Choice of Lumbar Spine Bone Density Reference Database for Fracture Prediction in Men and Women: A Population-Based Analysis

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Abstract

The diagnosis of osteoporosis in men is controversial, although most studies demonstrate similar fracture rates for men and women with the same level of hip bone mineral density (BMD). Whether this applies to the lumbar spine is currently uncertain and has important implications with respect to choice of reference population for T-score calculation and osteoporosis diagnosis. This question was specifically addressed in the population-based Canadian Multicentre Osteoporosis Study cohort of 4745 women and 1887 men ages 50+ yr at the time of baseline lumbar spine dual energy x-ray absorptiometry. In up to 10 yr of observation, incident clinical major osteoporotic fractures occurred in 110 men (5.8%) vs 543 women (11.4%) ($p < 0.001$). Mean lumbar spine BMD in men was greater than in women, both among those with and those without incident major osteoporotic fracture ($p < 0.001$). Men were at slightly lower risk for incident major osteoporotic fracture than women for an equivalent lumbar spine BMD (age- and BMD-adjusted rate ratio 0.75,

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95% confidence interval 0.60–0.93, $p = 0.008$) with similar findings after adjustment for the World Health Organization fracture risk assessment clinical risk factors or competing mortality. No significant sex difference in the BMD relationship was seen for vertebral fractures (clinical or radiographic) or for all fractures. In summary, this large population-based longitudinal cohort study found similar or lower fracture risk for men vs women after adjustment for absolute lumbar spine BMD and additional covariates. The least complicated model for describing fracture risk is therefore to use the same reference lumbar spine data for generating T-scores in men and women.

Keywords

Bone mineral density; dual energy x-ray absorptiometry; fractures; lumbar spine; sex

Introduction

Bone mineral density (BMD) assessment with dual energy x-ray absorptiometry (DXA) is well established in the diagnosis of osteoporosis and for fracture risk assessment in postmenopausal women (1,2). The diagnosis of osteoporosis in men remains more controversial, and in a review, Khosla et al (3) concluded that the most appropriate definition for osteoporosis in men, in the absence of fractures, was a major unresolved issue and should be the focus of future research.

Since 2001 the International Society for Clinical Densitometry Official Position was to use young female reference data in women and young male reference data in men for T-scores until additional data could clarify the BMD-fracture risk relationship in men (4). Several prospective studies have now shown that men and women with identical hip BMD have the same fracture rates if all other risk factors are the same (5–7). Therefore, the World Health Organization recently has clarified diagnostic criteria for postmenopausal women by emphasizing a reference site (femoral neck) and reference population (white women ages 20–29 yr based upon the Third National Health and Nutrition Examination Survey) (8).

The 2013 International Society for Clinical Densitometry Position Development Conference, after considering the new data available on the BMD-fracture risk relationship in men, recommended “Use a uniform Caucasian (nonrace adjusted) female reference for men of all ethnic groups” (J. Schousboe, personal communication). This recommendation was assigned a grade of “Fair” based upon the paucity of nonhip BMD data, and most particularly the lack of equivalent lumbar spine data, since this is one of the primary clinical assessment sites for DXA. Therefore, this question was specifically addressed in the population-based Canadian Multicentre Osteoporosis Study (CaMos) cohort, one of the first population-based cohorts to include both men and women.

Methods

Study Population

The study sample was selected from participants in an ongoing population-based longitudinal cohort study, the CaMos. We included all CaMos participants ages 50 and over

at study entry for whom follow-up data and lumbar spine BMD measurements were available.

The methodological details of CaMos have been described elsewhere (9). In brief, eligible participants were at least 25 yr of age at the start of the study, lived within a 50-km radius of 1 of 9 Canadian cities (St John's, Halifax, Quebec City, Toronto, Hamilton, Kingston, Saskatoon, Calgary, and Vancouver) and were able to converse in English or French (Chinese in Toronto and Vancouver only). Households were randomly selected from a list of residential phone numbers and participants were randomly selected from eligible household members using a standard protocol. Of those selected, 42% agreed to participate. Ethics approval was granted through McGill University and the appropriate ethics review boards for each participating center. All participants gave written informed consent in accordance with the Helsinki declaration.

Data Collection

Participants completed a standardized interviewer-administered questionnaire (CaMos questionnaire) at baseline, 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 information about previous fractures, and as such assessed: all previous fractures (fracture site, date, and circumstances), family history of osteoporosis/fracture, and falls in past month. Participants had a baseline clinical assessment that included measurement of height, weight, BMD (hip and lumbar spine), and (for subjects aged 50 years and older) lateral thoracic and lumbar spine X-rays.

BMD Measurements

BMD was measured at the lumbar spine (L1–L4) and proximal femur. Seven centers used Hologic densitometers (Hologic, Bedford, MA), and 2 used GE-Lunar densitometers (GE-Lunar, Madison, WI). All Lunar measurements were converted to equivalent Hologic values by the use of standard reference formulas (10). All densitometers were cross-calibrated with a European spine phantom circulated among study centers. A more detailed description of BMD quality control appears elsewhere (11). To more closely match the BMD ranges for men and women, we excluded those who had BMD outside the distribution range of the opposite sex, that is, men with greater BMD than all women ($N = 9$), and women with lower BMD than all men ($N = 17$).

Fracture Assessment

Self-reported incident clinical fractures were identified by yearly postal questionnaire or at the scheduled interval for reassessment (3rd, 5th, and 10th yr after study entry). Confirmation and further information concerning the fracture was gathered with a structured interview that included date, fracture site, circumstances leading to fracture, and medical treatment. Participants who reported fractures were asked for consent to contact the treating physician or hospital for verification and for acquisition of further details. Fractures that occurred without trauma or from a fall of standing height or less were considered to be low trauma. For the current analysis, all low-trauma major osteoporotic fractures (clinical spine, hip, forearm, proximal humerus) that occurred up to the year 10 annual follow-up were

included for the primary analysis. In secondary analyses, we also considered clinical spine fractures alone, any low trauma fracture or any fracture (excluding head, fingers, and toes). In individuals with spine x-rays performed at both baseline and 10 yr, we also studied the occurrence of a new vertebral fracture (grade 2 or higher) using the semiquantitative system of Genant et al (12).

Statistical Methods

Simple descriptive statistics and multiple regression analyses are reported. Absolute lumbar spine BMD (g/cm^2) was used in all analyses because this is equivalent to using a common reference database for men and women. If men and women have the same fracture risk for a given level of BMD then the rate ratio should be 1; a rate ratio significantly greater than unity implies that men have greater risk for fracture for a given level of BMD, whereas a rate ratio significantly less than unity implies that men have lower risk for fracture for a given level of BMD. We used Cox proportional hazards models to determine the importance of male sex (female sex referent) as a BMD-independent risk factor for incident fracture. For the base model, observations were censored at time of death or loss to follow-up. The primary endpoint was time to first major osteoporotic fracture, but sensitivity analyses also were conducted on the basis of other fracture definitions (clinical vertebral, any low-trauma fracture, and any fracture). Age, sex, and lumbar spine BMD were included as covariates in the base model.

There were notable differences between men and women in clinical risk factors for fractures. In a fully adjusted model, we repeated the analysis adjusting for the clinical risk factors used in the World Health Organization fracture risk assessment (FRAX) paradigm: body mass index, previous low-trauma fracture after age 50, parental hip fracture, high alcohol intake, current smoking, rheumatoid arthritis, and prolonged glucocorticoid use (secondary causes of osteoporosis was not included as it is ignored by FRAX when BMD is provided) (13). A parallel logistic regression analysis was performed for radiographic incident vertebral fractures. Because men and women have different underlying mortality risk, we considered 2 options in the case of death: as censored (base model) and as a competing risk (a design component of FRAX) (14,15). All statistical analyses were performed with Statistica (Version 10.0, StatSoft Inc, Tulsa, OK).

Results

There were 4745 eligible women and 1887 eligible men who were similar with respect to mean age (women 65.8 yr vs men 65.3 years, $p = 0.021$). Women had a significantly greater prevalence of previous fracture, parental hip fracture, and rheumatoid arthritis, whereas men had a greater prevalence of current smoking and high alcohol intake (Table 1). As expected, mean lumbar spine BMD was significantly greater in men than women ($p < 0.001$).

Mean follow-up for men was 8.3 years vs 8.7 years for women ($p < 0.001$). The difference reflected greater mortality among men than women (17% vs 11%, $p < 0.001$) whereas loss to follow-up for reasons other than death was similar (22% vs 21%, $p = 0.812$, respectively). Incident clinical major osteoporotic fracture within 10 yr occurred in 110 men (5.8%) vs 543

women (11.4%), corresponding to fracture rates of 7.0 and 13.2 per 1000 person-years, respectively, and the differences were statistically significant ($p < 0.001$).

Men with incident major osteoporotic fracture had significantly greater mean lumbar spine BMD than women with major osteoporotic fracture (0.971 ± 0.175 vs 0.851 ± 0.164 , $p < 0.001$; Fig. 1). However, men without incident major osteoporotic fracture also had higher mean BMD than women without incident major osteoporotic fracture (1.049 ± 0.170 vs 0.927 ± 0.168 , $p < 0.001$). In fact, even mean lumbar spine BMD for men with major osteoporotic fracture was higher than for women without major osteoporotic fracture ($p = 0.007$).

Increasing age and lower lumbar spine BMD were significantly associated with incident major osteoporotic fracture in both men and women in all analyses ($p < 0.001$). No significant sex-BMD interaction was seen in an age-adjusted model (P-interaction = 0.292) or after adjustment for FRAX risk factors (P-interaction = 0.657). In the base model (adjusted for age and lumbar spine BMD only, death censored), men were at lower risk for incident major osteoporotic fracture than women (rate ratio 0.75, 95% CI 0.60–0.93, $p = 0.008$; Table 2). Adjustment for FRAX clinical risk factors (death censored or with competing mortality) did not meaningfully alter this relationship. Similar results were seen for any low trauma fracture, with a rate ratio for men vs women significantly less than unity. For clinical vertebral fractures or for any fracture, men and women showed the same adjusted fracture risk.

Paired baseline and year 10 spine x-rays were available in 822 men (70.7% of those attending the years 10 visit) and 2214 women (68.3% of those attending the year 10 visit). Of these, new vertebral fractures were identified in 60 (6.7%) and 167 (7.5%), respectively. Radiographic vertebral fracture risk for men vs women adjusted for lumbar spine bone density did not differ significantly from unity.

Discussion

We found that unadjusted risk of incident major osteoporotic fractures were much less in men (approximately half) than in women. As expected, mean lumbar spine BMD was greater in men than women overall and when stratified by fracture status. The finding of greater mean BMD in men with (or without) low-trauma fracture is attributed to the sex-related difference in BMD distribution rather than an intrinsic difference in skeletal fragility. In fact, men were at slightly lower (not higher) major osteoporotic fracture risk than women for an equal level of absolute lumbar spine BMD (equivalent to using a common reference population for T-score generation). This would argue against the use of sex-specific reference data. Secondary analyses in which various fracture definitions and covariate adjustments were used provided similar results with equal or lower fracture risk for men vs women after adjustment for absolute lumbar spine BMD and additional covariates.

Our findings are consistent with those that had been noted for hip BMD, where men have not been found to be at a greater risk of fracture than women at an equivalent level of absolute BMD despite the observation that men sustaining fractures have greater average

BMD than women sustaining fractures (5–7). This has led to the recommendation from the World Health Organization that a common reference database based upon US white women be adopted for diagnosis of osteoporosis from DXA T-scores in both women and men (8). The same would appear to apply for lumbar spine DXA when used to assess fracture risk. Our data indicate that use of male reference data with greater peak mean BMD for T-score calculation would widen the apparent difference between men and women, with overestimation in the apparent fracture risk for men.

Limitations to this study include the relatively small number of men and, by extension, a relatively small number of men with fractures. This results in relatively wide confidence intervals for the effect of sex in the regression models. We also had limited power to conduct detailed testing for interactions and our study does not preclude sex-differences in the gradient of risk. Significant age-BMD and sex-BMD interactions have been reported by others (16,17). Cummings et al (17) reported that the risk of nonvertebral fracture was substantially lower in men than in women for all T-scores of hip BMD, regardless of whether sex-specific or female reference values were used.

In summary, this large population-based longitudinal cohort study found similar or lower fracture risk for men vs women after adjustment for absolute lumbar spine BMD and additional covariates. The least complicated model for describing fracture risk is therefore to use the same reference lumbar spine data for generating T-scores in men and women.

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Appendix

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Fig. 1. Mean lumbar spine BMD for men and women with and without incident MOF. Error bars are 95% confidence limits. BMD, bone mineral density; MOF, major osteoporotic fractures.

Table 1Baseline and Follow-Up Characteristics of the Study Sample (Women and Men Ages 50 and Older^a)

Characteristic	Women	Men	<i>p</i> Value
	N = 4797	N = 1921	
Age, yr	65.8 ± 8.8	65.3 ± 9	0.021
Body mass index, kg/m ²	27.1 ± 4.9	27.2 ± 3.8	0.388
Prior fracture	539 (11.4)	95 (5)	<0.001
Parental hip fracture	398 (8.4)	112 (5.9)	0.001
Rheumatoid arthritis	43 (0.9)	5 (0.3)	0.005
Prolonged glucocorticoid use	68 (1.4)	25 (1.3)	0.735
Current smoking	624 (13.2)	333 (17.6)	<0.001
High alcohol intake	41 (0.9)	128 (6.8)	<0.001
Lumbar spine BMD, g/cm ²	0.918 ± 0.17	1.045 ± 0.171	<0.001
Follow-up, yr	8.7 ± 2.4	8.3 ± 2.7	<0.001
Incident major osteoporotic fractures	543 (11.4)	110 (5.8)	<0.001
Incident vertebral fractures (clinical)	133 (2.8)	29 (1.5)	0.003
Incident vertebral fractures (radiographic) ^b	167 (7.5)	50 (6.1)	0.165
Incident low-trauma fractures	625 (13.2)	126 (6.7)	<0.001
Incident any fractures	771 (16.2)	195 (10.3)	<0.001

Note: Data are mean ± SD or N (percentage).

Abbr: BMD, bone mineral density.

^aExcludes outliers (17 women and 9 men) with BMD outside the range for the opposite sex.

^bFrom paired baseline and year 10 spine x-rays in 2214 women and 822 men.

Table 2

Effect of Male Sex (vs Female Referent) for Incident Low-Trauma Fracture From Cox Proportional Hazards Models Using Absolute Lumbar Spine BMD

Model and fracture type	Rate ratio	95% Confidence interval	p Value
Base model: Age and lumbar spine BMD adjusted (death censored)			
Any major osteoporotic fracture	0.75	0.60–0.93	0.008
Vertebral fracture (clinical)	1.01	0.66–1.55	0.961
Vertebral fracture (radiographic)	1.32	0.93–1.89	0.122
Any low-trauma fracture	0.75	0.61–0.92	0.005
Any fracture	0.93	0.78–1.09	0.371
Fully adjusted model: FRAX covariates and lumbar spine BMD (death censored) ^a			
Any major osteoporotic fracture	0.79	0.64–0.99	0.040
Vertebral fracture (clinical)	1.09	0.70–1.68	0.705
Vertebral fracture (radiographic)	1.32	0.92–1.91	0.133
Any low-trauma fracture	0.79	0.65–0.97	0.026
Any fracture	0.97	0.82–1.14	0.686
Fully adjusted model: FRAX covariates and lumbar spine BMD (competing mortality) ^a			
Any major osteoporotic fracture	0.76	0.61–0.94	0.012

Abbr: BMD, bone mineral density; FRAX, fracture risk assessment.

^aAge, body mass index, previous fracture, parental hip fracture, rheumatoid arthritis, prolonged glucocorticoid use, current smoking, high alcohol intake.