Determining Whether Women with Osteopenic Bone Mineral Density Have Low, Moderate, or High Clinical Fracture Risk

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Abstract

Background—The majority of low-trauma fractures occur among women with osteopenic bone mineral density (BMD), a population considered to have moderate absolute fracture risk. Our purpose was to refine the fracture risk prediction in women with osteopenic BMD in order to determine the subgroups at lowest and highest risk.

Methods—We included 2588 women ages 50–90 with osteopenic BMD (femoral neck BMD between –1 and –2.5) participating in the Canadian Multicentre Osteoporosis Study (CaMos), an ongoing prospective cohort study of randomly-selected Canadians. Baseline variables in addition to known risk factors, age, and BMD were considered for inclusion in a model for the prediction of 5-year absolute risk of low-trauma fracture. Models were derived using logistic regression and assessed by the Bayesian Information Criterion.

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Conflicts of Interest

Dr. Goltzman serves as a consultant for Eli Lilly, Novartis, Merck, Procter & Gamble, and Amgen. Dr. Morin serves as a consultant for Procter & Gamble, sanofi-aventis, Amgen, Novartis. Dr. Kovacs serves as a consultant and has received grants from Eli Lilly, GlaxoSmithKline, Merck, Novartis, Procter & Gamble, sanofi-aventis, Servier, Novo Nordisk and MacroGenics. Dr. Hanley serves as a consultant and has received grants from Abbott Laboratories, Amgen, Eli Lilly, Merck, Novartis, Procter & Gamble, sanofi-aventis, Servier, Wyeth-Ayerst, Nycomed, Paladin. Dr. Adachi serves as a consultant to Amgen, Astra Zeneca, Eli Lilly, GlaxoSmithKline, Merck, Novartis, Nycomed, Pfizer, Procter & Gamble, Roche, sanofi-aventis, Servier, Wyeth, and Bristol-Myers Squibb and has received grants from Amgen, Eli Lilly, GlaxoSmithKline, Merck, Novartis, Pfizer, Procter & Gamble, sanofi-aventis, Roche, Wyeth and Bristol-Myers Squibb. Dr. Josse serves as a consultant for Amgen, Bayer Corporation, Eli Lilly, GlaxoSmithKline, Merck, Novartis, Procter & Gamble, sanofi-aventis, Servier, Wyeth-Ayerst. Dr. Papaioannou acts as a consultant and has received grants from Amgen, Eli Lilly, Merck, Novartis, Procter & Gamble, sanofi-aventis, Servier, Wyeth-Ayerst. Dr. Jamal acts a consult for Alliance for Better Bone Health, Genzyme, Procter & Gamble, sanofi-aventis. All other authors have no conflicts of interest.

Results—We found an increased fracture risk among those with lower BMD, OR=1.53 (95% CI: 1.06–2.21) for each decrease in femoral neck T-score (e.g. from –1 to –2); those with prior low trauma fracture, OR=2.06 (95% CI: 1.46–2.92); those with self-reported worse general health, OR=1.35 (95% CI: 1.15–1.59) for each lower category (categories: excellent, very good, good, fair, poor); and those with height loss, OR=1.44 (95% CI: 1.16–1.90) for each 5 cm difference between current and maximal height. The new model had yielded a better risk stratification than a model with WHO risk factors.

Conclusions—Including risk factors such as general health and height loss can be used to provide a highly effective assessment of fracture risk among women with osteopenic BMD.

Introduction

Studies have consistently reported that the highest number of fractures in a given population occurs in those with osteopenic or normal bone mineral density (BMD) ^{1, 2}. In fact, the National Osteoporosis Foundation has singled out those with osteopenic BMD as a population in which fracture risk assessment is merited ³. Nevertheless, appropriate prevention and treatment strategies for these individuals are uncertain ⁴. A key therapeutic dilemma in management of patients with osteopenia is that absolute fracture risk is typically assessed to be in the “moderate” category. As a result, recent studies have focused on identifying clinical risk factors that may be used together with BMD in order to improve fracture prediction in this group with a high frequency of fractures.

Several clinical risk factors, in addition to age and BMD, have been identified to predict fracture. Risk factors for fracture identified by the World Health Organization (WHO) collaborating center based on meta-analysis include: previous fracture, body mass index, smoking, alcohol use, rheumatoid arthritis, glucocorticoid use, and parental history of hip fracture ⁵. Indeed, inclusion of these clinical risk factors in a prediction model improves the estimates of 10-year absolute fracture risk ⁵ and forms the basis of the WHO FRAX® calculators ⁶. Other variables shown to be associated with fracture risk include change in height, change in weight, inflammatory bowel disease, kidney disease, health-related quality of life ⁷ and previous falls ⁸.

It is important to note that most studies on fracture include women with osteoporotic BMD, hence it is possible that the risk factors and model parameters might not be generalizable to those with better BMD. As well, most models focus on factors that increase fracture risk, but do not examine factors such as overall good health that may indicate reduced fracture risk. Including such risk factors may be important to ensure that those at lower risk of clinical fracture can forego unnecessary follow-up and treatment. Finally, calibration of models in a general population may result in a narrow range of risk for those with osteopenic BMD, and model performance may be largely determined by separation of the high risk (osteoporotic BMD) from the low risk (normal BMD).

The aim of the current study was to determine the relative importance of clinical risk factors for fracture among women with osteopenia and to incorporate the most important independent risk factors in a new model specific to these women.

Materials and Methods

Subjects

We included women 50 to 90 years old, participating in an on-going cohort study, the Canadian Multicentre Osteoporosis Study (CaMos) with follow-up fracture data and a baseline femoral neck BMD T score between -1 and -2.5 . There were 6539 women at baseline; 4092 women met the age and follow-up criteria; 2588 women had the requisite osteopenic BMD and were included in the study.

A description of the CaMos study together with associated publications can be found on the study web site: www.camos.org. Briefly, eligible participants were at least 25 years at the start of the study, lived within a 50-kilometer radius of one of nine Canadian cities (St John's, Halifax, Quebec City, Toronto, Hamilton, Kingston, Saskatoon, Calgary, and Vancouver). Households were randomly selected from a list of residential phone numbers and participants were randomly selected from eligible household members. Of those selected, 42% agreed to full participation with complete baseline interview. Ethics approval was granted through McGill University and the appropriate ethics review boards for each participating center.

Data collection

At baseline in 1995–96, participants were given a standardized interviewer-administered questionnaire (CaMos questionnaire © 1995), which assessed demographics, general health, nutrition, medication use, and medical history. The questionnaire was designed to capture detailed information about risk factors for fractures including all previous fractures (fracture site, date, and circumstances), family history of osteoporosis/fracture, and falls in past month. Participants completed the Medical Outcomes Trust 36-Item Health Survey (SF-36). We used the standardized physical component SF-36 score. We also used the response to the SF-36 question “In general, would you say your health is: Excellent, Very good, Good, Fair, Poor” as a measure of general health. Participants had a baseline clinical assessment that included measurement of height, weight, and BMD. BMD T-scores were based on published reference standards for Canadians⁹. A more detailed description of BMD quality control appears elsewhere¹⁰. Follow-up visits were scheduled in the third year for those between 40 and 60 years old and in the fifth year and tenth year for everyone. The follow-up visits included an interviewer-administered questionnaire together with measured height, weight, and BMD.

Fracture assessment

Self-reported incident clinical fractures were identified by yearly postal questionnaire or at the scheduled interview (Year 3 and Year 5). Confirmation and further fracture information was routinely gathered using a structured interview that included date, fracture site, circumstances leading to fracture, x-ray report (if obtainable), and clinical treatment. Low-trauma fractures were those that occurred without trauma or from a fall of standing height or less. The main outcome was low-trauma fracture of any skeletal site except the skull, face, hands, ankles and feet.

Statistical methods

We used logistic regression models to determine the association between clinical risk factors (assessed at baseline) and incident low-trauma fracture between baseline and year 5. We derived several models for the prediction of fracture risk. There were two comparison models: Model I (including age and BMD) and Model II (including the WHO risk factors: age, BMD, prior fracture, parental history of fracture, body mass index, current smoking, alcohol intake, rheumatoid arthritis, and use of glucocorticoids) ⁵.

Variables were assessed for inclusion in a prediction model using the Bayesian Information Criterion (BIC)¹¹. BIC is a single parameter that allows the comparison of non-nested models. Age and BMD were included in all models. For the construction of the new model we considered the following additional variables: prior fracture (low-trauma clinical fracture after age 50 years), parental history of fracture, body mass index, smoking, alcohol intake, rheumatoid arthritis, use of glucocorticoids, physical health status (SF-36 physical health summary score), general health (from SF-36), falls in month prior to baseline, height loss (maximal adult height minus current height), weight loss (maximal adult weight minus current weight), weight cycling (number of times lost/gained 20 lbs or more), vertebral deformity, age of menarche, age of menopause, use of antiresorptives (hormone therapy, bisphosphonates, raloxifene, calcitonin) and specified comorbidities (heart disease, diabetes, hypertension, osteoarthritis, rheumatoid arthritis, inflammatory bowel disease, kidney disease, liver disease, stroke, neuromuscular disease, breast cancer, uterine cancer, and eating disorders).

We assessed for linearity in continuous variables and statistical interaction between pairs of continuous variables and between age and all other variables. For variables that were highly correlated we included only one of the variables into the model selection process at a time. Our first derived model (Model III) included the SF-36 physical health summary score, a measure that is not readily available in clinical practice. Therefore we repeated the model selection process replacing this measure with self-reported general health to obtain a more usable model (Model IV). Model fit was assessed using a Hosmer-Lemeshow test. Internal validation was done using bootstrap samples of the study population. Model comparison was done using gradient of risk, area under receiver operator curve, and net reclassification index¹². For the net reclassification index we considered three categories of 5-year fracture risk for each model as clinically relevant: low (0–5%), moderate (5–10%) and high (10%+). We used a Kaplan-Meier analysis to estimate absolute 5-year and 10-year risk of clinical fracture within low, moderate and high risk categories. Analysis was performed using Stata Version 9.2.

Results

The baseline characteristics of the 2588 women in the study sample are given in Table 1. A total of 214 women had at least one clinical low-trauma fracture within 5 years, and the overall 5-year fracture risk in the cohort was 8.3 percent. The number of first fractures at a given skeletal site was: forearm/wrist (72), ribs (45), upper arm/shoulder (28), hip/pelvis (19), back (21), leg (14), and multiple sites (15).

There were two models derived by model selection: Model III included age, BMD, physical health status (SF-36), prior fracture, and height loss and Model IV included age, BMD, self-reported general health, prior fracture, and height loss. Table 2 shows the list of covariates included in all comparison models. The predicted absolute 5-year risk of clinical low-trauma fracture by selected low risk covariate patterns based on all models is shown in Table 3. The minimum absolute risk in the Model I and Model II are notably higher within each age and BMD stratum than the absolute risk derived for those in excellent physical health (Model III), or excellent general health (Model IV). The table provides the lowest risk for a given age and BMD as individuals with different risk profile (i.e. including additional risk factors) will have higher risk. It is also clear that the risk gradient for age and BMD was higher in the first two models compared with the latter two models.

Model III

We found an increased fracture risk among: those with lower BMD, OR=1.61 (95% CI: 1.11–2.32) per change in BMD T-score within the osteopenic range (e.g. from –1 to –2); those with prior low trauma fracture, OR=2.00 (95% CI: 1.41–2.84); those with worse physical health, OR=1.40 (95% CI: 1.22–1.60) for each 10 points decrease SF-36 physical health summary score; and those with height loss, OR=1.40 (95% CI: 1.12–1.75) for each 5 cm of height loss. Age, included as an *a priori* specified risk factor in all models, was associated with increased risk that was not statistically significant, OR=1.15 (95% CI: 0.94–1.41) per decade.

Model IV

Each category of lower general health was associated with increased fracture risk with OR=1.35 (95% CI: 1.15– 1.59) per category change. We found an increased fracture risk among: those with lower BMD, OR=1.53 (95% CI: 1.06–1.50) per 1 unit change in BMD T-score; those with prior low trauma fracture, OR=2.06 (95% CI: 1.46–2.92); and those with height loss, OR=1.40 (95% CI: 1.12–1.75) for each 5 cm of height loss. Age was associated with increased fracture risk, but this association was statistically marginal, OR=1.23 (95% CI: 1.00–1.50) per decade.

We compared the distributions of predicted risk by computing the gradient of risk per standard deviation of risk scores and found a risk gradient of 1.55 for Model I (base model), 1.75 for Model II (WHO risk factors), 1.88 for Model III (including SF-36), and 1.84 for Model IV (including general health). Furthermore, Model I had AUC= 0.62 (95% CI: 0.58, 0.68), Model II had AUC=0.67 (95% CI: 0.63, 0.71), Model III had AUC=0.69 (95% CI: 0.65, 0.72), and Model IV had AUC=0.68 (95% CI: 0.65, 0.72). Internal validation by a bootstrap with 200 replications yielded a bias of 0.004, resulting in a nominally lower corrected AUC for both new models. Finally we used the net reclassification index (NRI) to compare Model IV to the other models, with NRI=0 indicating no difference. Model IV was an improvement over both comparison models with NRI=24.7% (95% CI: 16.0–33.5) with respect to Model I, and NRI=9.3% (95% CI: 1.1– 17.5) with respect to Model II. Model IV was similar to Model III with NRI=2.7% (95% CI: –3.2, 8.5).

The distribution of predicted risk by age group for all models is shown in Figure 1. We note that the addition of any risk factors other than age and BMD increases the number of younger women classified as low fracture risk (less than 5% 5-year risk), and simultaneously increases the number of older women classified as very high risk (more than 15% 5-year risk), thus shifting the age distribution of risk categories.

The predicted 5-year fracture risk for women by age, BMD T-score, and selected risk profiles using Model IV is shown in Figure 2. Women with self reported excellent health and no prior fracture or other risk factors have low fracture risk (less than 5% 5-year risk) over much of the age and osteopenic BMD ranges. The graph also indicates the marked difference in the risk of future fracture between women with and without prior fracture. Prior fracture is associated with a doubling of the risk of future fracture. Women with self reported good health and prior fracture have high fracture risk (between 10–15% 5-year risk) over much of the age and BMD range. Women with self reported poor health and prior fracture have very high fracture risk (greater than 15% 5-year risk) over much of the age and osteopenic BMD ranges. Finally, we assessed longer term fracture risk by the above specified 5-year risk categories. The absolute 10-year fracture risk was 8.1% (those with low 5-year risk) 15.8% (those with moderate 5-year risk), 20.2% (those with high 5-year risk), 32.2% (those with very high 5-year risk).

Interpretation

We developed two new models (Model III and Model IV) for the prediction of 5-year absolute fracture risk among women with osteopenic BMD and compared them with calibrated models based on standard risk factors (Model I: age and BMD, Model II: the standard WHO clinical risk factors). The new models had a higher risk gradient than the standard models and showed an improvement in risk classification as assessed by the NRI. The major difference between Models III and IV and standard models is the inclusion of self reported health status. This inclusion accounts for a variety of health conditions as a proxy, but also accounts for difference in fracture risk among those without any comorbidities. The general health variable included in Model IV was also a part of another model predicting hip fracture risk for postmenopausal U.S. women including those with osteoporosis, suggesting the importance of this variable across populations¹³.

Our analysis is not a head to head comparison with the FRAX® model as the specific parameters associated with the different variables and interactions within the model are unknown to us. However, we have shown that the variables age, BMD, self reported health status and height loss provide improvement in fracture prediction over Model II. Our comparison Model II includes the same risk factors as the FRAX® model but is derived from the study population, and as such likely to provide a more optimal classification than the FRAX® model itself. One of the assumptions behind the FRAX® model is that there is a single best model, and that this model can be calibrated to account for known geographic variation in fracture using only hip fracture and mortality data specific to that geographical region. Current country specific FRAX® models indicate substantial between-country differences in fracture risk prediction not explained by the model itself. This suggests that

the model might be missing important risk factors for fracture and/or that there might be heterogeneity in one or more of the model parameters.

Other researchers have considered the clinical problem of assessing absolute fracture risk in osteopenic women. Our final model includes three of the four clinical markers (age, BMD, and prior fracture) that were found to be important in a cohort of French women with osteopenic BMD¹⁴. The fourth marker (high bone turnover) was not available in our study and hence was not included in any of our models. Our final model also includes variables related to all four of the classifiers noted in a cohort of U.S. women with osteopenia¹⁵. Previous fracture and BMD were the two first classifiers, while general health and mobility were the next two classifiers. While there are advantages of including continuous measures of physical health, the model with the SF-36 physical component score does not perform much differently than the categorical measure of general health.

We also established that height loss defined as the difference between measured height and self-reported maximal height is an independent predictor of future clinical low-trauma fracture. Height loss (both historical and measured) is an easily assessed proxy for the presence of vertebral fracture^{16, 17}. X-ray assessment to determine the presence of vertebral fracture is strongly recommended for those with self reported height loss regardless of the absolute risk, as vertebral fracture strongly predicts future fracture¹⁸.

Fall history did not appear in our models, but was associated with modest but not statistically significant increased risk. A study with similar design found that previous falls were an important independent predictor of absolute fracture risk in men and women without osteoporotic BMD¹⁹. We note that physical health status is related to some of the underlying factors related to the propensity to fall. Further adjustment of the model might be warranted for those with poor balance, but otherwise good health. One possible way to assess underlying fall propensity is to simply ask about balance²⁰.

Some but not all comorbidities were associated with increased fracture risk, but models including them did not perform better than the main models. It is likely that most diseases modify fracture risk through their effects on BMD²¹ and/or health status²². Alternatively, the sample size was insufficient to establish a moderate association between comorbidity and fracture risk above that attributable to BMD and/or health status. We note that the SF-36 physical score is also strongly related to other measures including the 6-minute walk test, lower-extremity muscle strength, standing balance, gait speed, and chair rise²³. Thus, if these other measures are available they may serve as potential surrogates for the SF-36 physical health score or self-rated general health.

Recommendations for reporting of bone-mineral density in Canada include a simplified classification of absolute risk based on age, BMD, the presence of fragility fracture and the use of corticosteroids²⁴. These profiles are based on fracture data from a Swedish population, but have since been validated for Canadian women²⁵. Since 10-year risk is roughly double the 5-year risk, Model I corresponds well with both the reported risks from the original Swedish data and the Canadian validation. We note that the models III and IV

show lower fracture risk for those without risk factors who have excellent or very good self-reported general health.

Our study has some limitations. Simple risk assessment models necessarily exclude some important risk factors for a given individual. The cohort only included community-dwelling women at the time of recruitment, and cannot be generalized to all women. Fracture outcomes were based on self-reported fracture with a possible ascertainment bias. Those who had a lower risk profile might under-report fracture, particularly vertebral fracture. This would lead to apparently stronger association between BMD or other risk factors and fracture. Finally, all predictive models should be validated with an independent study sample.

In summary, we have derived two models (Models III and IV) which upon comparison yield a better risk stratification than models with age and BMD alone (Model I) or together with clinical risk factors (Model II). Our risk diagram provides a fracture prediction over the complete age and BMD range, and stratified by fracture and health status thus providing a simple way to determine which women with osteopenia are at low or high risk of fracture. Since these women are mostly found to be at moderate risk of future fractures with the currently available fracture prediction models, the results of our analysis can be used in practice to guide the clinician in further refining fracture risk.

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Figure 1.

Figure 2.

Table 1

Baseline characteristics of the study sample (Osteopenic women ages 50–90 with femoral neck BMD T-score between –1 and –2.5)

		Women (N=2588)	
		Mean	(SD)
Age (years)		66.7	8.3
Weight (kg)		67.3	11.7
Body mass index (kg/m ²)		26.6	4.5
Total hip BMD (g/cm ²)		0.795	0.082
Femoral neck BMD (g/cm ²)		0.646	0.051
SF-36 physical		46.7	10.0
SF-36 mental		53.4	8.7
		n	(%)
Prior fracture (after age 50)		489	18.9
Height loss (5 cm or more)		644	24.9
Comorbidity ^I		597	23.1
Prior falls (last month)		161	6.2
Glucocorticoid use (3+ months)		383	14.8
Antiresorptive use		750	29.0
Current smoker		348	13.5
Alcohol use, 2+ drinks per day		123	4.8
Vertebral Deformity	Normal	1481	57.2
	Grade 1	367	14.2
	Grade 2+	219	8.5
	Missing	521	20.1

^I Previous diagnosis of rheumatoid arthritis, inflammatory bowel disease, kidney disease, liver disease, stroke, neuromuscular disease, uterine cancer, or eating disorder

Table 2

List of risk factors included in comparison models (I and II) and new models (III and IV)

	Risk factors
Model I	Age, BMD
Model II	Age, BMD, prior fracture, parental history of fracture, body mass index, current smoking, alcohol intake, rheumatoid arthritis, and use of glucocorticoids.
Model III	Age, BMD, prior fracture, physical health status (SF-36), and height loss.
Model IV	Age, BMD, prior fracture, self-reported general health (5 categories), and height loss.

Table 3

Comparison of the predicted 5-year absolute fracture risk (%) of clinical fragility fracture for given age, BMD, and profile/ based on four different models

Age	BMD T-score	Model			
		I	II	III	IV
50	-1.0	2.9	2.4	2.1	1.9
	-2.5	6.4	6.6	4.2	3.5
60	-1.0	4.2	3.1	2.5	2.3
	-2.5	9.2	8.3	5.0	4.2
70	-1.0	6.1	3.9	3.1	2.8
	-2.5	13.0	10.5	6.0	5.1
80	-1.0	8.7	5.0	3.6	3.4
	-2.5	18.1	13.2	7.1	6.2

Model I profile: none. Model II profile: Body mass index=26.5 and no additional risk factors. Model III profile: SF-36 at 90th percentile by age and no additional risk factors (prior fracture, height loss). Model IV profile: Excellent general health and no additional risk factors (prior fracture, height loss)