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Underestimated Fracture Probability in Patients with Unilateral Hip Osteoarthritis as Calculated by FRAX®

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Abstract

Osteoporosis (OP) and osteoarthritis (OA) are age-related diseases often considered to be mutually exclusive. We previously found that 25% of women with advanced OA had occult OP, and that femoral neck (FN) bone mineral density (BMD) T-scores were significantly higher for osteoarthritic vs. contralateral hips. The FRAX® calculator incorporates clinical risk factors and FN BMD T-score to estimate 10-year total fracture probability and hip fracture probability. In 35 women and men 41 years with unilateral hip OA scheduled for hip replacement, we tested whether FRAX® fracture probability is underestimated when using data for the OA rather than the contralateral hip. There were between-hip differences for FN BMD T-score ($p < 0.0001$), total fracture probability ($p = 0.0004$), and hip fracture probability ($p = 0.0009$). Use of FN BMD T-scores resulted in OP treatment recommendations for 0% and 11% of subjects compared with 11% and 17% for total fracture probability and hip fracture probability, respectively. In 6–11% of subjects in this series, the FRAX® calculator underestimated fracture probability with data for the OA hip. With the increased use of FRAX® in clinical use, these data suggest that measurement of BMD at the contralateral hip may yield higher calculated FRAX® total and hip fracture probabilities.

Keywords

FRAX®; Osteoarthritis; Osteoporosis; Hip Fracture; Total Fracture; BMD

Introduction

Osteoarthritis (OA) is an age-related degenerative disease of articular cartilage that is associated with changes in adjacent bone including osteophytes and subchondral sclerosis (1, 2, 3, 4, 5, 6, 7). Worldwide estimates suggest that 10% of men and 18% of women 60 years of age have symptomatic osteoarthritis (OA) (8). Like OA, the prevalence of OP increases with age. OP is characterized by low bone mass and deterioration of bone microarchitecture, with an increase in skeletal fragility and fractures. An estimated 200 million adults worldwide have osteoporosis, and 40% of women and 20% of men 50 years

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and older are expected to develop an osteoporotic fracture in their remaining lifetime (9). OA and OP were thought to be mutually exclusive diseases in which the presence of OA protected against OP (10, 11) and risk of fractures (12, 13). Other authors found an increased risk of fractures in subjects with hip OA and suggested that this was due to OA causing an increased risk of falls (14).

In a study of bone mineral density (BMD) in post-menopausal women scheduled for hip arthroplasty due to advanced OA, we found that 25% of these women had occult OP, as defined by a T-score at any site of -2.5 or lower (15). They also had significantly elevated markers of bone turnover. A further analysis of the characteristics in study subjects showed that those with both OA and OP had significantly lower body weight and BMI, and were older than those without OP (16). Subsequent reports confirmed that 20% to 29% of men and women with advanced OA have occult OP (17, 18, 19).

In an analysis of another series of women and men scheduled for hip replacement due to advanced unilateral OA, we tested whether hip BMD measures were confounded by the presence of OA compared with the contralateral hip (20). The femoral neck (FN) BMD and T-score for the OA hip were significantly higher than for the contralateral hip. In that series of 34 subjects, there were 12 (35%) whose FN BMD T-scores for the OA hip were in the normal range, but for whom the contralateral hips were classified as osteopenic or osteoporotic (20). Data from all subjects in the previous analysis, for whom we had complete data for FRAX[®], were included in this analysis of the impact of discordance on calculations of fracture probabilities (Figure I).

This study is an analysis of the clinical impact of BMD discordance in unilateral hip OA on assessments of fracture probability and on OP treatment decisions with the FRAX[®] calculator. The FRAX[®] calculator is a tool to integrate clinical risk factors with BMD at the FN to estimate 10-year total (clinical spine, hip, forearm, and humerus) and hip fracture probability in adults with osteopenia (21, 22). The goals of this study were to determine whether there is a difference in estimated probabilities of fracture when using BMD data for both hips in patients with unilateral hip OA and to determine the impact of this difference on clinical treatment decisions.

Materials and Methods

Women and men who were scheduled for unilateral hip arthroplasty due to OA were recruited with approval and annual review by the Partners Internal Review Board for Human Research. Eligible subjects were enrolled after consent. Women and men were scheduled for total hip replacement based on clinical, functional, and radiographic data. Clinical criteria for OA included limited motion, pain at rest or during activity, and lack of response to non-invasive treatment such as rest, modified activity, or use of anti-inflammatory agent or analgesics. Eligible subjects with unilateral OA had loss of joint space either concentrically or in the superolateral portion of the joint often with reactive changes such as sclerosis and cyst formation on the acetabular side, prevalent in only one hip. All subjects in this study met the clinical, functional, and radiological criteria for unilateral hip arthroplasty (20). Subjects were excluded if they had confounding disorders that could possibly affect analysis, such as such as rheumatoid arthritis, avascular necrosis, osteomyelitis, premature menopause, primary hyperparathyroidism, hypercalciuria, hyperthyroidism, Paget's disease, cancer within 5 years, high-impact trauma, and the recent use of medications such as glucocorticoids or calcitonin. These study subjects were without co-morbidities or medications associated with osteoporosis.

We analyzed data for 35 subjects with unilateral hip OA. BMD, T-scores, and Z-scores for the FN, trochanter, and total hip were obtained for both the OA and contralateral hips by dual x-ray absorptiometry (DXA) (Discovery QDR 4500, Hologic, Bedford MA). The hip scans were performed in fast-array mode. At our center, the same-day reproducibility (coefficient of variation %) of the FN bone density in postmenopausal women is 1.28%, and the average least significant change at the FN BMD is 0.032 g/cm², as assessed with validated computation tools previously published (29).

The FRAX[®] calculator (Web Version 3.1) uses data for age, sex, weight, height, BMD, and other parameters to estimate fracture probabilities. In our series of 35 subjects, there were 14 with previous fracture, 5 having a parent with fractured hip, and none who were positive for the other parameters: current smoking, glucocorticoid intake, rheumatoid arthritis status, secondary osteoporosis status, or intake of 3 or more units of alcohol per day (Table I). The 10-year probability of total fracture probability and hip fracture probability was calculated with FN BMD T-score for the OA and the contralateral hips.

Data analysis was done with GraphPad InStat 3 (GraphPad Software, La Jolla, CA). Data are also presented as medians and interquartile limits because they did not pass the normality tests for analysis of statistical significance. The Wilcoxon matched-pairs, signed-ranks, two-tail tests were used for within-subject comparisons of the FN BMD T-scores, total fracture probability, and hip fracture probability for OA and contralateral hips.

According to the National Osteoporosis Foundation (NOF), subjects for whom OP treatment would be recommended are those with 1) a self reported hip or spine fracture; 2) a femoral neck or spine BMD T-score -2.5 or; 3) a femoral neck T-score between -1 and -2.5 SD with a 10-year or total fracture probability 20% or hip fracture probability 3% (23, 24, 25, 26, 27). In our study, subjects were recommended for OP treatment if they met the third criterion.

Results

The mean age $\pm$ standard deviation of the 35 subjects in this series with unilateral hip OA was 67 ± 10 years. There were 22 women and 13 men.

The median values of FN BMD T-score were -0.6 for the OA hip and -1.2 for the contralateral hip; there was a significant difference in FN BMD T-scores between the OA BMD T-score and the contralateral BMD T-score ($p < 0.0001$). The interquartile limits were -1.3 to 0.1 and -2.0 to -0.4 for the OA hip and contralateral hip, respectively (Table II). Of these OA subjects, 57% were determined to have occult osteoporosis or osteopenia by DXA measurements of BMD at the contralateral, non-OA hip.

The median FRAX[®] total fracture probabilities calculated with FN BMD T-scores were 7.1% for the OA hip, and 8.5% for the contralateral hip; these differences were significant ($p = 0.0004$). The interquartile limits for total fracture probability were 5.8 to 12.0% and 5.7 to 14.0% for the OA hip and contralateral hip, respectively (Table II). As a result, calculated probability for total fractures with data for the OA hip was 84% of that for the contralateral hip.

The median FRAX[®] hip fracture probabilities calculated with FN BMD T-scores were 0.5% for the OA hip, and 1.3% for the contralateral hip; these differences were significant ($p = 0.0009$). The interquartile limits for hip fracture probability were 0.3 to 1.4% and 0.4 to 2.5% for the OA hip and contralateral hip, respectively (Table II). As a result, the calculated probability for hip fractures with data for the OA hip was 38% of that for the contralateral hip.

The median FRAX[®] hip fracture probability and total fracture probability calculated without FN BMD T-scores were 10% and 2.3%, respectively.

FRAX[®]-derived estimates of 10-year fracture probability and NOF treatment thresholds were used to determine the percentage of subjects who would receive recommendations for OP treatment with NOF treatment thresholds. From the calculations of total fracture probability, 0% of these subjects would receive recommendations for OP treatment based on data for the OA hip, compared with 11% when based on data for the contralateral hip. From the calculations of hip fracture probability, 11% of subjects would receive recommendation for OP treatment based on data for the OA hip, compared with 17% when based on data for the contralateral hip. Thus, 6 to 11% more subjects would receive osteoporosis treatment if data for the contralateral hip was included in the FRAX[®] calculator (Table II). In contrast, FRAX[®] calculations in this cohort without the use of FN BMD T-scores led to overestimation of total fracture probabilities and hip fracture probabilities, with 26% and 37% of subjects who would receive recommendations for OP treatment, respectively.

Discussion

The results of this study indicate that the calculated probabilities for total or hip fracture according to the FRAX[®] calculator were confounded by the presence of OA. On the basis of the contralateral (non-OA) hip, four additional subjects (11%) were identified who would receive recommendations for OP treatment on the basis of total fracture probability alone. Thus, the use of FN BMD T-score data from a hip with known or occult OA in the FRAX[®] calculator may alter estimation of fracture probabilities and important OP treatment decisions.

Although it had been customary to recommend OP treatment based on BMD T-score below -2.5 and/or a history of fragility fractures, > 50% of patients with osteopenia are among those who will fracture (28). The FRAX[®] calculator was developed by the World Health Organization (WHO) to integrate clinical risk factors with BMD at the FN to estimate 10-year total (clinical spine, hip, forearm, and humerus) and hip fracture probability in adults with osteopenia (21, 22). FRAX[®] is used as a guide by physicians to determine whether a particular patient is at increased fracture probability and should be treated for OP (25, 29). According to the NOF, FRAX[®] is a tool that can guide both physicians and patients to estimate fracture probabilities and to consider possible treatment options (27).

With the projected increase in the number and cost of fractures in the next two decades (30), the development of FRAX[®] was a major achievement. Now that the FRAX[®] tool is available worldwide and incorporated into bone density machines, it is necessary to assess the impact of confounding variables that may alter calculated FRAX[®] total fracture probability and hip fracture probability. One confounding variable may be the presence of OA, which is associated with increased BMD due to reactive bone formation (31). There were no data available on whether inclusion of the BMD for a hip with OA affects FRAX[®] calculations and OP treatment decisions. For this study, we used BMD and clinical data for a cohort of subjects with unilateral hip OA.

Bone density testing generally includes the measurement of the non-dominant hip for total fracture probability and hip fracture probability calculation. Petley et al. suggested that there is limited benefit in measuring bilateral bone density (32), but other authors suggested that in certain individuals there may be a significant difference in the BMD of the right and left side, and speculated that one possible cause for discrepancy could be occult OA (33, 34). Cole and Larson estimated that bilateral hip BMD measurements can be of value in at least 5.2% of women who would have a different OP classification depending on which hip data

were used (35). Others detected no correlation between BMD at OA sites and at sites distant from the osteoarthritic site without OA. (36, 18, 37). Our previous studies showed that women with unilateral hip OA have lower BMD levels on the contralateral side, with discordance in osteoporosis classification according to BMD measures (15, 20). We attribute BMD differences to the presence of reactive osteosclerosis in hip osteoarthritis. Our current study shows the clinical impact on estimation of FRAX[®] fracture probability in adults with advanced OA. When BMD data for the OA hip was used in the FRAX[®] calculator to estimate fracture probability rather than the contralateral hip, 6 to 11% fewer patients would be recommended for OP treatment. Consequently, when using the FRAX[®] calculator to determine OP treatment recommendations, our data indicate that BMD measurement at the contralateral hip may yield higher calculated FRAX total and hip fracture probabilities. A technologist may be unable to recognize hip OA according to the DXA scan, thus in patients with a documented history of OA in one hip, a physician may consider ordering a BMD measurement on the contralateral hip.

The FRAX[®] tool has been validated in large population-based studies (38, 39), but some investigators suggest that it may underestimate probability (25, 29, 40). For example, the calculator does not take into account low spinal BMD, bone turnover markers, glucocorticoid dose and duration, use of aromatase inhibitors, androgen deprivation therapy, and vitamin D deficiency among others. In addition, the calculated fracture probabilities do not include more than one cause of secondary osteoporosis, and when a BMD is entered, the effect of the secondary causes of osteoporosis is eliminated (27). Use of the FRAX[®] calculator without BMD measurements led to higher estimates of fracture probability, which would need to be validated in a larger population-based study. Thus, the use of the current tool is valuable in providing thresholds for recommending fracture probability treatment in different populations. Future versions of FRAX[®] may incorporate additional variables that affect bone density (e.g. years of smoking, multiple factors associated with secondary osteoporosis) (27).

We recognize that there may be limitations in generalizing the findings of this study, which included subjects with advanced OA. Most adults with hip OA do not undergo hip replacement surgery (41). Studies in subjects with less severe OA could add further information about discordance in BMD measurements and its impact on fracture probability estimates. Future studies may also show gender and age differences that we were unable to detect.

Our data suggest that in patients undergoing bone density testing who have documented OA in one hip with limited motion and/or pain at rest or with activity, it is possible that measurement of bone density at the contralateral hip may yield higher calculated FRAX[®] total and hip fracture probabilities. Future studies are needed to determine whether calculated FRAX[®] fracture probability using this approach accurately predicts the incidence of fractures in patients with unilateral hip OA.

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a: Initial Eligible Enrolled Subjects (20)

Figure I. Subject Enrollment

Table I
FRAX® Clinical Risk Factors in Patients with Unilateral Hip Osteoarthritis

Age $\pm$ SEM (years)	67 $\pm$ 2
Sex	13 males, 22 females
Weight $\pm$ SEM (kg)	85.9 $\pm$ 4.4
Height $\pm$ SEM (cm)	169.2 $\pm$ 1.5
Previous fracture?	14
Parent Fractured Hip?	5
Current Smoking?	0
Glucocorticoids?	0
Rheumatoid Arthritis	0
Causes of Secondary Osteoporosis	0
3 units of alcohol per day	0

Table II
Comparison of 10-Year Fracture Probabilities Calculated by FRAX[®] with BMD Data for the OA or Contralateral Hips in 35 Subjects with Unilateral Hip OA

	OA Hip	Contralateral Hip	Mean Difference	^a <i>p</i> -value
FN BMD T-SCORE				
Median	-0.6	-1.2		
Interquartile limits	-1.3 to 0.1	-2.0 to -0.4		<i>p</i> < 0.0001
TOTAL FRACTURE PROBABILITY				
Median	7.1%	8.5%		
Interquartile limits	5.8 to 12.0%	5.7 to 14.0%		<i>p</i> = 0.0004
^b Percent (number) at risk	0% (0/35)	11% (4/35)	11%	
HIP FRACTURE PROBABILITY				
Median	0.5%	1.3%		
Interquartile limits	0.3 to 1.4%	0.4 to 2.5%		<i>p</i> = 0.0009
^c Percent (number) at risk	11% (4/35)	17% (6/35)	6%	

^aWilcoxon matched-pairs, signed-ranks, two-tail tests

^bPercent (number) of subjects with total fracture probability 20%

^cPercent (number) of subjects with hip fracture probability 3%