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The diagnostic threshold for osteoporosis impedes fracture prevention in women at high risk for fracture: A registry-based cohort study

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ABSTRACT

The diagnostic threshold for osteoporosis, a bone mineral density (BMD) T-score ≤ −2.5, signals an increased risk for fracture. However, most fragility fractures arise among the majority of women with 'osteopenia' or 'normal' BMD. We hypothesized that a BMD T-score of −2.5, even if not intended as a treatment threshold, paradoxically may create disincentive to initiating treatment of women with osteopenia or normal BMD at high risk for fracture. From a population-based BMD registry covering the Province of Manitoba, Canada, we identified 3735 untreated women aged ≥ 50 years undergoing BMD screening in 2006–2015 found to qualify for Osteoporosis Canada guidelines-based treatment. The main outcome was prescription of an approved osteoporosis medications in the year after BMD testing ascertained from a population-based pharmacy database. We estimated adjusted odds ratios (OR, 95% confidence interval [CI]) for treatment initiation based on BMD, major fracture history (non-traumatic vertebral, hip or multiple fractures), age, and calendar year (to examine the impact of treatment guidelines published in 2010). Among these women, 50% (1853) initiated treatment: 71% with osteoporosis, 21% with osteopenia, and 5% with normal BMD with similar values in those with a prior major fracture (71%, 19%, 5%, respectively). Compared to women with osteoporosis, adjusted ORs for treatment of high risk women with osteopenia or normal BMD alone were 0.10 (95% CI 0.09–0.12) and 0.02 (95% CI 0.01–0.04), respectively, and no higher in women with a prior major fracture (OR 1.00, 95% CI 0.84–1.19) or following introduction of treatment guidelines (p = 0.294). In summary, we found evidence that the diagnostic threshold for osteoporosis may serve as a disincentive to initiation of treatment in many women at high risk for incident fracture.

1. Introduction

Fractures of the hip, vertebra and upper extremity impose high morbidity, mortality and cost to society [1]. Studies demonstrate that bone mineral density (BMD) correlates with the breaking strength of bone *in vitro* and with the incidence and prevalence of fractures *in vivo* [2, 3]. To formalize the definition of osteoporosis and the epidemiology of fractures associated with low BMD, a committee of the World Health Organization (WHO) established a diagnostic threshold of 'osteoporosis' as a femoral neck BMD T-score −2.5 or lower denoting a high fracture risk [4].

Like blood pressure or serum cholesterol, BMD is not a dichotomous trait; there is no level of BMD T-score above which women remain fracture-free and below which all women sustain a fracture event [3]. BMD provides a continuous gradient of risk; the lower the BMD the higher the fracture risk. Clinical practice guidelines for fracture prevention emphasize the need to identify and treat individuals at high risk for fracture [5] – women with osteoporosis, a prior fracture, prolonged glucocorticoid treatment and other risk factors – some of which are captured in tools such as the Fracture Risk Assessment (FRAX) score [6].

Since BMD is normally distributed, most postmenopausal women in the population have BMD in the 'bell' of the frequency distribution of this trait, not from the 'tail' of the BMD distribution that represents

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women with 'osteoporosis'. As postmenopausal women with osteopenia (T-score between −2.5 and −1.0) or so-called 'normal' BMD (T-score −1.0 and above) comprise the bulk of the postmenopausal population, they contribute the majority of fractures in the population [7–9].

This study addressed the question of whether a BMD measurement adversely influences decision-making in an era in which absolute fracture risk has replaced BMD as the major determinant for intervention [10]. We hypothesized that in postmenopausal women qualifying for pharmacologic treatment based on the presence of high fracture risk as defined by the Osteoporosis Canada clinical practice guidelines [11], a BMD T-score found to be less reduced than −2.5 paradoxically produces a disincentive to treatment even in the presence of a prior fracture, a known predictor of further fractures [6].

2. Materials and methods

2.1. Patient population

We performed a registry-based cohort study to examine factors affecting prescription of an approved osteoporosis medications in the year after BMD testing among women found to qualify for guidelines-based treatment. Under the Osteoporosis Canada clinical practice guidelines, pharmacologic therapy is recommended to reduce fracture risk in individuals with a 10-year major fragility fracture probability over 20% or 'high risk' fractures (prior vertebral, hip or multiple non-hip/non-spine fractures) [11]. This guideline does not have a specific intervention threshold for BMD T-score or hip fracture probability.

In the Province of Manitoba, health services are provided to virtually all residents through a single public health care system which maintains a population-based BMD registry linked to a comprehensive population-based computerized health database repository through an anonymous personal identifier. This repository includes detailed information covering hospitalizations, physician claims and prescription drug use [12]. Bone density testing with dual-energy x-ray absorptiometry (DXA) is managed as an integrated program which ensures uniform criteria for quality control, testing and reporting [13, 14]. The BMD Registry has completeness and accuracy in excess of 99% [14].

Using the BMD Registry, we identified women age 50 years and older having baseline testing between January 1, 2006 (when 10-year fracture probability was first routinely reported) and September 30, 2015, five years after publication of the national clinical practice guidelines [11]. We identified women meeting one or more criteria for treatment: a 10-year major fragility fracture probability over 20% or prior vertebral, hip or multiple non-hip/non-spine fractures (high risk fractures). Fractures since 1987 were ascertained from hospital and physician claims records using definitions that have been validated and adopted for national surveillance of osteoporosis [15, 16]. We excluded women who had filled prescriptions for treatment for osteoporosis in the year prior to BMD testing using the population-based pharmacy prescription database. The study was approved by the Health Research Ethics Board for the University of Manitoba.

2.2. Primary outcome

Prescription of an approved osteoporosis medications (bisphosphonate, raloxifene, salmon calcitonin, denosumab, teriparatide, systemic estrogen) in the year after BMD testing was ascertained from the pharmacy database. To allow sufficient opportunity for treatment initiation, we excluded women with < 6 months of observation (95% of women had a full year of observation after BMD testing). Median time to first prescription was 2 months, with over 90% of treatment initiated by 5 months.

2.3. Bone densitometry

Proximal femur and lumbar spine DXA scans were performed in accordance with manufacturer recommendations (Prodigy, GE Healthcare, Madison WI). Hip T-scores were calculated from the NHANES III reference values for white females as required by FRAX. Manufacturer reference values for white females were used for lumbar spine T-scores. BMD reports include individual T-score measurements (femur neck, total hip, lumbar spine) and 10-year major fracture probability as recommended under national clinical practice guidelines [11]. A BMD category is assigned based upon the minimum T-score: osteoporosis as a T-score less than or equal to −2.5, between −2.5 and −1 as osteopenia, and −1 or above as normal BMD. All instruments were monitored through a quality assurance program. The instrument coefficient of variation was < 0.5%.

Ten-year probability of a major fracture and hip fracture with femoral neck BMD was calculated for each subject using the Canadian FRAX tool (FRAX® Desktop Multi-Patient Entry, version 3.8). The Canadian FRAX tool was calibrated using nationwide hip fracture and mortality data [17]. The Manitoba BMD Registry was not used in the creation or calibration of the FRAX tool. FRAX predictions with the Canadian FRAX tool agree with fracture rates in this cohort and in the Canadian population [18, 19].

2.4. Statistical analysis

Continuous variables were reported as means with standard deviations (SD); frequencies and percentages were also reported. Univariate differences between cohort members who did and did not initiate treatment were tested using *t*-tests and χ^2 tests of independence. Inferential analyses examined initiation of treatment as a function of minimum BMD T-score category (osteoporosis as the referent), age decade at baseline (50–59 years as the referent), calendar year (2006 as the referent), and prior high risk fracture (vertebral fracture, hip fracture, or multiple non-vertebral/non-hip fractures). Adjusted odds ratios (OR, 95% confidence intervals CI) for treatment initiation in the year following BMD measurement were estimated using multivariable logistic regression. Primary analyses considered all women eligible for guideline-based treatment regardless of criteria. Secondary analyses were stratified by probability of major fragility fracture ≥ 20%, probability of hip fracture ≥ 3%, prior vertebral, hip, or multiple non-vertebral/non-hip fractures, and time since the last fracture. Analyses were performed using Statistica (Version 13.0, StatSoft Inc., Tulsa, OK). Statistical significance was assessed using a nominal $\alpha = 0.05$ with 2-sided testing.

3. Results

We identified 3735 women with a mean age of 74.2 ± 10.5 years, ranging from 50 to 99 years, eligible for inclusion (Table 1). The mean BMD T-score (from the minimum measurement) was −2.5 ± 1.2. Of these women, 2255 (60%) had osteoporosis, 1085 (29%) had

Table 1
Baseline characteristics of the study women stratified by osteoporosis treatment status.

Descriptives	Overall	Not treated	Treated	*p*-Value
N =	3735	1882	1853	
Age (years)	74.2 ± 10.5	72.2 ± 11.2	76.2 ± 9.4	< 0.001
Minimum BMD T-score	-2.5 ± 1.2	−2.0 ± 1.2	−3.1 ± 0.8	< 0.001
Major fracture probability (10-year %)	23.4 ± 9.1	20.7 ± 8.7	26.3 ± 8.7	< 0.001
Hip fracture probability (10-year%)	8.8 ± 8.0	6.8 ± 6.9	10.9 ± 8.5	< 0.001
Prior vertebral fracture	634 (17)	442 (23)	192 (10)	< 0.001
Prior hip fracture	503 (13)	225 (12)	278 (15)	0.006
Prior multiple fractures	578 (15)	372 (20)	206 (11)	< 0.001

Data are mean ± SD or N (%).