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Original article

Clinical significance of trabecular bone score for prediction of pathologic fracture risk in patients with multiple myeloma

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ABSTRACT

Objectives: Osteolytic bone lesions are common complications in multiple myeloma (MM), and can have an impact on quality of life due to the risk of fractures. Trabecular bone score (TBS) is a novel texture index derived from dual energy x-ray absorptiometry (DXA) of lumbar spine (LS) images that provides information about bone microarchitecture. The aim of this study was to evaluate whether TBS is useful in predicting bone fractures in MM patients.

Methods: TBS was calculated retrospectively from existing DXA images of the LS, in 20 patients with newly diagnosed MM. We analyzed the development of fractures in these patients.

Results: The median age of the patients was 66 years (range, 49–77 years). Osteolytic bone lesions were observed in 18 patients (90%) at the time of diagnosis. The median duration of follow-up was 40.0 months (95% confidence interval [CI], 33.2–46.2), 6 fracture events (long-bone fractures in 5 events, vertebral fracture in 1) occurred in 5 patients (25%). There were no significant differences between patients who experienced new onset fractures and patients who did not for all TBSs and T-scores, although the fracture group had lower levels than the no fracture group. However, among TBSs of individual LSs, only L2 showed significantly lower scores in patients who developed fractures (1.135 ± 0.085 [95% CI, 1.030–1.241] vs. 1.243 ± 0.169 [95% CI, 1.149–1.336], $P = 0.032$).

Conclusions: TBS of the LS in MM patients may be helpful in predicting development of fractures; however, further investigation is needed.

1. Introduction

Multiple myeloma (MM) is characterized by neoplastic proliferation of plasma cells that produce a monoclonal immunoglobulin, accounting for approximately 1% of malignant diseases and 13% of hematologic malignancies [1,2]. The plasma cells proliferate in the bone marrow, which often results in extensive skeletal destruction with osteolytic lesions [1]. Approximately 80% of patients with myeloma have osteolytic bone lesions at diagnosis and up to 60% of patients develop pathologic fractures over the course of their disease [1,3]. Although recent advances in management of MM have resulted in significant improvement in survival, fractures are a concern in patients with MM because they are associated with increased morbidity and reduced survival [3–5].

Bone mineral density (BMD) measured with dual-energy x-ray absorptiometry (DXA) is the most widely used tool for diagnosing osteoporosis and assessing fracture risk. The efficacy of BMD by DXA in MM has been also reported. Some studies have suggested that using DXA could predict the risk of vertebral fracture and treatment response in MM [6–9]. However, all of these reports focused on vertebral fracture. Some reports showed that spine BMD in MM was significantly reduced, but that femoral BMD was not. Therefore, in MM, the discrepancy of spine BMD and femoral neck BMD was greater than that in the control group [10,11]. Another study reported no correlation between BMD and osteolytic extent in MM [12].

Since MM is one of the etiologies of secondary osteoporosis, fractures occurring in MM are likely due to changes in microarchitecture rather than due to bone density. There have been several reports of quantitative computed tomography (QCT) being used as a method for evaluating bone quality in MM [13–16]. However, high-resolution QCT is not a routine method utilized in clinical practice.

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An increasing body of evidence suggests that trabecular bone score (TBS), a surrogate of bone microarchitecture extracted from DXA of spines, may have the potential utility for evaluating bone texture in patients with conditions related to increased fracture risk [17–20]. It does not require any additional examination and uses only DXA images. TBS measures incorporation of gray-level variations in DXA images of the lumbar spine (LS), and can be a reflection of microarchitecture status. To the best of our knowledge, no prior studies have performed fracture risk assessment using TBS in MM patients. The current study investigated whether TBS calculated with DXA might have clinical significance for fracture risk assessment in MM.

2. Methods

2.1. Patients

This study retrospectively analyzed the clinical data of patients who were newly diagnosed with MM at Kosin University Gospel Hospital from May 2012 to September 2015, who underwent DXA study of the LS at the time of diagnosis and experienced newly onset fractures during follow-up period. Patients with monoclonal gammopathy of undetermined significance were excluded from this analysis. This study was approved by the Institutional Review Board of Kosin University Gospel Hospital (approval number: 2018-02-009).

2.2. TBS calculations

BMD was measured with DXA (GE Lunar Prodigy, GE Healthcare, Milwaukee, WI, USA) in the LS and femur. For purposes of the study degenerative or compressed vertebrae were not excluded. The center's coefficient of variation for BMD is 0.937% in the LS All DXA scans were analyzed, and TBS was calculated using TBS Insight software ver. 2.1 (GE Healthcare) with DXA images on the same vertebrae as in the BMD measurements. The coefficient of variation for TBS measurement is 1.408% in the LS at our center.

2.3. Statistics

The objective of this study was to investigate whether patients with and without development of pathologic fractures showed differences in TBS. Statistical analysis was performed using IBM SPSS ver. 18.0 (IBM Co., Armonk, NY, USA). BMD and TBS by DXA of the LS in patients with and without fracture were compared using the Mann-Whitney *U* test.

3. Results

3.1. Patient characteristics

Patient characteristics are summarized in Table 1. The median age of the patients was 66 years (range, 49–77 years), and 25% were male. Ten patients (50%) had osteoporosis by DXA, and 5 patients (25%) exhibited osteopenia. Osteolytic bone lesions were identified in 18 patients (90%), and 8 patients already had pathologic bone fractures at the time of diagnosis with MM. Sites of pre-existing fractures were: axial skeletons in 5 patients (3 patients with multiple vertebral fractures), long bones in 2 patients (both with humerus fractures), and a rib in 1 patient.

3.2. Treatment and development of fractures

Eighteen patients received chemotherapy with a corticosteroid-based regimen. One patient underwent corticosteroid noncontaining chemotherapy, and another patient refused chemotherapy. Bisphosphonate therapies to reduce skeletal-related events were administered in all patients except for 1 with grade 3 chronic kidney disease who did not have an osteolytic lesion (19 of 20, 95%). Among 8 patients who had pre-existing fractures, 2 patients who had a fracture of the humerus received surgical treatment, and all patients except the patient with a rib fracture underwent radiation therapy to osteolytic lesions with pathologic fractures.

Table 1
Anthropometric and clinic characteristics between the new- onset fracture and no fracture groups.

Characteristic	Fracture (n = 5)	No fracture (n = 15)	P-value
Body mass index, kg/m^2			
Underweight (<18.5)	0 (0)	2 (13.3)	0.528
Normal-weight	2 (40)	6 (40)	
Overweight (≥23)	3 (60)	7 (46.7)	
Ostoeporosis/osteopenia			
Normal	1 (20)	4 (26.7)	0.133
Osteopenia	0 (0)	5 (33.3)	
Osteoporosis	4 (80)	6 (40.0)	
Osteolytic bone lesions			
Yes	5 (100)	13 (86.7)	0.553
No	0 (0)	2 (13.3)	
Fractures at the diagnosis of myeloma			
Yes	2 (40)	6 (40.0)	
No	3 (60)	9 (60.0)	
International Staging System			
I	1 (20)	5 (33.3)	0.663
II	2 (40)	7 (46.7)	
III	2 (40)	3 (20.0)	
Anemia			
Yes	2 (40)	7 (46.7)	0.604
No	3 (60)	8 (53.3)	
Hypercalcemia			
Yes	2 (40)	1 (13.3)	0.140
No	3 (60)	14 (86.7)	
Renal insufficiency			
Yes	1 (20)	1 (13.3)	0.447
No	4 (80)	14 (86.7)	
Hypoalbuminemia			
Yes	1 (20)	5 (33.3)	0.517
No	4 (80)	10 (67.7)	

Values are presented as number (%).

During the median follow-up period of 40.0 months (95% CI, 33.2–46.2), a total of 6 events of pathologic fractures in 5 patients occurred (Table 2). Of these, 5 events were long bone fractures and 1 event was a vertebral fracture. Surgical treatments were needed in all cases. One patient (patient 1 in Table 1) experienced 2 episodes of pathologic fractures at an interval of almost 10 months, without a specific history of trauma. In 2 patients (patients 2 and 4 in Table 2), pathologic fractures reoccurred at pre-existing fracture sites at the time of diagnosis.

3.3. BMD and TBS analysis

There were no significant differences between patients who experienced new onset fractures and patients who did not in all BMD and T-scores, although the fracture group had lower levels than the no fracture group. The mean TBS of the LS (L1–4) in the fracture group (1.162 ± 0.032 [95% CI, 1.122–1.201]) was lower than in the no fracture group (1.255 ± 0.154 [95% CI, 1.170–1.3]), but it was not statistically significant ($P = 0.061$). However, in the TBSs of individual LSs, L2 showed significantly lower scores in patients who developed fractures (1.135 ± 0.085 [95% CI, 1.030–1.241] vs. 1.243 ± 0.169 [95% CI, 1.149–1.336], $P = 0.032$) (Table 3).

Table 2
Characteristics of new-onset fractures during the follow-up period.

Patient	Age/sex	Osteoporosis by BMD	ISS	Time to fractures, mo	Site of fractures	Management of fractures
Patient 1	67/M	Yes	III			
1st event				20.8	Rt. humerus	Surgery
2nd event				30.1	Lt. femur	Surgery
Patient 2	49/F	Yes	I	3.5	L4 spine	Surgery
Patient 3	77/F	No	II	27.9	Lt. femur	Surgery
Patient 4	74/F	Yes	III	16.9	Rt. humerus	Surgery
Patient 5	69/F	Yes	II	15.8	Lt. radius	Surgery

BMD, bone mineral density; ISS, International Staging System; Rt, right; Lt, left.

Table 3
Mean lumbar spine BMD and TBS scores between the new-onset fracture and no fracture groups.

Variable	Fracture (n = 5)	No fracture (n = 15)	P-value
L1			
BMD (g/cm^2)	0.820 ± 0.094 (0.728–0.893)	0.904 ± 0.203 (0.804–1.011)	0.458
T-score	−2.150 ± 0.717 (−0.453 to 1.807)	−1.473 ± 1.651 (−0.945 to 2.997)	0.392
TBS	1.004 ± 0.075 (0.956–1.090)	1.152 ± 0.228 (1.041–1.260)	0.106
L2			
BMD (g/cm^2)	0.818 ± 0.133 (0.691–0.948)	0.925 ± 0.207 (0.814–1.026)	0.239
T-score	−2.689 ± 1.052 (−0.529 to 2.259)	−1.825 ± 1.645 (−0.798 to 2.528)	0.289
TBS	1.135 ± 0.085 (1.056–1.214)	1.243 ± 0.169 (1.156–1.323)	0.032
L3			
BMD (g/cm^2)	0.886 ± 0.156 (0.755–1.045)	0.966 ± 0.211 (0.860–1.071)	0.513
T-score	−2.581 ± 1.315 (−1.004 to 2.349)	−1.908 ± 1.770 (−1.150 to 2.495)	0.448
TBS	1.242 ± 0.108 (1.156–1.356)	1.303 ± 0.148 (1.227–1.376)	0.206
L4			
BMD (g/cm^2)	0.942 ± 0.202 (0.766–1.114)	0.970 ± 0.213 (0.867–1.081)	0.896
T-score	−2.028 ± 1.675 (−1.826 to 2.294)	−1.794 ± 0.765 (−1.660 to 2.128)	0.798
TBS	1.267 ± 0.0560 (1.221–1.315)	1.323 ± 0.135 (1.259–1.388)	0.513
L1–4			
BMD (g/cm^2)	0.870 ± 0.132 (0.755–0.999)	0.942 ± 0.196 (0.843–1.043)	0.458
T-score	−2.371 ± 1.066 (−0.812 to 0.971)	−1.791 ± 1.581 (−1.029 to 2.188)	0.459
TBS	1.162 ± 0.0320 (1.133–1.200)	1.255 ± 0.154 (1.179–1.328)	0.061

Values are presented as mean ± standard deviation (95% confidence interval).
BMD, bone mineral density; TBS, trabecular bone score; SD, standard deviation; CI, confidence interval.

4. Discussion

MM is a hematologic malignancy that causes progressive and destructive osteolytic bone disease leading to severe bone pain, pathological fractures, secondary osteoporosis and hypercalcemia [1]. Although myeloma bone disease (MBD) is the major cause of morbidity in MM, the mechanism is not clearly understood. Myeloma cells are found in close association with sites of active bone resorption and secrete a number of osteoclast activation. The receptor activator of nuclear factor-kappa B (RANK)/RANK ligand (RANKL)/osteoprotegerin (OPG) system may play a key role in the pathogenesis of MBD. In patients with MM, the ratio of RANKL and OPG has been shown to be markedly decreased. Direct interactions between myeloma cells and bone marrow stromal cells or osteoclasts may also play a critical role in the development of MBD. In addition, myeloma cells inhibit the development of osteoblasts by alteration of dickkopf-1, secreted frizzled-related proteins, interleukin-3, runt-related transcription factor 2, and tumor growth factor-β [21,22].

Approximately 80% of patients with myeloma have osteolytic bone lesions at diagnosis [1,3]. About 40% of the patients included in this study had a fracture at the time of diagnosis. Nearly 75% of the patients exhibited osteopenia or osteoporosis. It is estimated that up to 60% of MM patients experience pathologic fractures over the course of their disease [1,3]. During the follow-up period, only 25% of patients in the current study experienced new fractures, perhaps because patients were not followed over their lifetime. All patients received bisphosphonate treatment at the beginning of treatment and radiation therapies to extensive osteolytic bone lesions ahead.

Since MM is a disease that causes extensive bone loss, many treatments are targeted to inhibit osteoclasts and reduce skeletal-related events [23–26]. Although treatments have been developed, there are not appropriate methods for evaluating the effects of these therapies or to assess the risk of fracture. Several studies have suggested methods for predicting MBD by measuring the number or extent of focal erosions [27,28]. However, bone-related problems in MM are not due to focal erosion of specific sites, but to extensive bone loss, meaning that change in the microarchitecture is starting before the lytic bone lesion can be seen in an image. In previous studies, trabecular separation is the most predictable factor associated with fracture [13,16].

TBS was developed to overcome the disadvantage of DXA, which does not reflect bone microstructure. TBS is less expensive than QCT without additional radiation exposure, and is easy for patients to examine. It analyzes local gray-scale variation in 2-dimensional images using DXA. A high TBS reflects good trabecular microarchitecture; in contrast, a low TBS may indicate poor microarchitecture quality. In this study, there were no significant differences in BMD, but TBS was significantly lower in the fracture group than in no-fracture patients. All new-onset fractures but 1 event occurred in long bone, suggesting that TBS reflects the long-bone quality and the 'trabecular separate.'

The limitations of this study include the small number of patients and bone events. Previously degenerative or compressed vertebrae were not included due to the small number of cases;

however, since TBS indicates bone quality, it could be more meaningful to include the affected vertebrae. Despite these limitations, this is the first report to demonstrate the clinical meaning of TBS in MM. This was not a cross-sectional study, and the median follow-up period was 40 months (95% CI, 33.2–46.2). This study demonstrated the possibility of routine use of TBS when patients are diagnosed with MM.

5. Conclusions

MM patients with fracture during the disease course had significantly lower TBS scores than patients with no fractures. In order to formally utilize TBS to predict fracture and therapeutic response in MM, more research is needed, including large-scale, prospective studies and those comparing TBS with QCT.

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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