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Effectiveness of Bone Density Measurement for Predicting Osteoporotic Fractures in Clinical Practice

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Context: Bone density measurement with dual-energy x-ray absorptiometry is widely used for fracture risk assessment. It has not been established that published gradients of fracture risk from study populations can be directly applied to clinical populations.

Objective: The objective of the study was to assess osteoporotic fracture prediction with dual-energy x-ray absorptiometry in a large clinical cohort.

Design: This was a historical cohort study (mean observation period 3.2 ± 1.5 yr).

Patients: The study population was drawn from the population-based database of the Manitoba Bone Density Program. Analyses were limited to women aged 50 yr or older at baseline (n = 16,505).

Main Outcome Measure: Each subject's longitudinal health service record was assessed for the presence of nontrauma fracture codes (hip, spine, wrist, and humerus) after bone density testing. Age-adjusted hazard ratios for fracture were derived from Cox proportional hazards models.

Results: Site-specific and overall fracture rates were significantly associated with each site of bone density measurement (all $P <$ 0.00001). The 95% confidence intervals overlapped those from a widely cited metaanalysis of fracture prediction from different sites. Although fracture prediction was not significantly different between the three hip measurement sites, each hip site was better than the lumbar spine for predicting overall fractures (nonoverlapping 95% confidence intervals). The manufacturer SD (equivalent to a unit change in T-score) resulted in a significantly smaller gradient of risk for the spine than when the population SD was used.

Conclusions: Bone density measurements are effective for predicting fractures in clinical practice. However, hip measurements were superior to the spine in overall osteoporotic fracture prediction. (***J Clin Endocrinol Metab* 92: 77–81, 2007**)

ACCURATE IDENTIFICATION of individuals at risk for osteoporotic fracture facilitates the clinical decision of when and how to intervene therapeutically. In the absence of an established clinical diagnosis of osteoporosis based on fragility fracture, bone density measurement with dual-energy x-ray absorptiometry (DXA) is widely used for risk stratification with a 10-fold increase in DXA testing rates observed over the last decade (1, 2). Bone density measurement is stated to provide a gradient of risk (usually expressed as a rate ratio per SD) that is as good as other commonly used risk stratification measures such as blood pressure for stroke and serum cholesterol for cardiovascular disease (1). Typically, large cohort studies with prospective fracture data collection are performed to obtain these risk estimates. Prospective cohort studies are expensive and challenging to perform and, despite the best attempts to obtain a random sample, there always exists the potential for recruitment bias and loss to follow-up.

Therapeutic effectiveness (a measure of the benefit resulting from an intervention for a given health problem under usual conditions of clinical care) differs from therapeutic efficacy (a measure of the benefit resulting from an intervention for a given health problem under the ideal conditions) (3). Clinical populations undergoing bone density measurement for purposes of clinical decision making are inherently different from the general population. This is partly due to the fact that most jurisdictions have established testing criteria that specify the conditions and risk factors that are most likely to benefit from skeletal density assessment. Although several guidelines promote bone density measurement in older women in the absence of other risk factors (4–7), no country has developed a mass screening program. It has not been established that published gradients of fracture risk from study populations can be directly applied to clinical populations. Because bone density testing has been routinely used for well over a decade, large numbers of women have undergone DXA testing, and it should be possible to use real-world data to measure the association between bone density and fracture risk in routine clinical practice.

The current project was designed to assess the clinical effectiveness of fracture risk prediction from bone density measurements and compare these predictions with a well-cited metaanalysis (1). We also wanted to assess fracture prediction using the total hip site because this was not available at the time of the previous metaanalysis and may become the preferred site for hip assessment. To achieve this, a large data set of clinical bone density measurements from the Province of Manitoba, Canada (8), was linked with an

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Abbreviations: BMD, Bone mineral density; CI, confidence interval; DXA, dual-energy x-ray absorptiometry; HR, hazard ratio; ICD-9-CM, *International Classification of Disease-9-Clinical Modification*; ROC, receiver operating characteristic.

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anonymized population-based repository of administrative health data that included hospitalizations and physician billing claims (9, 10). Linkage between these data sets made it possible to assess clinical fracture outcomes and their association with bone density results directly.

Patients and Methods

Patient population

The study population was drawn from the Manitoba Bone Density Program and its population-based database, both of which have been previously described in detail (11). All clinical bone densitometry in the province of Manitoba, Canada, is performed within a single program structure that maintains uniform testing indications, requisition, and reporting. Criteria for testing are broadly consistent with most published guidelines and emphasize the importance of female sex, age 65 yr or older, premature ovarian failure, prior fragility fractures or x-ray evidence of osteopenia, prolonged corticosteroid use, and other clinical risk factors (www.gov.mb.ca/health/programs/mbd). Access to testing is not restricted to these indications, however, and a wide range of clinical justifications are accepted. The program's database includes all DXA test results since the first instrument was installed in 1990. This database is more than 99% complete and accurate as judged by chart audit (8).

The study population was limited to women aged 50 yr or older who had baseline lumbar spine (L1–4) and proximal femur (total hip, femoral neck, and trochanter) bone densitometry performed before October 31, 2002, with one of the program's primary instruments (DPX or Prodigy; GE Lunar, Madison, WI) and who had medical coverage with Manitoba Health during the observation period ending March 31, 2004. As a clinical effectiveness study, there were minimal exclusion criteria. We did not use test results analyzed with earlier software versions (before May 1998) that did not provide total hip measurements. For women with more than one densitometry record, only the first measurement for that individual was included. The study population consisted of 16,505 women aged 50 yr or older at the time of baseline bone density assessment with complete spine and hip bone density information. The mean observation period after bone density assessment was 3.2 $\pm$ 1.5 yr. The study was approved by the Research Ethics Board for the University of Manitoba and the Health Information Privacy Committee of Manitoba Health.

Bone density measurements

Before 2000, DXA measurements were performed with a pencil-beam instrument (Lunar DPX; GE Lunar) and after this date fan-beam instruments were used (Lunar Prodigy; GE Lunar). Instruments were cross-calibrated *in vivo* with 59 volunteers, and no clinically significant differences were identified (T-score differences < 0.2). Therefore, all analyses are based on the unadjusted numerical results provided by the instrument. DXA scans were performed and analyzed in accordance with manufacturer recommendations. Lumbar spine T-scores [number of SDs above or below young adult mean bone mineral density (BMD)] and Z-scores (number of SDs above or below age-matched mean BMD) used the manufacturer U.S. white female reference values. Hip T-scores and Z-scores were based on the revised National Health and Nutrition Examination Survey III reference data (Prodigy version 8.8) (12). All equipment and technologist performance is subject to a rigorous quality assurance program developed from published models and monitored by a medical physicist (13–15). Densitometers underwent daily assessment of stability using an anthropomorphic spine phantom, and each showed stable long-term performance (coefficient of variation = SD/mean $<$ 0.5%). *In vivo* precision has been previously reported (coefficient of variation 1.7% for L1–4 from 198 spine scan pairs and 1.1% for the total hip from 193 hip scan pairs) (16).

Fracture outcomes

Manitoba Health maintains computerized databases of physician billing claims and hospital discharges for all residents of the province eligible to receive health services. Each health system contact includes information on a patient's demographics, date and type of service, and diagnoses, which are coded using the *International Classification of Disease-9-Clinical Modification* (ICD-9-CM). Anonymous linkage of these databases to the BMD database was possible via a unique scrambled health identification number, thereby allowing for the creation of a longitudinal record of health services and outcomes. The accuracy of these administrative data has been established for a wide range of clinical disorders including osteoporotic fractures (17, 18).

Each subject's longitudinal health service record was assessed from the date of bone density measurement to March 31, 2004, for the presence of ICD-9-CM fracture codes using previously described definitions (19). Fractures were classified as incident if they occurred after the bone density test. Specific fracture sites of interest were the hip (ICD-9-CM 820–821), spine (ICD-9-CM 805), wrist (ICD-9-CM 813), and proximal humerus (ICD-9-CM 812) because they are the basis for the 10-yr absolute fracture risk estimates published by Kanis *et al.* (20). We excluded fractures associated with nonaccidental ICD-9-CM trauma codes (ICD-9-CM E800-E879 and E890-E999). In addition, we required that hip fractures and wrist fractures be accompanied by a site-specific fracture reduction, fixation, or casting code. This would exclude less severe fractures such as isolated trochanteric fractures not requiring surgical fixation and distal radius fractures not requiring immobilization. Hip, spine, wrist, and proximal humerus were collectively designated as osteoporotic fractures. Our primary comparator was the widely cited metaanalysis of Marshall *et al.* (1) because this assessed site-specific and overall fracture outcomes in relation to various measurement sites. The more recent metaanalysis of Johnell *et al.* (21) was a secondary comparator because it assessed only fracture outcomes in relation to femoral neck BMD.

Statistics

Cox proportional hazards models were used to model time to incident fracture for site-specific and combined fracture events. The predictor variable was absolute bone density measurement (grams per square centimeter). Age, coded as a continuous variable, was included as a covariate in each model. Separate models were constructed for each bone density measurement site (L1–4, femoral neck, trochanter, and total hip). All models converged and demonstrated a significant improvement in global fit when the bone density measurement was added to a model with age alone. Age-adjusted hazard ratios (HRs) per SD in bone density were obtained by the appropriate scaling of the beta coefficient. We compared results using SD values for the study population unadjusted for age (hereafter termed population-SD) and the manufacturer reference population (manufacturer-SD, equivalent to a unit change in T-score). The Durbin-Watson statistic confirmed linearity in the relationship between age and BMD. Manufacturer hip SD values were based on the revised National Health and Nutrition Examination Survey III reference data (12). Homogeneity of variances in bone density measurements between sites was tested using Levene's test. Overall test performance in terms of fracture prediction was also assessed using nonparametric receiver operating characteristic (ROC) curve analysis. $P < 0.05$ was taken to indicate a statistically significant difference.

Results

Population

The characteristics of the study population are summarized in Table 1. The mean age was 65 yr (SD 9). The population was predominantly white with a low prevalence of visible minorities (1.8%). Mean T-scores for each of the measurement sites fell within the World Health Organization osteopenic (low bone mass) category. The prevalence of measurements within the osteoporotic range (T-score -2.5 or lower) was greatest for the lumbar spine (21.2%), followed by the femoral neck (15.9%) and trochanter (15.3%) and least for the total hip (11.2%). Mean Z-scores were very close to zero implying that our clinical population has bone density measurements comparable with those from the manufacturer's reference population. The SDs in the Z-scores varied from 1.1 for the femur neck to 1.6 for the lumbar spine. A value of one (1.0) would be expected if the clinical population had the

TABLE 1. Study population baseline characteristics (n = 16,505)

Characteristics	
Age (yr)	65 ± 9
Ethnicity (%)	
White	16,210 (98.2)
Asian	217 (1.3)
Hispanic	4 (<0.1)
Black	47 (0.3)
Other	27 (0.2)
Height (cm)	160 ± 7
Weight (kg)	68 ± 14
Scanner type (%)	
Pencil beam	4,428 (26.8)
Fan beam	12,077 (73.2)
Lumbar spine (L1–L4)	
BMD (g/cm^2)	1.029 ± 0.186
T-score	−1.3 ± 1.5
Z-score	0.1 ± 1.6
Femur neck	
BMD (g/cm^2)	0.823 ± 0.134
T-score	−1.5 ± 1.0
Z-score	0.0 ± 1.1
Trochanter	
BMD (g/cm^2)	0.701 ± 0.135
T-score	−1.3 ± 1.2
Z-score	−0.1 ± 1.3
Total hip	
BMD (g/cm^2)	0.871 ± 0.150
T-score	−1.1 ± 1.2
Z-score	0.0 ± 1.2

Continuous variables are expressed as mean ± SD.

same dispersion in bone density as the reference population. The variance in lumbar spine bone density (both absolute BMD and Z-score) was significantly greater than for each of the hip sites ($P < 0.00001$).

Incident fractures

Fracture events subsequent to bone density testing were identified during a mean observation period of 3.2 ± 1.5 yr. At least one incident osteoporotic fracture was identified in 765 (4.6%) of the cohort including 189 (1.1%) hip fractures, 209 (1.3%) spine fractures, 230 (1.4%) wrist fractures, and 191 (1.2%) proximal humerus fractures.

Each individual fracture site and the combined fracture definitions were significantly associated with each site of bone density measurement (all $P < 0.00001$). The highest HR per population-SD was for hip fracture prediction derived from the total hip measurement [age-adjusted HR 2.87, 95% confidence interval (CI) 2.40–3.43]. Hip fracture prediction was not notably different between the three hip measurement sites (Table 2). Each hip site was better than the lumbar spine for predicting hip fractures and any osteoporotic fracture as demonstrated by the nonoverlapping HR confidence limits.

For the three hip measurement sites, the HR per manufacturer-SD (equivalent to a unit change in T-score) was similar to when the population-SD was used. However, in the case of the lumbar spine the HR per manufacturer-SD was significantly lower with 95% confidence limits that did not overlap the HR per population-SD (1.22–1.35 *vs.* 1.36–1.59).

ROC analysis

ROC curve analysis was performed for various combinations of fracture site and measurement site (Table 3). All ROC areas under the curve were significantly greater than chance ($P < 0.00001$). The highest area under curve was for hip fracture prediction derived from the total hip site (total hip 0.82, 95% CI 0.79–0.85), albeit only marginally greater than for the femoral neck or trochanter. ROC areas for hip fracture prediction derived from any hip site were considerably better than hip fracture prediction from the lumbar spine (area 0.66, 95% CI 0.62–0.72), whereas each site showed comparable ROC areas for prediction of spine, wrist, and proximal humerus fractures. Overall prediction of osteoporotic fractures was slightly better with the hip sites than with the lumbar spine as demonstrated by the nonoverlapping 95% confidence limits.

Comparison

Figure 1 compares the HR per population-SD from the current study with those from the primary comparator meta-analysis of Marshall *et al.* (1). Each of the 95% CIs overlapped. In the secondary comparator metaanalysis of Johnell *et al.* (21), the gradient of risk in women for osteoporotic fracture based on femoral neck bone density was 1.53 (95% CI 1.46–1.62) per SD and for hip fracture was 2.03 (95% CI 1.87–2.21) per SD, and again these confidence limits overlapped those from the current study.

Discussion

Our study confirms that bone density measurements are as effective for predicting fractures in clinical practice as has been reported in a widely cited metaanalysis of fracture prediction based on multiple prospective cohort studies (1). This is reassuring in light of the proliferation of bone density testing that has been observed over the last decade (2).

TABLE 2. Age-adjusted HRs for fracture (95% CI) per SD in bone density

Fracture site	Prediction site			
	Spine L1–L4	Femoral neck	Trochanter	Total hip
Population SD	0.185 g/cm^2	0.134 g/cm^2	0.136 g/cm^2	0.150 g/cm^2
Hip	1.37 (1.17–1.59)	2.49 (2.07–3.01)	2.73 (2.31–3.24)	2.87 (2.40–3.43)
Spine	1.80 (1.54–2.10)	1.70 (1.44–2.01)	1.64 (1.41–1.91)	1.73 (1.47–2.03)
Wrist	1.45 (1.26–1.68)	1.55 (1.33–1.81)	1.46 (1.26–1.68)	1.53 (1.32–1.78)
Humerus	1.38 (1.19–1.62)	1.68 (1.41–1.99)	1.68 (1.43–1.97)	1.75 (1.48–2.07)
Osteoporotic (any of the above)	1.47 (1.36–1.59)	1.76 (1.62–1.92)	1.77 (1.63–1.92)	1.85 (1.70–2.01)
Manufacturer SD	0.120 g/cm^2	0.139 g/cm^2	0.115 g/cm^2	0.126 g/cm^2
Hip	1.22 (1.11–1.35)	2.59 (2.13–3.14)	2.34 (2.03–2.70)	2.43 (2.09–2.82)
Spine	1.46 (1.32–1.62)	1.74 (1.46–2.07)	1.52 (1.34–1.73)	1.58 (1.38–1.81)
Wrist	1.27 (1.16–1.40)	1.58 (1.35–1.85)	1.38 (1.22–1.55)	1.43 (1.26–1.63)
Humerus	1.23 (1.12–1.37)	1.71 (1.43–2.05)	1.55 (1.36–1.77)	1.60 (1.39–1.85)
Osteoporotic (any of the above)	1.29 (1.22–1.35)	1.80 (1.65–1.97)	1.62 (1.51–1.73)	1.68 (1.56–1.80)

TABLE 3. Area under the curve (95% CI) from the ROC analysis for fracture

Fracture Site	Prediction site			
	Spine L1–L4	Femoral neck	Trochanter	Total hip
Hip	0.66 (0.62–0.70)	0.79 (0.76–0.83)	0.81 (0.77–0.84)	0.82 (0.79–0.85)
Spine	0.70 (0.66–0.74)	0.69 (0.65–0.73)	0.68 (0.64–0.72)	0.70 (0.66–0.74)
Wrist	0.63 (0.60–0.66)	0.65 (0.61–0.68)	0.63 (0.60–0.67)	0.65 (0.61–0.68)
Humerus	0.63 (0.59–0.67)	0.67 (0.63–0.71)	0.67 (0.63–0.70)	0.68 (0.64–0.72)
Osteoporotic (any of the above)	0.65 (0.63–0.67)	0.69 (0.68–0.71)	0.69 (0.67–0.71)	0.71 (0.69–0.73)

The difference between the clinical population-SD and manufacturer-SD fracture risk estimation is usually not considered. In general, SD derived from a heterogeneous population will produce a larger SD than that from a homogeneous population. Given that the manufacturer-SD used for T-score calculation is based on a young adult population, the resulting SD will typically be smaller than one derived from a clinical population with a wide age range. Thus, the risk estimate per manufacturer-SD would be proportionately smaller than when the risk estimate uses the clinical population-SD. The spine showed a large difference between population-SD and manufacturer-SD (54% greater in the former) with a smaller difference for the hip sites (less than 20%), and this contributed to the reduced overall performance of the spine as a fracture prediction site based on manufacturer-SD. In fact, even the HRs per manufacturer-SD for spine fracture prediction were slightly greater (although not significantly) for hip measurement sites than for the lumbar spine.

The present study used the HR per population-SD as the primary measure of comparison with the study by Marshall *et al.* (1), who expressed bone density differences in terms of SDs of the control group mean value. Our findings based on femoral neck measurements demonstrated excellent agreement with those of the metaanalysis. However, we found slightly reduced performance of spine fracture prediction from lumbar spine measurement. We speculate that this may partially reflect the confounding effect of degenerative artifact on spine measurements (22). Age-related spine artifact may be a greater problem in clinical populations who are often selected for testing based on back pain and/or abnormal spine x-rays. Age-adjusted HR for fracture (per population-SD) reported by the Study of Osteoporotic Fractures (23) for total hip and femoral neck measurements are similar to our study but superior in terms of the spine [spine fracture prediction from spine measurement HR 2.06 (95% CI 1.80–2.35)]. Incomplete spine fracture ascertainment in our cohort is unlikely to explain the difference because this would be expected to affect also the ability of hip measurements to predict spine fractures, and this did not appear to be the case. Furthermore, the incidence of clinical spine fractures (as a proportion of all spine, hip, wrist, and humerus fractures) for a 65-yr-old woman reported by Kanis *et al.* (24) and our study were quite similar (spine 23.8 *vs.* 25.5%, respectively). We also found good agreement with the recent metaanalysis of fracture prediction from femoral neck bone density (21). The latter used bone density measurements adjusted for age, and no relevant difference was seen when we recalculated HR per age-regressed SD [any osteoporotic fracture 1.68 (95% CI 1.55–1.82) and hip fracture 2.31 (95% CI 1.95–2.74)].

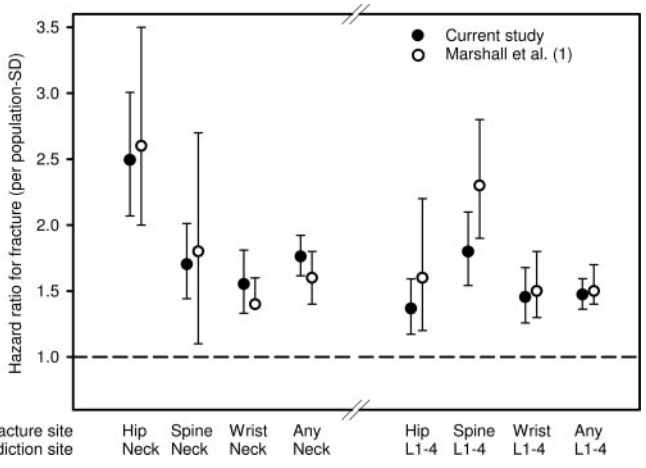

FIG. 1. HRs for fracture (95% CI bars) per population SD for femoral neck and L1–L4 spine.

The commonly used rule of thumb that fracture rates double for each unit change in T-score clearly oversimplifies a more complex situation. In our clinical population, each unit change in spine T-score had a much smaller effect on fracture rates than a unit change in hip T-score. A woman with spine T-score of −4.0 would be predicted to have only 2.8 times the risk of fracture of an otherwise identical woman with spine T-score of 0.0, whereas a femoral neck T-score of −4.0 would result in over a 10-fold relative fracture risk. A larger gradient of risk has been reported to lead to better test performance, increased efficiency, and enhanced cost-effectiveness (25). Therefore, the hip may be preferred as the primary site for diagnosis and fracture risk assessment as proposed by others (26, 27), although skeletal sites differ significantly in terms of the proportion of women classified as osteoporotic based on a T-score of −2.5 or lower (28).

The size of the data set and its population-based coverage are obvious strengths of our study. Compared with traditional prospective cohort studies, loss to follow-up is infrequent in the context of our provincial health care system because individuals must be registered to receive medical and/or hospital services. Therefore, outcomes are efficiently identified at a fraction of the cost of a traditional cohort study. On the other hand, fracture ascertainment from administrative health data has known limitations. Specifically, minor fractures or fractures that produce few symptoms may not lead to a physician interaction and hence are not recorded in the administrative health databases. This is particularly likely to occur with vertebral compression fractures because the majority are not clinically diagnosed (29), although it should be noted that the large prospective cohort studies previously cited were also limited to clinically diagnosed (symptomatic) spine fractures. Prevalent fractures (occurring

before bone density measurement) could potentially confound identification of incident fractures (occurring after bone density measurement). To minimize this possibility, two of our four fracture definitions (hip and wrist) required site-specific orthopedic codes. In a secondary analysis, we also excluded individuals with any prevalent osteoporotic fracture and the risk estimates were unaffected (data not shown). Our risk estimates are age-adjusted but are not adjusted for treatment history, prior fractures, corticosteroid use or other clinical risk factors that have been linked to increased fracture risk (27, 30–32). Our analysis assumed that gradient of risk was independent of age to make valid comparisons with other studies. Recent data suggest that this may not be the case with a larger gradient of hip fracture risk per SD in younger women and a larger gradient of risk for all fractures in older women (21). Furthermore, our study population was limited to women aged 50 yr and older and may not be applicable to males or younger females. Our study population included very few nonwhite women, and results may not be applicable to other ethnic populations.

In summary, we have confirmed that bone density measurements in clinical practice are as effective for predicting fractures as has been reported in other prospective cohorts. However, hip measurements were superior to the spine in overall osteoporotic fracture prediction.

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