A commentary by James F. Kellam, BSc, MD, FRCS(C), FRCSI(Hon), is linked to the online version of this article.

Longitudinal Changes in Serum Markers of Bone Metabolism and Bone Material Strength in Premenopausal Women with Distal Radial Fracture

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Background: Markers of bone metabolism (MBM) play an important role in fracture evaluation, and changes have been associated with increased fracture risk. The purpose of the present study was to describe changes in MBM in premenopausal women with distal radial fractures.

Methods: Premenopausal women with distal radial fractures (n = 34) and without fractures (controls) (n = 39) were recruited. Serum MBM in patients with distal radial fractures were obtained at the time of the initial presentation, 6 weeks, and 3, 6, and 12 months. MBM included 25(OH) vitamin D, PTH, osteocalcin, P1NP, BSAP, CTX, sclerostin, DKK1, periostin, and TRAP5b. Areal bone mineral density (aBMD) was assessed with dual x-ray absorptiometry, and the bone material strength index (BMSi) was assessed with microindentation.

Results: Most MBM reached peak levels at 6 weeks after the injury, including osteocalcin (+17.7%), sclerostin (+23.5%), and DKK1 (12.6%). Sclerostin was lower (−27.4%) and DKK1 was higher (+22.2%) at 1 year after the fracture. CTX declined below baseline levels at 6 and 12 months, whereas TRAP5b, BSAP, and periostin did not significantly change. At 12 months, sclerostin was lower (p = 0.003) and DKK1 was higher (p = 0.03) in the distal radial fracture group than in the control group. Greater fracture severity was associated with greater increases in P1NP and BSAP. aBMD and BMSi were not associated with fracture.

Conclusions: Distal radial fractures caused increases in several MBM, which typically peaked at 6 weeks after injury and gradually decreased over 6 months. Sclerostin and DKK1 remained below and above baseline at 1 year, respectively. Increasing fracture severity resulted in larger changes in MBM. aBMD and BMSi did not discriminate between patients with distal radial fractures and controls. Continued efforts to identify markers of skeletal fragility in young women are warranted to mitigate future fracture risk.

Level of Evidence: Prognostic Level II. See Instructions for Authors for a complete description of levels of evidence.

Fragility fractures pose a substantial economic burden in the United States, with annual costs projected to rise by nearly 50% from 2005 to 2025[1]. While research has focused on the postmenopausal population, fractures in early adulthood may be important predictors of risk of subsequent fracture[2,3]. Recent studies of distal radial fractures in premenopausal women have suggested that these fractures may signify a sentinel event and present a critical opportunity for osteoporosis prevention[4]. However, factors that predispose premenopausal women to distal radial fractures are poorly understood.

Whereas areal bone mineral density (aBMD) as determined with dual x-ray absorptiometry is the clinical standard for the assessment of fracture risk, up to 50% of postmenopausal women with hip and other non-vertebral fractures do not have osteoporosis on aBMD testing[5-7]. Furthermore, BMD does not differentiate between premenopausal women with and without distal radial fractures[4]. As bone strength is also determined by structural and mechanical properties[8], recent efforts have focused on assessing bone structure and strength to improve the prediction of fracture risk[9]. Impact microindentation, a newly

Disclosure: The **Disclosure of Potential Conflicts of Interest** forms are provided with the online version of the article (http://links.lww.com/JBJS/G743).

developed technique that reflects cortical bone material properties at the tibial diaphysis, may reflect fracture risk independent of aBMD on dual x-ray absorptiometry[10]. However, little is known about the ability of impact microindentation to discriminate between premenopausal women with and without distal radial fractures.

Another approach to improving the identification of fracture risk is the assessment of bone metabolism via serum-based biomarkers. While increased markers have been associated with osteoporosis and fractures[11-13], markers are not routinely used for the diagnosis of osteoporosis and do not improve the prediction of fracture risk in postmenopausal women[14,15]. Instead, markers of bone metabolism (MBM) may be useful for monitoring the response to anti-osteoporosis therapies, identifying possible secondary causes of osteoporosis, and monitoring fracture healing[14,15]. The utility of MBM in a younger patient cohort has not yet been established. Although changes in MBM in premenopausal women with distal radial fractures have been reported, it is unclear whether MBM may have been influenced by the fracture itself[16]. It is currently unknown how MBM fluctuate after fracture in premenopausal women and whether changes in these biomarkers are associated with the risk of fracture and/or the trajectory of fracture healing.

The primary aim of the present study was to establish the longitudinal changes in MBM in premenopausal women with distal radial fractures. The secondary aims were to determine whether changes in MBM are influenced by fracture severity, whether these markers differ between patients with fractures and individuals without fractures (controls), and whether aBMD and the cortical bone material strength index (BMSi) can differentiate between patients with fractures and controls. We hypothesized that premenopausal women with distal radial fractures would show elevated levels of MBM in the first 6 weeks after fracture and that changes in MBM would be more pronounced in patients with more severe fractures. We also hypothesized that premenopausal women with distal radial fractures would have a lower BMSi compared with controls.

Materials and Methods

Premenopausal women with and without recent distal radial fractures were recruited between 2017 and 2020 at Beth Israel Deaconess Medical Center (BIDMC) and Brigham and Women's Hospital (BWH) in Boston, Massachusetts. Exclusion criteria for both groups included allergy to lidocaine; the inability to undergo a dual x-ray absorptiometry scan; a history of skeletal metastasis, primary hyperparathyroidism, Paget disease, or multiple myeloma; treatment with estrogen (within 3 years); use of bisphosphonate (within 5 years); use of teriparatide, calcitonin, or selective estrogen receptor modulators (SERMs) (within 3 years); and use of glucocorticoids or anticonvulsants continuously for >3 months.

Subject Recruitment

Women <50 years of age with distal radial fractures were identified from the orthopaedic clinic. A control group of women <50 years of age with no prior fractures in adulthood (controls) was recruited from the greater Boston community. The study protocol was approved by the institutional review boards of BIDMC and BHW, and all subjects provided informed written consent prior to screening and participation. Our cohort consisted of 34 patients with distal radial fractures and 39 controls (Fig. 1).

Cortical Bone Tissue Properties by Reference Point Indentation

We used impact microindentation (OsteoProbe RUO; Active Life Scientific) to measure BMSi at the anterior surface of the middle of the tibial diaphysis[17]. We measured the non-dominant tibia for all participants according to a previously described technique[18]. The test probe was inserted to rest on the anterior bone surface, where a 40-N impact force was applied to achieve 10 measurements, each separated by at least 2 mm. Measurements that were classified as "poorly performed" (e.g., because of probe malpositioning or leg movement) were excluded. After 10 acceptable indentations, 5 indentations were performed on a polymethylmethacrylate calibration phantom. BMSi was computed as 100 times the harmonic mean of the indentation distance into polymethylmethacrylate, divided by the average indentation distance into the bone. A higher indentation distance into the bone leads to a lower BMSi measurement. All BMSi measurements were carried out by 1 of 2 investigators trained in the technique.

Bone Mineral Density by Dual X-Ray Absorptiometry

aBMD (g/cm^2) of the femoral neck, total hip, lumbar spine, and distal one-third of the radius were measured with dual x-ray absorptiometry (Horizon and Discovery; Hologic).

Blood Samples and MBM

Serum MBM in patients with distal radial fractures were obtained at the time of initial presentation (0 to 32 days after the fracture) and then at approximately 6 weeks (range, 4.4 to 9.6 weeks), 3 months (range, 11 to 19.7 weeks), 6 months (range, 25.9 to 39.1 weeks), and 12 months (range, 40.9 to 66.6 weeks) after the fracture. Serum samples from the controls were obtained once, at the time of initial enrollment. We measured bone formation markers, including N-terminal extension propeptide of type-I collagen (P1NP), bone-specific alkaline phosphatase (BSAP), and osteocalcin, as well as bone resorption markers, including C-terminal telopeptide of type-I collagen (CTX) and tartrate-resistant acid phosphatase (TRAP5b), a marker of osteoclast number. We also measured sclerostin and Dickkopf 1 (DKK1), which inhibit Wnt signaling and thereby bone formation[12], and periostin, a new biomarker with pleiotropic effects in bone[19].

All blood samples were obtained in the morning after an overnight fast to reduce the effects of diurnal variation and feeding and were stored at −70°C until assayed. Assays were analyzed in batches at Maine Medical Center Research Institute use of the iSYS automated immunoassay system (Immunodiagnostics Systems [IDS]) as follows: 25(OH)D (IDS-iSYS VitD^s assay), P1NP (IDS-iSYS Intact amino-terminal P1NP assay), BSAP (IDS-iSYS Ostase assay), sclerostin (Quantikine Human SOST Immunoassay), CTX (CrossLaps), TRAP5b (IDS-iSYS BoneTRAP assay), periostin (Reagent Diluent DuoSet ELISA assay; R&D Systems), osteocalcin (IDS-iSYS N-Mid Osteocalcin

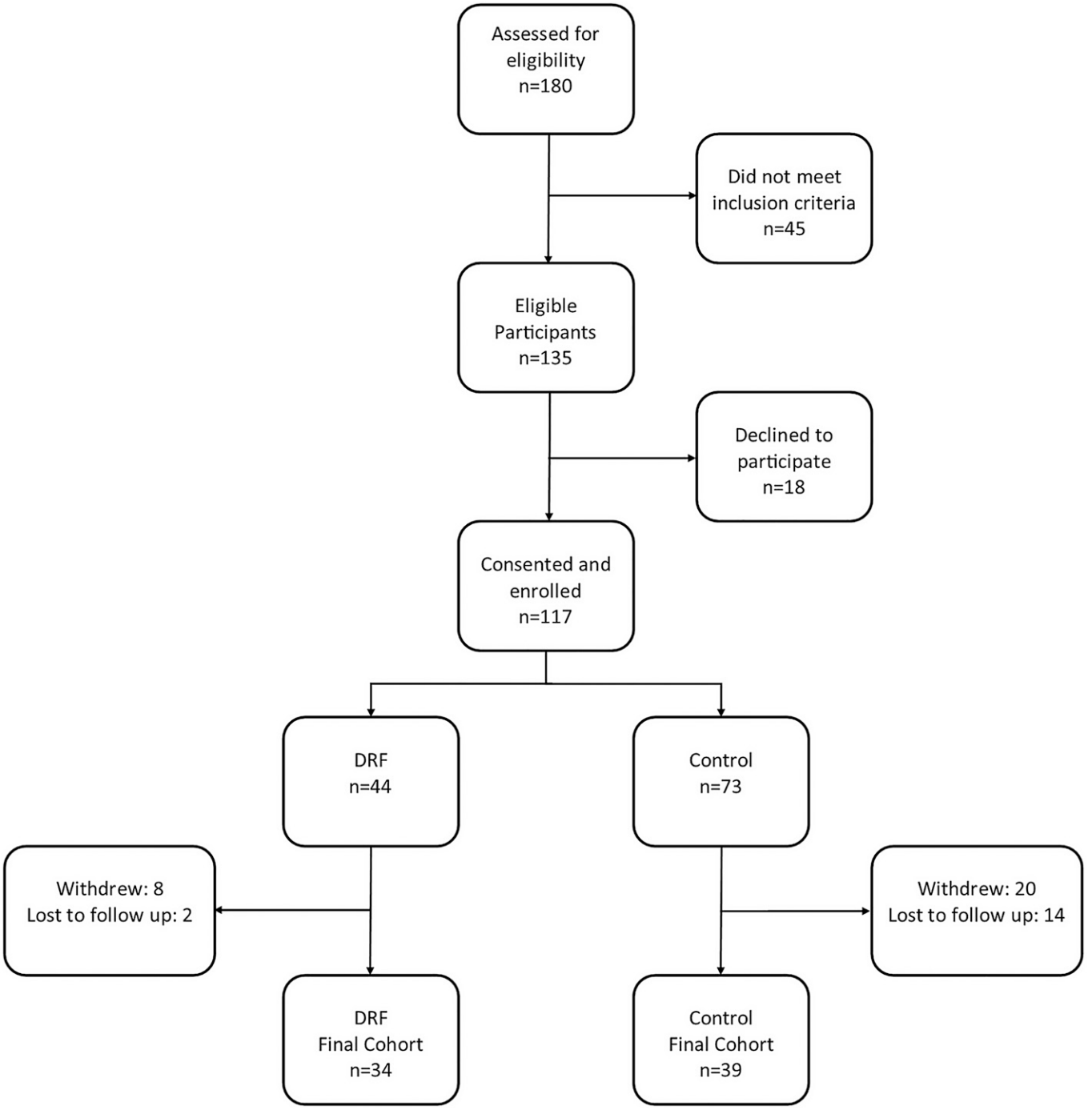

Fig. 1
Overview of study design. DRF = distal radial fracture.

assay), and intact PTH (parathyroid hormone) (IDS-iSYS intact PTH assay). Intra-assay variability for vitamin D, P1NP, BSAP, OC, PTH, CTX, and sclerostin were 4%, 2.9%, 1.6%, 2.5%, 2.7%, 3.2%, and 2%, respectively.

Other Clinical Data

We measured each participant's weight with use of a calibrated scale and height with use of a stadiometer. Fracture severity was assessed on the initial radiographs according to the OTA/AO classification system[20]. Type-A1, A2, B1, B2 and C1 fractures were classified as non-severe (n = 13), whereas type-A3, B3, C2, and C3 fractures were classified as severe (n = 21). Twenty patients had low-energy mechanisms of injury, and 14 patients had high-energy mechanisms of injury. Fifteen patients were managed with a cast, and 19 underwent open reduction and internal fixation (ORIF) with a volar plate.

Statistical Analysis

Standard descriptive statistics are reported, with use of the mean and standard deviation (SD) or the median and interquartile range (IQR) for continuous variables and with use of counts and proportions for categorical variables. Groups were compared with use of the 2-sample t test for continuous variables, the chi-square test for categorical variables, and the Wilcoxon rank sum test for non-normally distributed variables. MBM were reported as absolute values and relative concentrations from the first visit. The Skillings-Mack test was used to detect whether MBM significantly changed during the course of the study. The paired Wilcoxon rank sum test was used to assess differences from visit 1. A robust locally weighted polynomial regression (LOESS smoothing) was used to visualize MBM as a function of time from fracture. In a subanalysis, differences in changes in MBM from visit 1 to visit 2 between fracture severity groups were evaluated with use of the Kruskal-Wallis test. All analyses were performed with use of R (version 3.6.0; R Foundation for Statistical Computing), and the level of significance was set at $p < 0.05$. The study had >80% power to detect longitudinal changes of >10% of the assay variability in osteocalcin, sclerostin, and DKK1 between visit 1 and visit 2 with an alpha level of 0.05.

Source of Funding

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Results

The women who enrolled in the study were predominantly white, with mean age of 33.2 ± 7 years and a mean body mass index (BMI) of 26.6 kg/m^2 (IQR, 22.5 to 31 kg/m^2) (Table I). The patients with distal radial fractures had a slightly lower BMI but otherwise did not differ from the controls, including in terms of

TABLE I Demographic, Lifestyle, and Bone Characteristics of Premenopausal Women with Distal Radial Fracture and No History of Fracture

	Distal Radial Fracture Group (N = 34)	Control Group (N = 39)	P Value
Age* *(yr)*	32.2 ± 7.2	33.2 ± 7.0	0.55
Race *(no. of participants)*			0.28
White	26 (76.5%)	28 (71.8%)	
Black	1 (2.9%)	5 (12.8%)	
Other†	7 (20.6%)	6 (15.4%)	
BMI† *(kg/m^2)*	24.4 (21.6, 27.1)	26.6 (22.5, 31.0)	0.06
Dietary calcium intake† *(mg)*	820 (485, 1,100)	739 (553, 1,067)	0.77
25-hydroxy vitamin D* *(ng/mL)*	27.5 ± 10.2	27.2 ± 9.3	0.88
Parathyroid hormone* *(pg/mL)*	40.0 ± 16.8	39.8 ± 12.8	0.96
Smoking, current *(no. of participants)*	0 (0%)	4 (10%)	0.17
Alcohol *(no. of participants)*			0.09
None	9 (26%)	15 (38%)	
1-3 drinks per week	19 (56%)	12 (31%)	
4-14 drinks per week	6 (18%)	12 (31%)	
Severe fracture *(no. of participants)*			
Yes	21 (62%)	—	—
No	13 (38%)	—	—
Fracture management *(no. of participants)*			
Open reduction and internal fixation	19 (56%)	—	—
Closed	15 (44%)	—	—
aBMD*§ *(g/cm^2)*			
Lumbar	1.01 ± 0.10	1.05 ± 0.10	0.10
Distal radius	0.59 ± 0.05	0.60 ± 0.04	0.39
Femoral neck	0.82 ± 0.11	0.85 ± 0.12	0.37
Total hip	0.94 ± 0.09	0.98 ± 0.13	0.19
BMSi*#	73.5 ± 11.4	73.4 ± 13.0	0.97

*The values are given as the mean and the standard deviation. †Other = Asian or Pacific Islander, Hispanic, and other. ‡The values are given as the median and the interquartile range. §aBMD = areal bone mineral density on dual x-ray absorptiometry. #BMSi = bone material strength index by impact microindentation.

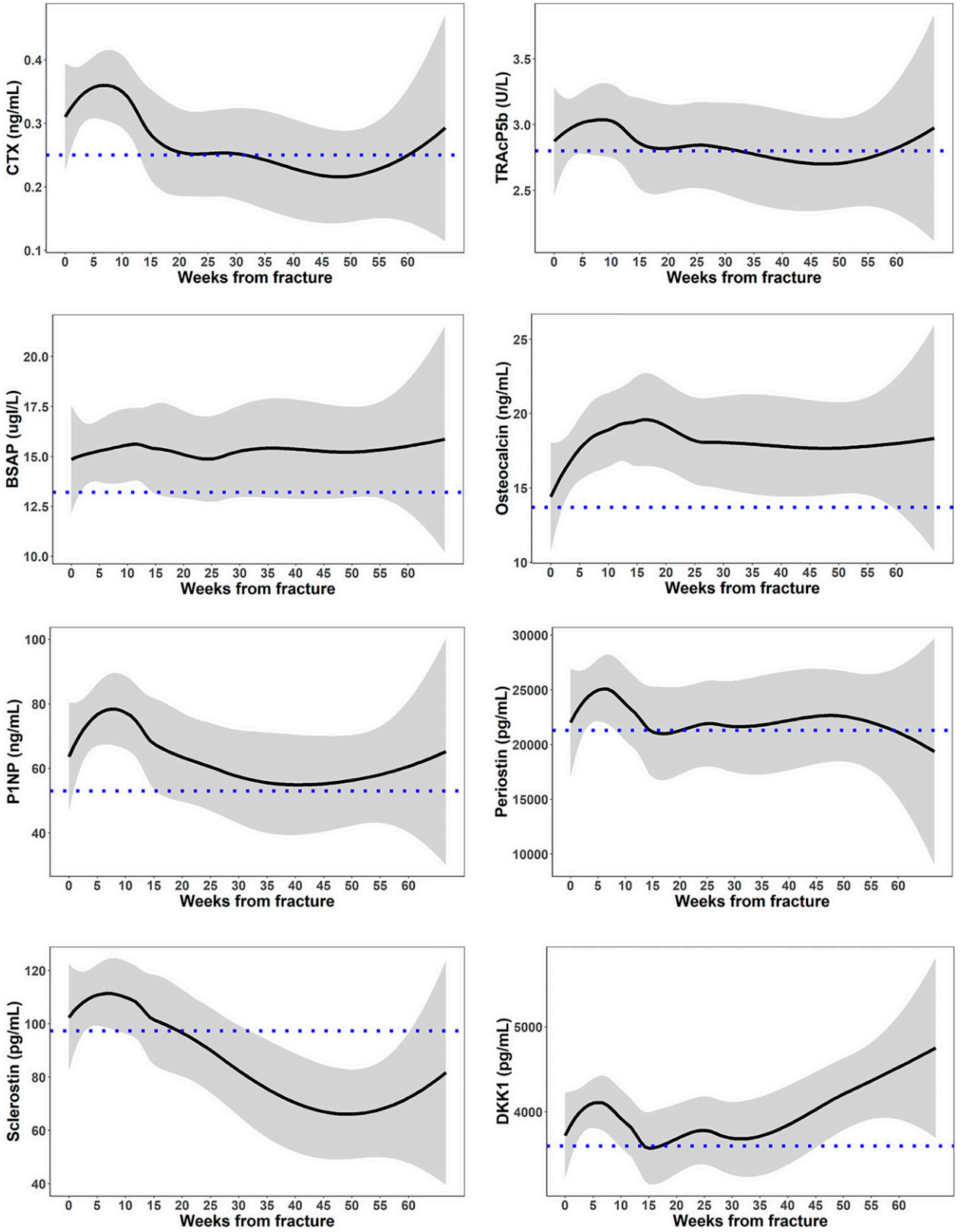

Fig. 2

Serum markers of bone metabolism up to 1 year after distal radial fracture. The solid black line is the LOESS curve fit, and the shaded region represents the 95% confidence interval. The horizontal dotted blue line represents the median value for the control group.

TABLE II Median Percent Change in Serum Markers of Bone Metabolism in Women with Distal Radial Fracture*

	Percent Change from Baseline			
	Visit 2 (~6 Weeks Post-Fracture)	Visit 3 (~14 Weeks Post-Fracture)	Visit 4 (~28 Weeks Post-Fracture)	Visit 5 (~55 Weeks Post-Fracture)
CTX	−1 (−14.8, 59)	−5.5 (−25.3, 9.4)	**−15.7** (−25, 6.6)	**−41.0** (−56.8, 2.1)
Osteocalcin	**17.7** (−3.4, 32.9)	**17.4** (3.2, 38.7)	**12.6** (3.5, 24.5)	7.4 (−4.4, 21.2)
BSAP	2.1 (−6.0, 17.3)	−3.6 (−8.15, 14.6)	−0.6 (−11.4, 18.0)	−3.8 (−11.9, 13.0)
P1NP	7.25 (−16.6, 40.1)	3.3 (−12.3, 28.8)	−11.4 (−35.1, 22.4)	−8.1 (−28.6, 1.12)
TRAP5b	−6.6 (−15.6, 17.3)	−3.05 (−20.3, 14.2)	−4.3 (−13.1, 7.1)	−15.3 (−24.8, 6.7)
Periostin	7.6 (−10.2, 21.3)	−10.2 (−21.2, 18.1)	−3.2 (−16.2, 4.2)	−5.4 (−10.6, 14.2)
Sclerostin	**23.5** (−1.4, 48.9)	5.0 (−8.1, 28.5)	**−13.0** (−33, 0.5)	**−27.4** (−41.9, −6.6)
DKK1	**12.6** (−23.6, 27.3)	−8.4 (−46.5, 8.2)	−1.2 (−21.0, 16.7)	**22.2** (−39.3, 36.9)

*The values are presented as the median, with the interquartile range in parentheses. Bold values were significantly different from baseline (visit 1) ($p < 0.05$).

dietary calcium intake and baseline levels of 25(OH)D and PTH. BMD at the lumbar spine, femoral neck, total hip, and radius was similar between the groups. BMSi by impact microindentation was also similar between the groups (73.5 versus 73.4) (Table I).

Changes in MBM Following Distal Radial Fracture

MBM were measured at 5 different time points. The median time from fracture for each visit was 1.4 weeks (IQR, 0.6 to 2.6 weeks) for visit 1, 6.1 weeks (IQR, 5.6 to 7.0 weeks) for visit 2, 13.6 weeks (IQR, 12.2 to 15.2 weeks) for visit 3, 27.7 weeks (IQR, 26.7 to 28.5 weeks) for visit 4, and 54.8 weeks (IQR, 52.5 to 57.3 weeks) for visit 5.

Qualitatively, most MBM reached peak levels approximately 6 weeks after the injury (Fig. 2). Several markers increased significantly at 6 weeks (visit 2) compared with the baseline visit, including osteocalcin (+17.7%), sclerostin (+23.5%), and DKK1 (+12.6%) (Table II). Osteocalcin remained significantly elevated through approximately 6 months after the fracture (visit 4) and then returned to baseline levels. Sclerostin showed a different pattern, with levels declining continuously after visit 2 and remaining significantly below the baseline visit at 6 months (−13%) and 1 year (−27.4%) after the fracture. DKK1 increased initially, returned to baseline levels at visits 3 and 4, and was significantly higher than baseline (+22.2%) at 1 year. CTX levels were unchanged through visit 3 and then declined below baseline levels at 6 and 12 months. TRAP5b, BSAP, and periostin did not significantly change up to 1 year after fracture (Fig. 2 and Table II).

Comparison of MBM in Distal Radial Fracture Versus Control

At the baseline visit, MBM were similar in the distal radial fracture and control groups. However, at visit 2 (~6 weeks after fracture), patients with distal radial fractures had significantly higher CTX (+20%), P1NP (+34%), and DKK1 (+15%) than controls (Table III). At 6 (visit 4) to 12 months (visit 5) after fracture, MBM were generally similar in both groups (Table III). However, at 1 year post-fracture (visit 5), patients with distal

TABLE III Serum Markers of Bone Metabolism at Each Visit for Distal Radial Fracture Group and at Baseline for Control Group*

	Distal Radial Fracture Group					
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Control Group
CTX *(ng/mL)*	0.32† (0.18, 0.44)	**0.30**† (0.21, 0.49)	0.26 (0.18, 0.35)	0.26 (0.15, 0.32)	0.19 (0.10, 0.32)	0.25 (0.14, 0.31)
Osteocalcin *(ng/mL)*	14.6 (10.5, 21.9)	15.1† (12.2, 23.0)	**18.1**† (12.1, 24.5)	15.0 (13.4, 23.4)	17.5† (11.7, 24.1)	13.7 (10.0, 18.1)
BSAP *(μg/L)*	14.0 (12.4, 16.6)	14.3 (12.7, 16.9)	13.8 (12.6, 16.3)	14.8 (12.9, 16.5)	14.0 (12.6, 15.5)	13.2 (11.2, 18.3)
P1NP *(ng/mL)*	62.1 (44.0, 83.2)	**71.0**§ (53.4, 88.9)	60.4 (47.0, 81.9)	49.7 (36.6, 77.6)	54.2 (43.7, 70.6)	53.0 (35.6, 69.4)
TRAcP5b *(U/L)*	2.8 (2.5, 3.5)	2.9 (2.4, 3.3)	2.7 (2.4, 3.2)	2.7 (2.2, 3.3)	2.7 (2.6, 3.1)	2.8 (2.3, 3.7)
Periostin *(ng/mL)*	19.8 (15.4, 28.3)	24.4 (17.7, 28.5)	20.2 (16.0, 26.7)	21.5 (16.2, 23.0)	20.4 (17.6, 25.4)	21.3 (13.3, 28.9)
Sclerostin *(pg/mL)*	91.7 (72.2, 115.3)	125.8 (75.1, 153.2)	95.6 (84.6, 118.0)	83.0 (50.8, 113.8)	**63.7**§ (53.8, 77.6)	97.3 (66.3, 137.1)
DKK1 *(pg/mL)*	3,779 (3,075, 4,186)	**4,138**§ (3,677, 5,241)	3,349 (2,964, 4,130)	3,597 (3,104, 4,252)	**4,032**† (3,662, 5,085)	3,599 (2,768, 4,258)

*The values are given as the median, with the interquartile range in parentheses. Bold values were significantly different from the value in the control group ($p < 0.05$). †$P < 0.10$. ‡$P < 0.05$. §$P < 0.01$.

TABLE IV Percent Change in Serum Markers of Bone Metabolism from Visit 1 to Visit 2 by Fracture Severity*

	Not Severe	Severe	P Value
CTX	−1.6 (−15.7, 26.2)	4.5 (−11.9, 68.7)	0.51
Osteocalcin	3.9 (−3.5, 28.8)	24.9 (−2, 33.9)	0.21
BSAP	−3.7 (−9.7, 2.3)	9.2 (−3.9, 27.7)	**0.03**
TRAP5b	−9.6 (−16.3, 12.5)	0.5 (−13.9, 20.0)	0.44
P1NP	−10.4 (−16.6, 9.2)	26.7 (−12.9, 52.0)	**0.05**
Periostin	−1.4 (−16.4, 15.6)	12.4 (−8.3, 25)	0.13
Sclerostin	32.1 (21.2, 63.4)	16.5 (−10.4, 39.9)	0.17
DKK1	11.3 (0.2, 16.7)	16.7 (−2.5, 31.1)	0.53

*The values are given as the median, with the interquartile range in parentheses. Bold values indicate that the fracture severity groups were significantly different from each other.

TABLE V Percent Change in Serum Markers of Bone Metabolism from Visit 1 to Visit 2 by Mechanism of Injury*

	Low-Energy	High-Energy	P Value
CTX	5.7 (−9.0, 60.5)	−1.9 (−17.0, 41.6)	0.46
Osteocalcin	3.9 (−6.2, 28.0)	29.1 (1.9, 34.9)	0.14
BSAP	−2.8 (−8.8, 8.6)	3.2 (−3.4, 24.2)	0.19
TRAP5b	−8.4 (−15.5, 17.0)	−4.2 (−14.6, 17.1)	0.89
P1NP	−11.4 (−17.0, 19.0)	32.6 (−7.0, 56.7)	0.062
Periostin	15.0 (−8.3, 31.0)	−5.3 (−13.6, 19.1)	0.35
Sclerostin	33.6 (14.1, 59.6)	11.0 (−12.5, 34.3)	0.079
DKK1	12.9 (1.5, 20.8)	12.3 (−0.2, 29.9)	0.92

*The values are given as the median, with interquartile range in parentheses.

radial fractures had lower levels of sclerostin ($p = 0.003$) and higher levels of DKK1 ($p = 0.03$) than controls.

Changes in MBM by Fracture Severity

To examine whether fracture severity influenced early changes in markers of bone metabolism, we compared bone marker changes in women with severe fractures (AO types A3, B3, C2, and C3) and non-severe fractures (AO types A1, A2, B1, B2 and C1) (Table IV). For most markers, the change from baseline to visit 2 (6 weeks after fracture) did not differ by fracture severity. However, BSAP and P1NP increased significantly more in women with severe fractures than in those with non-severe fractures. The change from baseline to visit 2 did not differ by mechanism of injury (Table V) or by treatment except for BSAP, which increased more in women managed with ORIF (Table VI).

Discussion

The present study provides the first longitudinal assessment of serum MBM in premenopausal women with distal radial fractures. We demonstrated that several MBM increased significantly after fracture, peaking at approximately 6 weeks after injury and generally returning to baseline by 6 months. In contrast, serum sclerostin increased initially after injury and then remained lower than baseline and control values at 1 year, whereas DKK1 increased initially, declined, and then remained higher than baseline and control values at 1 year.

While the dynamic nature of changes in MBM following fracture is not completely understood, other studies have demonstrated similar patterns[21]. The Osteoporosis Population-Based Risk Assessment study (OPRA) showed significant elevations at 4 months after low-energy fractures, particularly in markers of bone formation[22]. This increase was more pronounced after hip fracture than after wrist fracture and persisted for a year after injury. Other studies have focused on elderly patients with operatively treated hip fractures and have shown that P1NP and CTX peaked 30 to 60 days after surgery and that P1NP demonstrated the greatest increase[23].

The present study is unique in assessing the values of periostin, sclerostin, DKK1, and TRAP5b in premenopausal women with distal radial fractures. Periostin is expressed in osteoblasts and is found in high concentrations within periosteum. The precise role of periostin in bone metabolism is under investigation, but mice lacking periostin have been shown to exhibit dwarfism and reduced bone mass[24] and periostin mRNA has been shown to be upregulated following long-bone fractures[25]. Changes in serum periostin after skeletal injury depend on the type of injury: in 1 study, levels increased after long-bone fracture but were relatively stable following small-bone fractures, suggesting that more severe injuries were associated with a longer duration of detectable increases[26]. Serum periostin also has been reported to increase in the first weeks after hip fracture, declining to baseline values within a few months[27]. In the current study, we did not see significant changes in periostin, perhaps because of the nature of the injury.

TABLE VI Percent Change in Serum Markers of Bone Metabolism from Visit 1 to Visit 2 by Treatment*

	Cast	ORIF	P Value
CTX	−1.6 (−13.4, 60.0)	4.5 (−13.8, 22.8)	0.76
Osteocalcin	3.9 (1.2, 33.2)	24.9 (1.2, 33.2)	0.20
BSAP	−3.7 (−11.5, 2.0)	10.9 (−2.3, 29.4)	**0.007**
TRAP5b	−6.8 (−15.3, 15.4)	−6.10 (−15.0, 26.0)	0.76
P1NP	−9.8 (−15.6, 15.1)	34.1 (−12.0, 46.4)	0.068
Periostin	7.6 (−14.6, 16.1)	3.2 (−8.3, 29.0)	0.25
Sclerostin	32.1 (16.5, 57.1)	16.5 (−7.3, 37.3)	0.21
DKK1	6.0 (−4.6, 13.7)	19.5 (−18.3, 36.4)	0.063

*The values are given as the median, with the interquartile range in parentheses. Bold value indicates that the fracture severity groups were significantly different from each other.

Sclerostin (a glycoprotein produced by osteocytes) and DKK1 inhibit Wnt signaling, thereby inhibiting bone formation. Genetic deletion of sclerostin has been shown to increase bone formation and bone mass in rodents and humans[28-30], and inhibition has been shown to improve long-bone fracture-healing[31,32]. Treatment of osteoporotic postmenopausal women with romosozumab (an anti-sclerostin monoclonal antibody) has been shown to increase aBMD and to reduce fracture risk[33,34]. In the present study, sclerostin increased initially but then decreased and remained at lower levels in patients than in controls, perhaps permitting bone formation in association with callus formation and remodeling. In comparison, DKK1 increased early after the injury, declined to baseline, and then increased at the end of the observation period. Although speculative, this latter increase in DKK1 may reflect a compensatory increase following decreased levels of sclerostin. Further studies are needed to elucidate the temporal nature and biological relevance of sclerostin and DKK1 changes during fracture healing.

Tartrate resistant acid phosphatase (TRAP5b) is a marker of osteoclast activity. Stoffel et al. showed that TRAP5b increased following surgical fixation of ankle and tibial fractures, peaking between 7 and 14 days, with a second smaller increase around 6 weeks[35]. Fractures in larger bones (tibial shaft) resulted in greater TRAP5b increases than fractures of smaller bones (malleolus). The authors hypothesized that this finding was due to larger fracture areas requiring more extensive bone remodeling[35]. In our distal radial fracture cohort, TRAP5b peaked once at approximately 6 weeks and was similar to that in controls by 6 months after injury.

Greater fracture severity was associated with greater increases in some MBM, particularly for markers of bone formation such as P1NP and BSAP. It is possible that additional associations between fracture severity and MBM would have been detected in a larger cohort. To date, the evidence examining the relationship between MBM and fracture severity is limited[36]. Zhao et al. did not detect any differences in MBM between patients with severe and less-severe hip fractures[37]. It is possible that a more robust change in MBM may be associated with a better healing response, whereas smaller changes after injury could predict poor healing. While we could not demonstrate this in the present study—indeed, distal radial fractures are rarely characterized by delayed union or nonunion—further research could elucidate whether MBM can be useful predictors of clinical and radiographic outcomes[38-41].

Consistent with the findings of previous reports[4,16], aBMD was not associated with fracture in our cohort of premenopausal patients with distal radial fractures. Similarly, BMSi did not discriminate between patients with distal radial fractures and controls. Prior work involving postmenopausal women has revealed slightly lower BMSi in patients with distal radial fractures compared with controls without fractures, independent of age, BMI, and femoral neck aBMD[42]. We were not able to establish similar differences in a younger population, and it seems likely that BMSi is not valuable for discriminating fracture risk in these younger women.

The present study had several limitations. Because of the acute nature of the event, we did not have data on MBM before distal radial fracture. Although we recruited similar controls, this limitation prevented us from definitively determining whether MBM are independent predictors of fracture risk. In addition, there was some variation in how many days after injury patients underwent blood draws, depending on the initial presentation to the orthopaedic clinic. This variability prevented us from identifying more subtle changes in MBM in the first few days after fracture. Indeed, in prior studies, bone turnover markers were already elevated 2 weeks after fracture[22,43], and some MBM may have changed in the initial weeks prior to the patients' first clinic visit. Thus, we may be underestimating the true changes from the pre-fracture status. Similarly, controls provided serum samples at a single time point, and fluctuations over time were not addressed. While we examined many MBMs, our study may have been insufficiently powered to detect changes in all of them, and larger studies will be important for corroborating our findings. Furthermore, data on the clinical meaningful change in MBM in the premenopausal population are currently limited. Last, our study included largely Caucasian women, and further research is needed before generalizing the results.

In conclusion, distal radial fractures result in increases in several MBM, typically peaking at 6 weeks and gradually decreasing over 6 months. While increasing initially, serum sclerostin then decreased again and remained below control values even 6 to 12 months after fracture. Increasing fracture severity resulted in larger changes in MBM. Establishing patterns of MBM changes in young women may prove useful for understanding fracture healing. aBMD by dual x-ray absorptiometry and BMSi did not discriminate distal radial fracture cases from controls. Continued efforts to identify markers of skeletal fragility in young women are warranted to mitigate future fracture risk. ■

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