EDITOR'S CHOICE

Elevated Bone Turnover Markers Are Associated With Distal Radius Fractures in Premenopausal Women

Beverlie L. Ting, MD,* Kempland C. Walley, BSc,† Thomas G. Travison, PhD,‡ Tamara D. Rozental, MD†

Purpose To examine whether premenopausal women with distal radius fractures (DRF) have lower levels of 25-hydroxyvitamin D (25[OH]D) and increased levels of serum bone turnover markers (BTM) compared with control subjects without fracture.

Methods Premenopausal women with DRF (n = 20) were prospectively enrolled and compared with age-matched individuals without a fracture (n = 20). Outcome measures included serum levels of 25(OH)D, parathyroid hormone (PTH), markers of bone formation (osteocalcin [OC], N-terminal extension propeptide of type I collagen [P1NP], and bone-specific alkaline phosphatase [BSAP]), and markers of bone resorption (C-terminal telopeptide of type I collagen [CTX]). We assessed associations between BTM and DRF with conditional logistic regression and the utility of markers for fracture prediction with a receiver operator characteristic analysis.

Results The fracture group and control group were comparable in terms of age at menarche and BMI. Patients who had fractures had significantly greater levels of OC and P1NP, and demonstrated a nonsignificant increase in CTX. Levels of 25(OH)D, PTH, and BSAP were similar between groups. Conditional logistic regression revealed independent associations between DRF and increased levels of OC and CTX. Levels of 25(OH)D and PTH were not associated with DRF. Receiver operator characteristic analyses demonstrated moderate performance for OC, P1NP, BSAP, and CTX in predicting DRF.

Conclusions Levels of 25(OH)D were not associated with DRF in premenopausal women. However, patients with DRF had increased levels of BTM of formation and resorption. Bone turnover markers may be helpful in predicting future fragility fractures in premenopausal women. *(J Hand Surg Am. 2017;42(2):71–77. Copyright © 2017 by the American Society for Surgery of the Hand. All rights reserved.)*

Type of study/level of evidence Prognostic II.

Key words Bone turnover markers, distal radius fracture, fragility fractures, osteoporosis, vitamin D.

*From the *Seattle Hand Surgery Group, Seattle, WA; the †Department of Orthopaedic Surgery, and the ‡Division of Gerontology, Beth Israel Deaconess Medical Center, Boston, MA.*

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Corresponding author: Tamara D. Rozental, MD, Department of Orthopaedic Surgery, Beth Israel Deaconess Medical Center, 330 Brookline Avenue, Stoneman 10, Boston, MA 02215; e-mail: trozenta@bidmc.harvard.edu.

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Fragility fractures pose a significant economic burden in the United States, with annual costs projected to rise by nearly 50% over the 20 years between 2005 and 2025.[1] Most of the literature on fragility fractures has focused on the postmenopausal population; however, bone loss begins once peak bone mass is attained in early adulthood, and recent research demonstrated that fractures in early adulthood may be important predictors of patients at risk for subsequent fragility fractures.[2–4]

Distal radius fractures (DRF) in particular have been shown to be predictive of future osteoporotic fractures in both younger and older cohorts of postmenopausal patients.[5] Furthermore, recent studies in premenopausal women with DRF demonstrated poorer bone microarchitecture compared with control subjects without fracture.[6] As such, DRF may be helpful markers of skeletal fragility in those at risk for future fracture.

Fracture risk assessment is currently based on bone mineral density measurements with Dual Energy X-ray Absorptiometry; however recent evidence suggests that this test alone does not always predict fracture risk accurately. In one study, 56% of postmenopausal women with a nonvertebral fragility fracture did not have osteoporosis confirmed by bone mineral density testing.[7] These findings have stimulated ongoing efforts to find improved means of identifying patients at risk for fragility fractures. Bone turnover markers (BTM) and 25(OH) vitamin D (25[OH]D) levels have been studied in postmenopausal women and found to be important predictors of bone mass.[8] Although the definition of vitamin D deficiency varies, 25(OH)D levels less than 20 ng/mL are associated with increased risk of distal radius fracture in postmenopausal women.[9–11] However, few studies have examined BTM and 25(OH)D levels in premenopausal patient cohorts.[9,12–15]

The purpose of our pilot study was to examine 25(OH)D and BTM in premenopausal women with DRF and nonfracture control subjects. We hypothesized that premenopausal women with DRF would have low levels of 25(OH)D and elevated levels of serum BTM compared with an age-matched cohort without fractures.

MATERIALS AND METHODS

Patient identification

After we obtained institutional review board approval, we prospectively enrolled consecutive premenopausal women aged 18 to 50 years, who presented to a Level 1 trauma center in Boston, Massachusetts, with an isolated DRF between May 2014 and August 2015. Patients were enrolled in the outpatient clinics in the Department of Orthopaedic Surgery. Inclusion criteria included premenopausal women with a history of a fracture of the distal end of the radius within 3 months of presentation. As in prior studies, both low-energy falls (fall from standing; n = 6) and high-energy injuries (falls from greater than a standing height, motor vehicle accidents, and sporting injuries, n = 14) were included.[6,16,17] Exclusion criteria included current pregnancy; history of endocrinopathy (insulin-dependent diabetes mellitus or thyroid disease) or metabolic bone disease (osteomalacia, Paget disease, or primary hyperparathyroidism); corticosteroid use or immunosuppressive medications; current treatment with hormone replacement therapy, bisphosphonates, parathyroid hormone, selective estrogen receptor modulators, or aromatase inhibitors; eating disorders; and prior fracture in adulthood. Age-matched control subjects with no history of fracture in adulthood were also simultaneously recruited from outpatient clinics. Age-matched control subjects were matched by season of injury (blood draw sampled within 3 months of study subject blood draw) to minimize the effects of seasonal variations on 25(OH)D and BTM. Patients evaluated in clinic for nonfracture diagnoses such as carpal tunnel syndrome, overuse injuries, and ganglion cysts were eligible for inclusion as control subjects. All participants provided written informed consent before study procedures.

At the time of enrollment, information was recorded regarding history of fractures, reproductive and menstrual history (including contraceptive pill use), smoking, alcohol and caffeine intake, physical activity (inactive, moderately inactive, moderately active, or active), and use of calcium and vitamin D supplements, using standardized questionnaires. Weight was measured on a calibrated scale and height was measured using a stadiometer.

Vitamin D levels and BTM

At the 3-month follow-up visit, patients who met the inclusion criteria underwent a morning fasting blood draw.[18] To measure whether vitamin D deficiency is associated with fracture, we analyzed 25[OH]D levels, which are considered the most accurate measure of vitamin D status.[19] Serum parathyroid hormone (PTH) was also collected to identify secondary hyperparathyroidism associated with vitamin D deficiency.[10] Bone formation markers including N-terminal extension propeptide of type I collagen