

## Bone Strength, Skeletal Muscle Area, and Biochemical Markers Associated with Bone Metabolism in Patients with Fragility Distal Radius Fracture

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### Abstract

Distal radius fracture (DRF) is often the first fragility fracture that occurs in postmenopausal women and exhibits the high risk of future fragility fractures at the other skeletal sites. So far, the other factors rather than bone mineral density have not been well investigated. Our aim was to determine the characteristics of the patients with previous fragility DRFs.

We enrolled 48 postmenopausal women with a history of fragility DRF (fracture group) and age-matched 96 healthy postmenopausal women volunteers (control group). Hip BMD of all the participants was obtained using DXA. Geometrical parameters and biomechanical indices of the femoral neck were obtained using quantitative CT. Using CT images, the cross-sectional area of the skeletal muscle and fat inside the fascia was calculated at the proximal thigh. Twelve biochemical markers and hormones associated with bone metabolism were also measured. Each parameter was compared between the patients and controls by analysis of variance (ANOVA), followed by ANCOVA adjusting for femoral neck areal BMD. BMD of the femoral neck was significantly lower in the fracture group than the control, while skeletal muscle area was not. Femoral neck cortical thickness was significantly smaller and buckling ratio was significantly greater in the fracture group; however, after adjusting for BMD, the differences were no longer significant. Further, 25(OH)D, Urinary deoxypyridinoline (DPD), and serum and urinary pentosidine levels were significantly higher in the fracture group than in the control group; those differences remained significant after adjusting for BMD. The patients with previous DRFs exhibited lower BMD, which was not accompanied by lower skeletal muscle area or muscle strength. Further, bone metabolism alterations such as low 25(OH)D, high DPD, and high serum and urinary pentosidine levels were also observed in such patients, independent of the areal BMD determined by DXA. Level of Evidence: Prognostic Study.

**Keywords:** Distal radius fracture; Osteoporosis; Skeletal muscle; Pentosidine

### Introduction

Fragility fracture is defined as a fracture that occurs as a result of a fall from standing height or less. Distal radius fracture (DRF) is unique because it is often the first fragility fracture that occurs in postmenopausal women [1] and compared with other fragility fractures, it occurs in relatively younger patients [2]. DRF is known to be a strong predictor of future fragility fractures [3], despite the fact that not all patients with DRFs have low bone mineral densities (BMD). This suggests that the patients with the fragility fracture could be associated with other risk factors of fracture rather than low BMD. Therefore, our aim was to determine the characteristics of fragility DRFs, by analyzing the parameters of bone strength at the proximal femur using quantitative computed tomography (qCT), as well as measuring various biochemical markers and hormones associated with bone metabolism.

### Method

#### Patients

We enrolled 48 postmenopausal women with a history of fragility DRF (fracture group). Those patients were referred to our hand clinic for the treatment of upper extremity disorders, including carpal tunnel syndrome, malunion of the DRF, extensor tendon rupture, and lateral epicondylitis, among others. The fracture occurred at least 6 months before the first visit. All the fractures were confirmed in plain radiographs of the wrist taken at first presentation to our hospital. It was judged as a fracture when deformities of the distal radial configuration such as increased dorsal tilt angle, decreased radial inclination, or increased ulnar plus variance were observed in

comparison with the contralateral normal wrists in plain radiographs of the wrist. All the patients developed their fracture after falling from standing height. The average age was 71.6 years (range, 56 to 88 years). Patients who had fragility fractures or history of fragility fractures in other skeletal sites were excluded. Total spinal plain radiograph films were taken to confirm any morphological compression fractures, which were evaluated using the semi quantitative method. Patients who had diseases that required systemic glucocorticoid administration and those who had chronic kidney disease with grade 3 or more, hyperparathyroidism, abnormalities of serum calcium and phosphorus, or diabetes were excluded. Furthermore, patients who had received osteoporotic medication from previous physicians were also excluded.

By posting and advertisement in a local newspaper, we recruited 164 healthy postmenopausal women volunteers for this study as a control group. The age-matched volunteers for the control group were randomly selected. As a result, the control group consisted of 96 volunteers with an average age of 71.5 years (range, 57 to 86 years).

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It was confirmed, prior to enrollment, that all the volunteers had no history of fragility fracture or took no medication for systemic disease.

### Examinations

Height, weight, and grip strength of all subjects were measured. Grip strength was measured 3 times in both hands using a Jamar<sup>®</sup> hydraulic hand dynamometer (Sammons Preston, Bolingbrook, IL, USA) and the average value of the stronger side were used.

### DXA

The BMD of the left proximal femur (total hip and femoral neck) and lumbar spine (L2–L4) was obtained using DXA (PRODIGY; GE Medical Systems, Madison, WI, USA). Daily calibration of the instruments using the manufacturer's internal standard was performed before use. Staff at A Hospital maintained quality assurance of BMD tests. The coefficients of variation for the lumbar spine and femoral neck were 0.7% and 1.1%, respectively.

### qCT bone analysis

Spiral CT scans (Light Speed VCT 64 Slice CT; GE Medical Systems, Waukesha, WI, USA) were acquired from the superior aspect of the acetabulum of the pelvis to approximately 5 cm distal to the lesser trochanter of the femur, with a slice thickness of 2.5 mm. The qCT calibration phantom (Mindways Software Inc., Austin, TX, USA) was placed beneath the pelvis on the table. Quality assurance scans were repeated 3 times to verify operational integrity of the qCT system during the data acquisition period. qCT data were transferred to the QCT PRO PC (Mindways Software Inc., Austin, TX, USA) and all analyses were performed automatically using QCT PRO Bone Investigational Toolkit (BIT) software. Details of the procedures for using this software have been described elsewhere [4]. The cortical bone segmentation threshold was set at 350 mg/cm<sup>3</sup> for all the subjects.

Geometric parameters of the left hip were cross-sectional area (CSA) and cortical thickness of the femoral neck. Calculated biomechanical indices included the cross-sectional moment of inertia of the total bone, section modulus, and buckling ratio.

### qCT analysis of soft tissue

Using the CT data obtained previously for proximal femoral geometric analysis, three 2.5-mm slices from a level that was 2 cm distal to the inferior aspect of the lesser trochanter were selected. Cross-sectional analysis of the soft tissue in these slices was performed using Tissue Composition Module software (Mindways Software, Inc., Austin, TX, USA).

First, initial segmentation was performed to segment the phantom from the image and to apply a set of default tissue composition thresholds to the image. Then, the left thigh image was isolated using a freehand tool; a semi-automated skin removal algorithm was used repeatedly until the epidermal layer was removed. The next step was advanced segmentation, in which the default tissue segmentation thresholds were optimized using a Gaussian Mixture Model. This provided iterative refinement of the initial segmentation thresholds derived by the software. Then, an optional contour was defined around the group of thigh muscles. A spline was used to constrain the location of the contour, and a "snake" operation fit the contour precisely to the muscle group. This isolated muscle group consisted of fat, bone, and lean tissue. Subcutaneous fat was not included in the analysis.

Calibration data were used to derive an estimate of BMD using standard methods and to estimate the expected pixel value for fat and skeletal muscle tissue using atomic compositions. Fat and skeletal

muscle density was assumed to be 0.923 g/cm<sup>3</sup> and 1.055 g/cm<sup>3</sup>, respectively [5,6].

The skeletal muscles analyzed in these CSAs were the quadriceps femoris, sartorius, gluteus maximus, tensor fasciae latae, and adductors. Twelve volunteers not included in this study were randomly selected to confirm validity and reproducibility of the Tissue Composition Software by comparing the data using validated EV Insite software (PSP Corporation, Tokyo, Japan), in which the lean tissues were outlined manually. One slice of the proximal thigh, 2 cm distal to the lesser trochanter, was analyzed. Using each software, CSAs of the fat, skeletal muscle, and bone was calculated. For Tissue Composition Software, calculation of those CSAs was repeated twice. Correlations between the software used were found to be substantial; the correlation coefficients for fat, muscle, and bone were 0.732, 0.958, and 0.965, respectively. Reproducibility was very good and the correlation coefficients for fat, muscle, and bone were 0.978, 0.997, and 1, respectively.

### Biochemical markers and hormones associated with bone metabolism

Regarding blood and urinary tests, the following parameters were measured: bone specific alkaline phosphatase (BAP) as µg/L by chemiluminescent enzyme immunoassay, tartrate-resistant acid phosphatase 5b (TRCP-5b) as mU/dL by enzyme immunoassay (EIA), urinary cross-linked N-telopeptide of type collagen (NTX) as nmol bone collagen equivalent/nmol creatinine by enzyme-linked immunosorbent assay (ELISA), urinary deoxypyridinoline (DPD) as nmol/mmol CRE by EIA, osteocalcin (OC) as ng/mL by immunoradiometric assay (IRMA), undercarboxylated osteocalcin (ucOC) as ng/mL by Electro-chemiluminescence immunoassay ECLIA, whole parathyroid hormone as pg/mL by IRMA, serum homocysteine as nmol/m by high performance liquid chromatography, serum pentosidine as µg/mL by ELISA, urinary pentosidine as µg/mg-CRE by ELISA, 1,25-(OH)<sub>2</sub>D as pg/mL by radioimmunoassay (RIA), and 25(OH) D as ng/mL by RIA. All the measurements were performed in SRL Inc., Tokyo, Japan.

Blood and urinary samples of the patients were collected between the mid-morning and early afternoon, depending on the time the patients visited the hospital. Samples of the volunteers were collected in the afternoon, after the routine outpatient care visits were completed.

### Statistical analysis

Each parameter was compared between the fracture group and the control group, using one-way analysis of variance. Analysis of covariance with BMD of the left femoral neck as covariance was then performed. P values less than 0.05 were considered to be significant. Power analysis for serum pentosidine, which was one of our interests, demonstrated that 38 patients in the fracture group and 76 volunteers in the control group were sufficient to detect clinically important differences of 0.0081 µg/mL (standard deviation, 0.0145; power, 0.8; and alpha error, 0.05) [7]. Statistical analyses were performed using JMP version 7.0.2. (SAS Institute Inc.). Data were collected from July 2010 to October 2013. This study was approved in the ethical committee of A and written informed consent was obtained from all the patients and volunteers.

### Results

All the patients and volunteers had complete data, except for 1 patient in the fracture group, who only had BAP, NTX, and 25(OH)D data from blood and urinary samples.

There were no significant differences in age, height, and weight

	Fracture n=48	Control n=96	p-value unadjusted/BMD-adjusted
Age (years)	71.6 ± 8.9	71.5 ± 7.1	0.976/0.243
Height (cm)	151.9 ± 7.6	153.1 ± 6.1	0.297/0.934
Weight (kg)	52.0 ± 9.6	51.8 ± 7.0	0.885/0.301
Grip strength (kg)	21.9 ± 6.1	23.7 ± 6.1	0.118/0.452
<b>DXA BMD</b>			
Spine (g/cm <sup>2</sup> )	<b>0.890 ± 0.189</b>	<b>0.978 ± 0.179</b>	<b>0.008/0.249</b>
Total hip (g/cm <sup>2</sup> )	<b>0.724 ± 0.106</b>	<b>0.775 ± 0.119</b>	<b>0.013/0.471</b>
Femoral neck (g/cm <sup>2</sup> )	<b>0.657 ± 0.109</b>	<b>0.708 ± 0.123</b>	<b>0.017/-</b>
<b>QCT Bone Femoral neck</b>			
CSA (mm <sup>2</sup> )	8.3 ± 1.0	8.4 ± 1.0	0.586/0.401
CSMI (cm <sup>4</sup> )	1.1 ± 0.3	1.2 ± 0.3	0.080/0.479
Section Modulus (cm <sup>3</sup> )	0.8 ± 0.2	0.9 ± 0.2	0.078/0.809
Cortical thickness (mm)	<b>1.9 ± 0.7</b>	<b>2.2 ± 0.8</b>	<b>0.025/0.769</b>
Buckling ratio	<b>10.4 ± 4.6</b>	<b>8.8 ± 4.0</b>	<b>0.035/0.733</b>
<b>QCT soft tissue proximal thigh</b>			
Skeletal muscle CSA (cm <sup>2</sup> )	94.0 ± 14.4	93.0 ± 13.7	0.668/0.107
Adipose tissue CSA (cm <sup>2</sup> )	10.9 ± 4.7	10.6 ± 4.2	0.695/0.906

Adjusted for femoral neck BMD, CSA:cross sectional area, CSMI:cross sectional moment of inertia.

Bold letter means statistically significant parameter and values. The data is shown as mean ± standard deviation.

**Table 1:** Characteristics, DXA and qCT data of the patients with distal radius fracture and the control.

between the groups. Grip strength was not significantly lower in the fracture group than in the control group (Table 1).

### DXA

The patients with a history of fragility DRF had significantly lower spine BMD or proximal femoral BMD than the control (Table 1).

### qCT bone analysis

Femoral neck cortical thickness was smaller in the fracture group than in the control group (p=0.025). Also, buckling ratio was greater in the fracture group than in the control group (p=0.035). After adjusting for femoral neck BMD, those differences were no longer significant (Table 1). Other parameters were not significantly different between the groups.

### qCT soft tissue analysis

There were no significant differences in skeletal muscle and fat CSA at the proximal thigh between the fracture group and the control group (Table 1).

### Biochemical markers and hormones associated with bone metabolism

The serum 25(OH)D level was significantly lower in the fracture group than in the control group (p=0.021). Urinary DPD, and serum and urinary pentosidine levels were significantly higher in the fracture group than in the control group (p=0.002, 0.002, and 0.028, respectively). Any other parameters were not significantly different between the groups. Differences in 25(OH)D, urinary DPD, and serum and urinary pentosidine were still significant after adjusting for femoral neck BMD (Table 2).

### Discussion

Some factors that may lead to the risk of proximal femoral or spine fracture in patients with fragility DRF have been suggested in previous literatures. First, it has been demonstrated that the BMD in the hip or other skeletal sites of patients with DRFs is lower than that in age-matched controls [8,9]. Low BMD at the proximal femur is a risk factor

	Fracture n=48	Control n=96	p-value unadjusted/BMD-adjusted
<b>Bone formation marker</b>			
BAP(µg/L) 3.8-22.6	16.8 ± 6.1	16.0 ± 5.4	0.493/0.486
Osteocalcin (ng/mL) 2.5-13	7.0 ± 2.8	7.1 ± 2.2	0.833/0.586
<b>Bone absorption marker</b>			
TRACP-5b (mU/dL) 120-420	433 ± 175	402 ± 151	0.273/0.455
NTX (nmolBCE/nmol.CRE) 14.3-89	45.7 ± 20.8	42.2 ± 17.6	0.289/0.284
DPD (nmol/nmol.CRE) 2.8-7.6	<b>6.9 ± 2.4</b>	<b>5.6 ± 2.1</b>	<b>0.002/0.006</b>
<b>Bone matrix related marker</b>			
ucOC (ng/mL) < 4.5	4.9 ± 5.5	4.6 ± 3.0	0.673/0.906
serum Pentosidine (µg/mL) 0.009-0.043	<b>0.041 ± 0.034</b>	<b>0.028 ± 0.014</b>	<b>0.002/0.002</b>
urinary Pentosidine (µg/mg.CRE) 0.019-0.070	<b>0.084 ± 0.180</b>	<b>0.041 ± 0.043</b>	<b>0.028/0.040</b>
Homocystein(nmol/mL) 3.7-13.5	8.6 ± 2.6	8.3 ± 2.4	0.515/0.405
<b>Hormone and vitamin</b>			
Whole PTH (pg/mL) 9-39	27.2 ± 10.4	25.9 ± 11.3	0.510/0.508
1,25(OH)2D (pg/mL) 20-60	60.8 ± 22.7	61.7 ± 17.0	0.792/0.918
25(OH)D (ng/mL) deficiency; 20 >	<b>20.7 ± 7.6</b>	<b>23.5 ± 6.3</b>	<b>0.021/0.017</b>

Mean and standard deviation are described.

Normal range for each parameter is described in the left column. Bold letters indicate statistically

significant parameters and values. BAP: Bone specific alkaline phosphatase, TRACP-5b: Tartrate-resistant acid phosphatase 5b,

NTX: urinary crosslinked N- telopeptide of type I collagen, DPD: deoxypyridinoline, ucOC: undercarboxylated osteocalcin, PTH: parathyroid hormone, OH: hydroxy.

Adjusted for femoral neck BMD.

**Table 2:** Biochemical markers for bone metabolism of the patients with distal radius fracture and the control.

of hip fracture and this is very strongly correlated [10]. However, in many of the patients with DRFs, the BMD at the hip fall within the osteopenic range (T-score from -2.5 to -1.0). We attempted to elucidate the risk factors of hip fracture by the structural analyses of the femoral neck using qCT in addition to areal BMD. Thinner cortical thickness or buckling ratio of the femoral neck is known to be a risk factor of hip fracture [11]. Although the cortical thickness of the femoral neck in the fracture group was significantly smaller or buckling ratio was greater than that of the control group, the differences were no longer significant when adjusted for BMD derived from DXA, suggesting that cortical thickness and buckling ratio as determined by qCT were mostly affected by areal BMD.

Second, in patients with fragility fractures of the spine or the hip, the 25(OH)D level has been shown to be lower than in healthy controls [12]. Vitamin D has been regarded as important for the development and maintenance of the skeleton [13] and 25(OH)D levels may correlate with BMD. Recently, some investigators reported that 25(OH)D levels in patients with DRFs are lower than that in healthy controls [8,9]. Our finding was consistent with theirs. However, the difference between the groups in our study was marginal (2.7 ng/mL). We are not sure if this difference was clinically important. Measuring circulating vitamin D levels and vitamin D binding protein may help to clarify these points [14,15].

Jang et al. [9] evaluated bone turnover markers in patients with DRFs. They measured osteocalcin, collagen type I cross-linked C-telopeptide (CTX), and NTX, which turned out not to be different from that of the controls. Our results demonstrated that urinary DPD was higher in the fracture group than in the control group even after adjusting for areal BMD, while NTX and TRACP-5b were not different. Similar results (DPD was significant, NTX was not) were also observed

in patients with or without vertebral fractures [12]. DPD is a cross-link of bone collagen, which provides structural stiffness to type I collagen, is excreted unmetabolized in urine, and is a marker of bone resorption and osteoclastic activity. DPD levels have been known to predict osteoporotic fractures of the hip [8] or vertebra [16]. The reasons for the discrepancy between the level of DPD and that of other markers of bone resorption in the current study are unclear, but they can reflect different aspects of bone metabolism.

Advanced glycation end products (AGEs) accumulate in various tissues such as bone [17], cartilage matrix [18], tendon [19], and muscle [20] with increase in age, and can adversely affect the biomechanical properties of such structures [18]. As a result, even patients with normal BMD can have fragility fractures due to poor bone quality [21]. Currently, in clinical practice, serum or urinary pentosidine is the only available surrogate marker for AGEs. We demonstrated that serum and urinary pentosidine was higher in the fracture patients than in the controls, suggesting poor bone quality in the patients with DRF.

The finding that our patients with DRF did not have a decrease in muscle area or increase in fat area could be somewhat inconsistent with the previous studies in which the patients with DRF had a tendency to fall or had balancing inability [22,23]. This could be explained if the muscle function and its cross-sectional area were not always correlated with each other, since muscle dysfunction could occur earlier and not be reflected in the cross-sectional area [24]. Although grip strength in our study was not different between the groups, our results were almost consistent with the recent report, in which overall physical performance level was not different between the patients with DRF and the control [25]. The strong points of this study were as follows. We evaluated the most amount of factors ever tested at the same time, including 12 biochemical markers of bone turnover, as well as BMD, bone structures and skeletal muscles. The patients with fragility DRF in this study did not experience other sites of fragility fractures previously, so that the characteristics of the DRF could be more highlighted.

This study has some limitations. The patients in this study were not representative of all the fragility DRF patients, since they were all referred to our department for the treatment of upper extremity disorders. Furthermore, selection bias of the controls was not ruled out. Since this was a cross-sectional study, the risk of future fragility fractures as well as pre-injury status could not be determined. Finally, balancing ability was not evaluated.

In conclusion, the patients with previous DRFs exhibited lower BMD, which was not accompanied by lower skeletal muscle area or muscle strength. Further, bone metabolism alterations such as low 25(OH)D, high DPD, and high serum and urinary pentosidine levels were also observed in such patients, independent of the areal BMD determined by DXA.

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