: PubMed, Embase, and Science Direct, and was made for retrospective, prospective or cohort studies written in the English language, with a sample of adults both males and females, with all their content freely available, and published between 2000-2023. After checking the inclusion and exclusion criteria, 12 articles were included in the review. MGUS was associated with a high fracture risk due to low bone mineral density, trabecular and cortical abnormalities at the radius, peripheral neuropathy from falls, and undetected progression of MGUS to multiple myeloma. Even before the development of myeloma, MGUS increases the risk of vertebral fractures. Understanding this relationship and addressing both MGUS and bone health is crucial to ensure the overall well-being of these patients. Regular monitoring and appropriate management can reduce the risk of fractures and provide a well-being of higher quality.

Keywords: Monoclonal gammopathy of undetermined significance, MGUS, Osteoporosis, Osteoporotic fractures, M immunoglobulin

Introduction

Monoclonal Gammopathy of Undetermined significance (MGUS) is a benign condition characterized by the presence of an abnormal serum protein called a monoclonal (or M) protein at concentration below 3g/dl. MGUS is considered a premalignant condition, meaning it carries a slightly increased risk of progressing to a cancerous condition, specifically multiple myeloma (MM)[1,2]. MGUS is characterized by increased production of the abnormal monoclonal paraprotein (M), infiltration of the bone marrow by a clonal population of plasma cells less than 10% but without any evidence of end-organ involvement. The concentration of this M protein in the blood serum should be less than 3g/dL (grams per deciliter) for IgG type M protein and less than 2g/dL for IgA or IgM type M protein[3,4]. In clinical practice, MGUS is usually diagnosed as a random finding in routine examinations or in investigation of an unrelated disease.

MGUS is a common condition among older individuals. It is estimated that around 3% of people over the age of 50 and 5% of those over 70 have MGUS[2]. Most people with MGUS do not experience progression to cancer or related disorders. The risk of progression to MM or another plasma cell disorder is estimated to be around 1% per year. In addition, studies have shown that 3,6% of osteoporotic individuals and 2% of non-osteoporotic individuals may be diagnosed with MGUS[2,5].

MGUS can be classified based on the 2014 International Myeloma Working Group updated criteria[5], including the

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type of monoclonal protein present, the concentration of the protein, and the presence or absence of specific clinical features (CRAB symptoms). Based on immunoglobulin type, there are 3 subtypes of MGUS: IgG MGUS, IgA MGUS, and IgM MGUS[6]. Based on protein concentration, we can figure 2 types of MGUS, non-IgM MGUS and IgM MGUS. Based on clinical features, there are the light-chain MGUS (is characterized by the production of only the free light chains [kappa or lambda] without the corresponding heavy chains) and the non-secretory MGUS (the M protein is not detectable in the blood or urine using routine laboratory tests)[6]. A malignant plasma cell neoplasm can develop from non-IgM MGUS. Immunoglobulin light chain amyloidosis, Waldenstrom macroglobulinemia, and lymphoma are possible progressions of IgM MGUS[6]. A monoclonal protein devoid of the immunoglobulin heavy chain component is the defining feature of light chain MGUS[6]. Light chain plasma cell myeloma, immunoglobulin light chain amyloidosis, light chain deposition disease, and idiopathic Bence Jones proteinuria can all progress from light-chain MGUS[6]. It is worth noting that the classification of MGUS may vary slightly among different medical sources or research studies[6]. The classification helps in understanding the characteristics of MGUS and provides a framework for monitoring and managing the condition.

Cohort studies as well as prospective and retrospective studies have shown that patients with MGUS have a higher risk of fractures compared to control groups, especially in areas such as the spine (RR=2.5) and the hip[7]. Additionally, the diagnosis rate of MGUS was found to be higher in patients with osteoporosis compared to individuals with normal bone mass.

Bone strength depends on quantitative (mass, volume, density), and qualitative (geometry, microarchitecture, macroarchitecture, rate of bone remodeling, cell apoptosis) parameters[8]. Decreased bone strength has been linked to an increased risk of fractures[9].

At a molecular level, MGUS and Multiple Myeloma appear to share almost the same pathophysiological mechanism that leads to excessive bone resorption and ultimately to osteoporosis and osteoporotic fractures. The excessive osteoclastic activity and inhibition of osteoblastic differentiation occur due to the disruption of the RANK-L/OPG ratio, which is responsible for bone formation, as well as other molecules such as MIP-1a, IL-1β, IL-6, TNF-α[10,11].

Both prospective and retrospective studies have been conducted with the aim of correlating MGUS with osteoporosis and fracture risk. The goal is to understand both the pathophysiology of the disease and risk factors, as well as to identify the fracture risk associated with it.

Materials and Methods

The present literature review aimed to study the association between MGUS and bone disease. Specifically, a search was performed through 3 databases: PubMed, Embase, and Science Direct. The following search algorithm was used: [(''monoclonal gammopathy of undetermined significance'' OR ''MGUS'') AND (''bone disease'' OR ''osteoporosis'' OR ''osteoporotic fractures'')].

The selection criteria were as follows:

- Articles written in the English language.
- The content of the articles was fully available and freely accessible.
- Research was retrospective, prospective or cohort.
- Research had a sample of adults.
- The articles have been published during the years 2000-2023.

The exclusion criteria were as follows:

- Articles written in any language other than English.
- Articles in which only their abstracts were freely accessible.
- Articles were case studies or literature reviews or systematic reviews or meta-analyses.
- Research in children or adolescents as a sample.
- Articles published before 2000.

Results

Based on the initial search, 278 articles were found. After exclusion of duplicates, 242 articles remained, of which 93 were excluded due to ineligibility (they were not relevant to the topic). Of the remaining 149 articles, 105 were excluded after reading the title and abstract because 67 articles were not relevant to the topic, 2 articles were not in English, 14 articles were meta-analyses, 9 articles were systematic reviews, and 13 articles were literature reviews. The remaining 44 articles were read in their entirety. After checking the inclusion and exclusion criteria, 12 articles were included in the review. Specifically, two population-based cohort studies[12,13], four prospective studies[2,14-16] and six retrospective studies[7,17-21] were included.

Population-based cohort studies

Thorsteinsdottir et al.[12] examined bone volume, bone mineral density (BMD), and fracture risk in patients with MGUS. Their sample included 5764 elderly people, of which 275 people had light-chain MGUS and 300 had MGUS. To assess bone geometry and BMD, quantitative computerized tomography was used on the hip and lumbar spine. The groups were compared using Tukey honest significance test and analysis of variance. Fractures were documented in hospital records, with a follow-up average of 6.9 years. The fracture risk was compared using the Cox proportional hazard. Between subjects with MGUS and others, there was no difference in BMD in the hip or spine. When compared to age-matched healthy controls, those with MGUS had significantly more bone volume in the spine and entire hip ($p < .001$). Overall, there was no discernible increase in the risk of fractures among both male and female popoulation with MGUS (HR= 1.19, $p < .001$). Compared to healthy controls, men with MGUS had a markedly higher fracture risk (HR=

1.46, p < .001). These findings demonstrate that while bone volume is elevated and MGUS men have a 50% higher risk of fracture, individuals with MGUS do not have decreased BMD. The authors stated that the observed increase in bone size could potentially be explained by a process akin to periosteal bone apposition, a known age-related phenomenon characterized by the loss of trabecular bone and the subsequent periosteal renewal of bone cells, which causes an increase in the cross-sectional bone area. These findings suggest that MGUS bone disease and fractures are not caused by the same mechanisms as osteoporosis.

Rögnvaldsson et al.[13] examined the relationship between MGUS and peripheral neuropathy, undetected multiple myeloma, and intrinsic MGUS bone disease. In their study, they included 30851 matched Swedish controls and 8395 MGUS patients. Fractures were found to be independently correlated with both MGUS and peripheral neuropathy (HR = 1.20 and HR= 1.34 respectively). Fractures were more frequent in cases of imminent MGUS progression (OD= 1.66, p < .05). There was no correlation between fractures and long-term risk of MGUS progression (HR= 1.08). Based on these results, the authors concluded that there are three separate ways in which MGUS causes fractures: peripheral neuropathy from falls, MGUS intrinsic bone disease, and undetected MGUS progression to multiple myeloma.

Prospective studies

Golombick et al.[2] examined the prevalence and the association of MGUS in patients who have experienced acute vertebral fractures due to osteoporosis. Their sample was 134 individuals. The research revealed that among the patients with acute osteoporotic vertebral fractures, a significant proportion were found to have MGUS (HR= 2.5) or myeloma (HR= 3.7). Detecting these plasma cell dyscrasias in osteoporotic patients can lead to early identification and management of these conditions, potentially preventing further complications and optimizing patient care. The study underscores the need for a comprehensive assessment of patients with osteoporotic vertebral fractures to identify underlying factors that may contribute to fracture risk and guide appropriate treatment strategies.

Pepe et al.[14] examined the potential correlations between biochemical measurements and radiographic and densitometric indices of skeletal fragility among 65 postmenopausal women. The MGUS group exhibited a notably elevated incidence of vertebral fractures in contrast to the control group (p= .05). Also, the MGUS patients were classified based on whether or not they had experienced at least one mild vertebral fracture. Compared to patients without fractures, patients with fractures had long-standing disease and were older. Patients with fractures had a higher ratio of receptor activator of nuclear factor kappa-B ligand/ osteoprotegerin than patients without fractures (0.092 vs. 0.082 g/cm^2). Comparing MGUS patients with and without fractures, femoral neck (0.660 vs. 0.747 g/cm^2), lumbar spine (0.811 vs. 0.956 g/cm^2), and BMD (0.788 vs. 0.884 g/cm^2) were all lower (p < .01) in the MGUS patients with fractures. Lumbar BMD was found to be the best predictor of vertebral fractures using receiver operating characteristic curves. In order to predict vertebral fractures in MGUS patients—especially those who are asymptomatic—this study suggests measuring BMD.

Piot et al.[15] identified the risk factors for vertebral fracture and described the bone status of MGUS patients prospectively. The sample of the study consisted of 201 patients with MGUS who had no known history of osteoporosis. In addition to the gammopathy assessment, all patients received bone mineral density assessment and spinal radiographs. It was found that 18.4% of the patients had at least one common non-traumatic vertebral fracture, and there weren't any differences between men and women (p > .05). In addition to being older and having less bone density, fractured patients also tended to have a pathologic light chain isotype more frequently. The odds ratio of fracture for patients with lambda light chain was 4.32, in contrast to those without. These findings imply that low bone density is not the only explanation for the high frequency of non-traumatic vertebral fractures in MGUS that are linked to the lambda light chain isotype.

Ng et al.[16] used high-resolution peripheral quantitative computed tomography (HR-pQCT) imaging to investigate bone microstructural changes in MGUS patients. The sample consisted of 50 adults with MGUS and 100 controls. The authors used radius measurements. The study revealed important changes in bone microarchitecture among MGUS patients when compared to healthy individuals, such as reduced bone density, compromised trabecular bone structure and increased cortical porosity (p < .05). In addition, the researchers measured the levels of specific biomarkers in MGUS patients' blood samples. Two of these biomarkers, DKK1 and MIP-1, were found to be significantly elevated in MGUS patients (p > .05), a fact that suggests a potential link between the dysregulation of bone- related signaling pathways and the observed microstructural changes in their bones. These findings shed light on the complex interplay between MGUS and bone health, highlighting the importance of early monitoring and intervention to reduce the risk of skeletal complications in patients with MGUS.

Retrospective studies

Melton et al.[1] examined the incidence of fractures in 488 patients with MGUS. A total of 385 fractures were reported by 200 patients. There were statistically significant increases in fractures at most axial sites (e.g., vertebrae; SIR = 6.35) when compared to expected community rates. Hip fractures (SIR=1.6) increased slightly, but distal forearm fractures (SIR=0.8) did not. The risk of vertebral fractures increased by a factor of 2.7, while the risk of limb fractures remained unchanged. Corticosteroid use (HR=1.8) and age (HR= 1.4) were the independent predictors of any subsequent

fracture in a multivariate analysis, while IgG monoclonal protein (HR=0.7) and higher weight at diagnosis (HR=0.8) were protective. Fracture risk was not predicted by baseline monoclonal protein level, which is a marker of myeloma progression. Therefore, even prior to the development of myeloma, patients with MGUS are at an increased risk of axial fractures but not peripheral fractures.

Gregersen et al.[17] investigated the risk of fractures in patients with MGUS. The sample consisted of 1535 patients with MGUS and 15.350 controls. During 9754 person-years of follow-up in the MGUS cohort, 187 first-time fractures were found, translating to an incidence rate of 19/1000 person-years. When comparing MGUS patients to population controls, the adjusted relative risk for fractures was 1.4. Following a 5-year period of observation, the risk difference was 1.8%. Among the 187 MGUS patients who had fractures, six subsequently developed malignant transformation. MGUS with kappa light chain (RR=1.4), IgM-type MGUS (RR= 1.6) and IgG-type MGUS (RR= 1.3) had higher relative fracture risks. Fracture risk was elevated in MGUS patients, a finding that was unrelated to comorbidity, gender, advanced age or malignant transformation.

Kristinsson et al.[18] evaluated the fracture risks in 5326 MGUS patients, compared to 20161 matched controls. Patients with MGUS were more likely to fracture at 5 (HR=1.74) and 10 (HR= 1.61) years. Compared to distal (leg and arm) fractures, the risk was significantly higher for axial (costae/sternum, pelvis/vertebral, and skull) fractures. An increased risk of costae/sternal (HR= 1.93), pelvic/vertebral (HR= 2.37), leg (HR= 1.40), arm (HR= 1.23) and other/multiple fractures (HR = 4.25) was observed based on a 10-year follow-up. Neither isotype nor M protein concentration at diagnosis affected the risk of fractures. MGUS patients did not exhibit an increased risk of Waldenström macroglobulinemia or multiple myeloma when compared to those without fractures. These findings imply that early myelomagenesis involves bone changes.

Stein et al.[20] claimed that, in comparison to controls, patients with MGUS exhibit aberrant microarchitecture at the tibia and radius, reflecting the disease's overall skeletal effects. The sample of the study consisted of 36 people (12 with MGUS and 24 controls). The authors used HRpQCT, vBMD and DXA. MGUS patients had lower areal BMD at the femoral neck, 1/3 radius, and lumbar spine ($p < .05$). Inflammatory and bone metabolism markers were identical. MGUS patients had increased trabecular heterogeneity and separation, and decreased trabecular number, and total cortical and trabecular density at the radius ($p < .05$). Also, patients with MGUS had decreased bone stiffness, increased heterogeneity and separation, and decreased trabecular number, and trabecular and total density at the tibia ($p < .01$). The authors concluded that compared to matched controls, patients with MGUS exhibited reduced volumetric BMD, and trabecular and cortical abnormalities at the radius. Trabecular abnormalities were the most common at the tibia. These findings imply that trabecular bone deterioration may additionally contribute to skeletal fragility in MGUS patients. It is worth noting, that this was the first study showing multiple skeletal site microarchitectural deficits in MGUS patients.

Orduna et al.[21] examined the quality of bone tissue in MGUS patients. The authors used spinal X-ray images, Bone Material Strength index and DXA. The sample consisted of 39 MGUS patients and 65 controls. Eleven patients (28.2%) in the MGUS group had fractures, with most of them being vertebral (45.45%). There were no significant differences at the total hip or femoral neck, but MGUS patients had decreased spinal BMD (0.900 vs. 1.003) and significantly lower Bone Material Strength index (70.72 vs. 78.29) compared to controls ($p < .05$). The two groups did not differ in terms of bone remodeling markers, such as type I collagen's C-terminal telopeptide, bone-alkaline phosphatase and procollagen type-1 N propeptide. The authors concluded that patients with MGUS had reduced mechanical characteristics of bone tissue and spinal BMD, as determined by impact microindentation.

Discussion

Monoclonal Gammopathy of Undetermined Significance is a benign hematologic condition, which is often incidentally diagnosed during routine laboratory tests. However, it is associated with progression of malignant disorders, such as multiple myeloma. In addition, there is a link between MGUS and osteoporosis, as MGUS can lead to increased rate of fractures[19,22,23].

The prevalence of MGUS increases with advancing age, and it appears to affect more men than women[22]. It is worth noting that the older the patient was at the given time of the studies, the more likely osteoporosis and lower bone strength were already present, and this fact may have affected the results. The most common MGUS subtype is IgG MGUS[14]. The presence of a high rate of MGUS individuals at risk for vertebral fractures suggests a partial contribution between MGUS and osteoporosis, and that is indicated by differences in bone microarchitecture and decreased BMD in the vertebral column and hip. There are a variety of factors contributing to this relationship. Some of these factors are DDK-1 (inhibits the Wnt signaling pathway, which is crucial for bone formation), MIP-1α (plays a role in inflammation)[16], and RANKL/OPG ratio (an increased RANKL/OPG ratio can lead to bone resorption and compromise bone density)[4,24].

Various pharmacological treatments have been proposed for the prevention of osteoporotic fractures in MGUS patients, with the most prevalent options being zoledronic acid and alendronate[25-27]. Bone-modifying treatments are crucial for the management of multiple myeloma patients. Because it reduces the incidence of skeletal-related problems and improves survival, zoledronate is preferred over other bisphosphonates[27]. On the other hand, denosumab, which is an anti-receptor activator of RANKL, has demonstrated

non-inferiority in preventing skeletal-related problems when compared to bisphosphonates in newly diagnosed bone disease patients[27]. However, it hasn't been shown the full effectiveness of these medications yet. It is important to emphasize that while these medications have shown promise in increasing bone density, their use in MGUS patients should be carefully considered on a case-by-case basis. Further research may be required to establish the optimal treatment protocols for MGUS-related bone health concerns.

In conclusion, while MGUS itself is a benign condition, it can be associated with an increased risk of osteoporosis and fractures. Understanding this relationship and addressing both MGUS and bone health is crucial to ensure the overall well-being of these patients. Regular monitoring and appropriate management can reduce the risk of fractures and provide a well-being of higher quality.

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