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ORIGINAL ARTICLE

Disrupted radial and tibial microarchitecture in patients with monoclonal gammopathy of undetermined significance

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Abstract

Summary Patients with monoclonal gammopathy of undetermined significance (MGUS) had abnormalities in volumetric BMD (vBMD), microarchitecture, and stiffness at both the radius and tibia by high-resolution peripheral quantitative CT compared to matched controls. This is the first report demonstrating that patients with MGUS have microarchitectural deficits at multiple skeletal sites.

Introduction Fracture risk is elevated in patients with monoclonal gammopathy of undetermined significance (MGUS). However, the pathogenesis of bone disease in these patients is poorly understood. Prior work using high-resolution peripheral CT (HRpQCT) demonstrated abnormal microarchitecture at the radius, with predominantly cortical abnormalities. We hypothesized that patients with MGUS have abnormal microarchitecture at both radius and tibia compared to controls, reflecting global skeletal effects of the disease.

Methods This case-control study enrolled 36 subjects; patients with MGUS ($n = 12$) were matched 1:2 by age, sex, and race to controls ($n = 24$). Areal BMD (aBMD) was measured by DXA, vBMD, and microarchitecture by HRpQCT, and whole bone stiffness by finite element analysis. Serum was drawn for markers of bone metabolism and inflammation.

Results By DXA, MGUS patients had lower aBMD at the lumbar spine, femoral neck, and 1/3 radius. Markers of bone metabolism and inflammation did not differ. By HRpQCT at the radius, MGUS patients had lower total, trabecular and cortical density, lower trabecular number, and greater trabecular separation and heterogeneity. At the tibia, MGUS patients had lower total and trabecular density, lower trabecular number, greater separation and heterogeneity, and lower whole bone stiffness.

Conclusions Patients with MGUS had lower vBMD, cortical, and trabecular abnormalities at the radius compared to matched controls. At the tibia, trabecular abnormalities predominated. These results suggest that in addition to previously described cortical deficits, deterioration of trabecular bone may contribute to a generalized skeletal fragility in patients with MGUS.

Keywords Bone quality · Microarchitecture · Monoclonal gammopathy of undetermined significance · Osteoporosis

Introduction

Monoclonal gammopathy of undetermined significance (MGUS) is one of the most common causes of secondary osteoporosis in the elderly population [1–4]. Its prevalence is approximately 3.2% in the adult population over age 50 and increases with advancing age [5, 6]. In one study, 15% of patients presenting with acute symptomatic low-trauma vertebral fractures had underlying MGUS [7]. Despite its prevalence, the pathogenesis of a bone disease in the MGUS population is poorly understood [8].

Prior work using high-resolution peripheral computed tomography (HRpQCT) in patients with MGUS has demonstrated abnormal microarchitecture at the distal radius, with predominant disruptions in the cortical bone [9, 10]. Microarchitecture and volumetric bone mineral density (vBMD) at the tibia have not been assessed in these studies. The goal of this study was to investigate the serum markers of monoclonal disease activity, bone metabolism, volumetric

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bone mineral density (vBMD), microarchitecture, and stiffness in patients with MGUS. We hypothesized that patients with MGUS have abnormal microarchitecture at both the radius and tibia, compared to healthy controls, reflecting global skeletal effects of the disease. We further hypothesized that these abnormalities would relate to biochemical markers of inflammation and disease activity in patients with MGUS.

Methods

Patients

Subjects in this study had MGUS diagnosed via blood and radiological tests as defined by plasma cell count < 10%, a monoclonal protein spike of < 30 g/l and no end-organ damage. Controls were healthy volunteers that had similar demographic characteristics, who had no evidence of a monoclonal gammopathy or other secondary cause of osteoporosis. Patients were recruited at Columbia University Medical Center (New York, NY) by advertisement and self- or physician referral. All subjects provided written informed consent, and the Institutional Review Board of Columbia University Medical Center approved this study.

Biochemistries

Serum calcium, albumin, and creatinine were measured using automated techniques. Serum 25-hydroxyvitamin D_2 and D_3 were measured by ultra-performance liquid chromatography combined with tandem mass spectrometry (UPLC-MS/MS) using a 1290 UPLC and a 6410 tandem mass spectrometer (Agilent, Santa Clara, CA). Inter-assay coefficient of variation (CV) was 2.9% for $25OHD_2$ and 5.4% for $25OHD_3$. Serum C-telopeptide (CTX) was measured by ELISA (Immunodiagnostics Systems, Scottsdale AZ; CV < 10%). Osteocalcin was measured by ELISA (Immunodiagnostic Systems, Scottsdale, Arizona; CV 2.7%). Pro-collagen type-1 amino-terminal propeptide (P1NP) was measured by RIA (Orion Diagnostica Oy Espoo, Finland; CV 7.0%). Macrophage inflammatory protein-1 alpha (MIP-1alpha) was measured by ELISA (R&D Systems, Minneapolis, MN; CV < 10%). Interleukin-6 (IL-6) was measured by ELISA (R&D Systems, Minneapolis, MN; CV < 10%). Pyridinoline cross-linked carboxyterminal telopeptide of type I collagen (ICTP-1) was measured by RIA (Orion Diagnostica, Espoo, Finland and distributed in the USA by Immunodiagnostics Systems Inc., Maryland, USA; CV 6.0%).

Serum was archived at – 80 °C and analyzed in one batch after all visits were completed.

Areal bone mineral density

Areal BMD (aBMD) was measured by DXA (QDR-4500, Hologic Inc., Walton, MA) at the lumbar spine (LS; L1–4), total hip (TH), femoral neck (FN), 1/3 radius (1/3R), and ultradistal radius (UDR). Lumbar vertebrae with significant deformity, osteosclerosis, osteophytes, or degenerative disease were excluded from the analysis. Z-scores compared subjects and controls with normative populations of the same age, race, and sex, as provided by the manufacturer.

HR-pQCT and image-based μFEA of the distal radius and tibia

HR-pQCT (XtremeCT, Scanco Medical AG, Brüttisellen, Switzerland) scans were acquired by immobilizing the non-dominant forearm and ipsilateral tibia in a carbon fiber shell and scanning using protocols as we have described in prior publications [11–14]. The European Forearm Phantom was scanned daily for quality control. All scans were acquired by a highly experienced technician. Automated contouring followed by dual threshold was used to segment the mineralized phase into cortical and trabecular compartments. In addition to the measurements of volumetric BMD, microstructure measurements for both compartments such as trabecular number, thickness, separation, and cortical thickness were also computed. Finite element analysis was applied to HR-pQCT scans to estimate whole bone stiffness, a measure of the bone's resistance to applied force [12, 13, 15]. Towards the end of the study, we transitioned from the first generation (XCT1) to the second generation HRpQCT (XCT2) scanner with a higher nominal isotropic resolution of 61 μm. Only two subjects were scanned on XCT2. For these subjects, the XCT2 data was calibrated to XCT1 based on a separate study in which we compared 51 adults and found excellent agreement between both generations of the scanner ($R^2 > 0.9$) for most measurements [16].

Statistical methods

Analyses were conducted with STATA version 11.0 (Stata Corp, College Station, Texas) and SAS version 9.1 (SAS Institute Inc., Cary, North Carolina). Normality testing (Shapiro Wilk) was performed, and variables that were not normally distributed were logarithmically transformed prior to group comparisons. Satterthwaite adjustment was performed in the case of unequal variance between the groups. Two-sided p values < 0.05 were considered to indicate statistical significance. Descriptive data are presented as the mean ± standard deviation (SD) and group comparisons as the mean ± standard error of the mean (SEM). Differences between MGUS and control subjects were assessed by Student's t test or chi-square.

Results

Thirty-six subjects were enrolled. Subjects with MGUS ($n = 12$) were matched 1:2 with healthy controls on the basis of age, sex, and race. The majority of patients were female (84%), 56% were Caucasian, 42% were Hispanic, and 2% of other race/ethnicity. Table 1 includes the demographic information, biochemistries, and DXA results for all of the patients enrolled. BMI was similar in the two groups.

Serum 25-hydroxy vitamin D levels were similar between groups and were above 20 ng/ml in the vast majority of subjects; the majority of MGUS (67%) and control (58%) subjects reported taking vitamin D supplements. Markers of the bone formation (P1NP) and resorption (CTX) did not differ. Interleukin-6 (IL-6) was numerically higher in MGUS subjects but not statistically different between groups. Similarly, ICTP-1 was numerically but not statistically higher in patients with MGUS. There was no difference in levels of MIP-1 alpha. No relationship was found between disease activity and any of these biochemical markers.

By DXA, MGUS patients had lower Z-scores at the lumbar spine, femoral neck, and 1/3 radius and tended to have lower Z-scores at the total hip compared to controls. Mean Z-scores, compared to an age-matched reference population, were in the normal range in both groups. Two control patients had Z-scores at the LS above 3.0, which review of the images revealed was related to extensive degenerative changes. However, compared to a young adult reference, 75% of MGUS patients and 25% of controls ($p < 0.01$) met the criteria for osteoporosis (T-score < -2.5) at one or more sites.

Table 1 Patient demographics, biochemistry, and DXA values

(Mean ± SD)	MGUS ($n = 12$)	Control ($n = 24$)	p value
Age (years)	68 ± 10	70 ± 9	0.98
BMI (kg/m2)	23 ± 3	26 ± 6	0.18
Years since MGUS diagnosis	5 ± 6	n/a	n/a
25OHD (20–50 ng/ml)	35 ± 9	28 ± 10	0.16
MIP-1 alpha	24 ± 9	23 ± 20	0.93
IL-6	3.0 ± 6	1.4 ± 0.7	0.30
P1NP	49 ± 36	52 ± 19	0.94
CTX	0.45 ± 0.23	0.45 ± 0.19	0.54
ICTP-1	4.6 ± 1.6	4.0 ± 1.0	0.15
Z-scores (DXA)			
Lumbar spine	−0.4 ± 0.8	1.1 ± 1.7	0.02
Total hip	−0.4 ± 0.9	0.4 ± 1.0	0.06
Femoral neck	−0.7 ± 0.9	0.1 ± 0.8	0.04
1/3 radius	−0.2 ± 1.1	0.9 ± 1.2	0.02

There were substantial differences between subjects with MGUS and controls by HRpQCT at both the radius and tibia (Fig. 1). There was no difference in the bone size, measured by cross-sectional area, at either site. At the radius, patients with MGUS had a lower total density (−34%; $p < 0.001$), trabecular density (−36%; $p < 0.001$), cortical density (−8%; $p < 0.01$), and cortical thickness (−29%; $p < 0.001$) compared to controls. With respect to trabecular microarchitecture, patients with MGUS had a lower trabecular number (−24%; $p < 0.001$), greater trabecular separation (+45%; $p < 0.01$), and greater heterogeneity (+72%; $p < 0.02$). Whole bone stiffness by FEA tended to be lower in MGUS patients (−25%; $p = 0.08$).

At the tibia, patients with MGUS had a lower total density (23%; $p < 0.01$) and trabecular density (−32%; $p < 0.001$). Cortical density was not significantly lower in MGUS patients (−4%; $p = 0.20$), nor was cortical thickness (−13%; $p = 0.28$). Patients with MGUS had a lower trabecular number (−19%; $p < 0.03$), greater trabecular separation (+41%; $p < 0.02$) and greater trabecular heterogeneity (+118%; $p < 0.05$). Whole bone stiffness was lower in MGUS patients (−28%; $p < 0.02$). Cortical porosity did not differ at either site. We did not find a relationship between disease activity and length of MGUS diagnosis with either DXA or HRpQCT parameters.

Discussion

In this study, we confirm prior reports of low volumetric BMD and abnormal microarchitecture in patients with MGUS compared with healthy controls [10, 17], and extend those findings to demonstrate that abnormalities are present not only at the radius but also at the tibia. These results suggest that there are global skeletal effects of MGUS and provide a potential structural basis for the fragility seen in this population [1, 2, 18, 19].

Ng and colleagues [10] reported that patients with MGUS had a larger cross-sectional area by HR-pQCT compared to controls, which they postulated might be due to a compensatory increase in the bone size. In contrast, we did not find that MGUS patients had a larger bone size either at the radius or the tibia. An important difference in our two cohorts is that our group was predominantly women whereas the majority of their subjects were men. This group subsequently analyzed cortical microarchitecture and found that MGUS patients had lower cortical vBMD, thickness, and higher porosity at the radius [9]. While we similarly found that cortical bone was abnormal at the radius, we found substantial abnormalities in the trabecular bone as

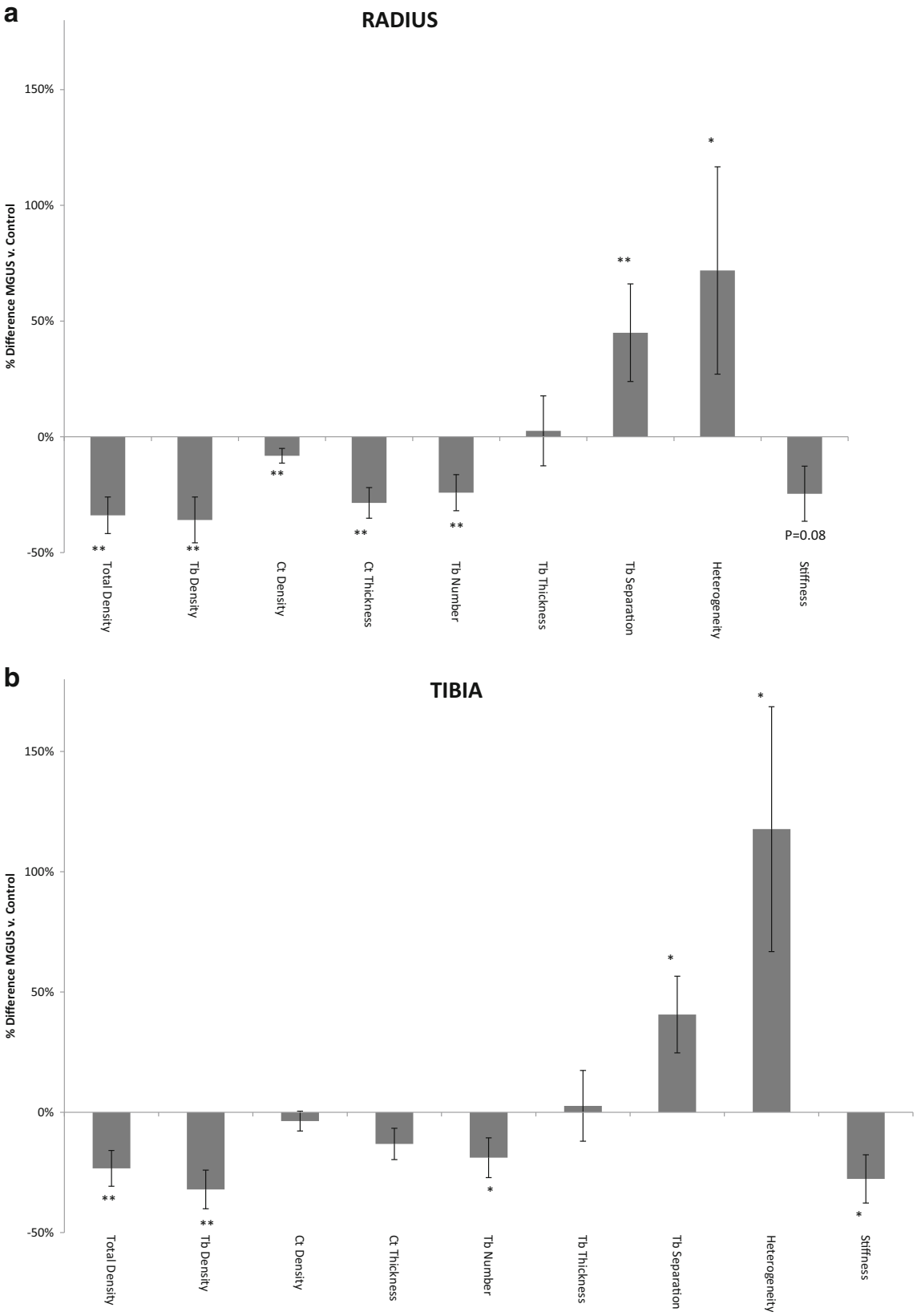

Fig. 1 Comparison of vBMD, microarchitecture, and stiffness in patients with MGUS and controls at the **a** radius and **b** tibia. *Ct*, cortical bone; *Tb*, trabecular bone. $^{**}p$ value < 0.01 and $^{*}p$ value < 0.05

well, with lower trabecular density and number, and greater trabecular separation and heterogeneity in MGUS patients. This finding corroborates reports by Ng and colleagues of the trabecular abnormalities at the radius in MGUS [10]. We found that MGUS patients had a lower trabecular number, greater trabecular separation, and heterogeneity at the tibia as well. Cortical bone at the tibia may have been preserved by the protective effects of weight bearing. We found that whole bone stiffness tended to be lower at the radius, similar to prior results at that site [9, 10, 17]. In addition, we found that stiffness was significantly lower at the tibia. Our findings of abnormalities in microarchitecture and biomechanical properties of bone at both sites provide further support that this disease has detrimental systemic skeletal effects.

Studies investigating biochemical markers of bone turnover in patients with MGUS have found conflicting results [17]. Some authors have reported that bone turnover markers are elevated in patients with MGUS [20–22], while others have not [10, 23]. In our study, neither markers of bone formation nor resorption differed between healthy individuals and those with MGUS. We found no difference in levels of MIP-1 alpha, an osteoclast activating factor. Similar to our results, another smaller study found that MIP-1 alpha did not differ between MGUS and control subjects [24]. In contrast, Ng et al. reported that MIP-1 alpha was sixfold greater in MGUS patients [10]. However, since MIP-1 alpha is secreted directly by multiple myeloma cells, there is probably a direct correlation between the extent of myeloma cell infiltration, the levels measurable in the blood and the bone resorption [25]. Therefore, a correlation between bone resorption and MIP-1alpha levels might vary depending on the patient cohort.

In this study, we also measured ICTP generated by matrix metalloproteinases (MMPs). MMPs have been shown to play a role in multiple myeloma bone disease [26], ICTP has not been previously assessed in patients with monoclonal gammopathies [27–29]. Unlike CTX-I and NTX-I, ICTP1 it is not released by cathepsin K degradation [30]. In patients with myeloma, ICTP-1 levels are elevated, correlate with histomorphometric changes, predict osteolysis and survival, and rise along with the stage of disease [27–29]. We found that ICTP-1 values were numerically higher in MGUS patients but the difference was not significant. While this lack of significance may be due to our small sample size, it is also possible, considering that ICTP levels are greatly raised in multiple myeloma (MM) when compared to MGUS [27–29] that these bone turnover markers are less abnormal in the precursor disease.

We did not find a relationship between disease activity or length of MGUS diagnosis and skeletal disease, possibly due to our small sample size but also because many patients may have had MGUS for years prior to the time of diagnosis.

There are several limitations of this work, most importantly, our small sample size. While we were able to detect many significant differences in vBMD, microarchitecture, and stiffness, the small sample size may have precluded our ability to detect significant differences in some of the biochemical markers. We did not find a relationship between disease activity or length of MGUS diagnosis and skeletal disease, possibly due to our small sample size but also because many patients may have had MGUS for years prior to the time of the diagnosis. Another biochemical marker, sclerostin, has been implicated in myeloma-induced bone loss [31] but was not measured as part of this study. We also did not measure DKK-1, which has been shown to be elevated in patients with both MGUS and MM and its level has been shown to be a measure of bone disease extent [32–34].

In summary, we found that patients with MGUS had abnormalities in the skeletal structure and biomechanical properties, with lower volumetric BMD, microarchitecture, and stiffness compared to controls. We demonstrate for the first time that MGUS patients have abnormalities at the tibia as well as the radius. That we were able to detect so many differences with this small sample size that suggests that MGUS has pronounced detrimental skeletal effects. Larger prospective studies are needed to investigate the cellular mechanisms underlying these structural abnormalities as well as potential therapeutic options for MGUS-associated bone loss. Better understanding of the skeletal effects of MGUS would help guide the clinical care of osteoporosis in the burgeoning population of older adults with this disease.

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Compliance with ethical standards

Conflict of interest Emily Stein, Alexander Dash, Sanchita Agarwal, Mariana Bucovsky, Jing Fu, Elizabeth Lentzsch, and Elizabeth Shane declare that they have no conflict of interest. Dr. Lentzsch is chief scientific advisor and shareholder of Caelum Biosciences and advisor for Janssen, Bayer, and Karyopharm.

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