ORIGINAL ARTICLE

JBMR®

Contribution of Lumbar Spine BMD to Fracture Risk in Individuals With *T*-Score Discordance

Dunia Alarkawi,[1] Dana Bliuc,[1] Tuan V Nguyen,[1,2] John A Eisman,[1,2,3,4,5] and Jacqueline R Center[1,2,3]

[1]Osteoporosis and Bone Biology, Garvan Institute of Medical Research, Sydney, Australia
[2]Faculty of Medicine, University of New South Wales (UNSW) Australia, Sydney, Australia
[3]Clinical School, St Vincent's Hospital, Sydney, Australia
[4]Clinical Translation and Advanced Education, Garvan Institute of Medical Research, Sydney, Australia
[5]School of Medicine Sydney, University of Notre Dame Australia, Sydney, Australia

ABSTRACT

Fracture risk estimates are usually based on femoral neck (FN) BMD. It is unclear how to address *T*-score discordance, where lumbar spine (LS) *T*-score is lower than FN *T*-score. The objective of this work was to examine the impact of LS BMD on fracture risk, in individuals with lower LS *T*-score than FN *T*-score. Participants aged 60+ years from the Dubbo Osteoporosis Epidemiology Study with LS and FN BMD measured at first visit, and were followed from 1989 to 2014. Five-hundred and seventy-three (573) of 2270 women and 131 of 1373 men had lower LS than FN *T*-score by $\geq$0.6 standard deviation (SD) (low-LS group based on least significant change). In low-LS women, each 1 SD lower LS *T*-score than FN was associated with a 30% increase in fracture risk (hazard ratio [HR] 1.30; 95% CI, 1.11 to 1.45). For low-LS men there was a 20% nonsignificant increase in fracture risk for each 1 SD lower LS than FN *T*-score (HR 1.20; 95% CI, 0.10 to 1.67). Low-LS women had greater absolute fracture risks than the rest of the women. This increased risk was more apparent for lower levels of FN *T*-score and in older age groups. At an FN *T*-score of –2, low-LS women had a 3%, 10%, and 23% higher 5-year absolute fracture risk than non-low LS women in the 60 to 69 year, 70 to 79 year, and 80+ years age-groups, respectively. Furthermore, an osteoporotic LS *T*-score increased 5-year absolute fracture risk for women with normal or osteopenic FN *T*-score by 10% to 13%. Men in the low-LS group had very few fractures; therefore, a meaningful analyses of fracture risk could not be conducted. This study shows the significant contribution of lower LS BMD to fracture risk over and above FN BMD in women. A LS BMD lower than FN BMD should be incorporated into fracture risk calculators at least for women in older age-groups.

KEY WORDS: OSTEOPOROSIS; GENERAL POPULATION STUDIES; FRACTURE RISK ASSESSMENT

Introduction

Bone mineral density (BMD) is currently the best tool for assessment of fracture risk. A 1 standard deviation (SD) lower BMD increases fracture risk by 1.5-fold to 2.0-fold.[1] BMD is measured at several skeletal sites, but the lumbar and femoral regions are the most widely used in clinical practice.[2] The femoral neck (FN) region is widely regarded as the optimum site for osteoporosis diagnosis and fracture risk assessment because it has good predictive value for all major osteoporotic fractures[3–5] and because lumbar spine (LS) bone density is often spuriously elevated by degenerative changes. Thus, FN BMD is currently the only validated BMD measurement for use in fracture risk prediction and fracture risk calculators, although LS BMD measurements are commonly performed, especially for monitoring responses.[6]

Osteoporosis is defined as a LS or FN *T*-score of $\leq$ –2.5 below a young normal mean. However, a significant proportion of the population has *T*-score discordance, in which different categories of *T*-scores (osteoporosis, osteopenia, and normal) are present at the LS and FN.[7,8] There are several potential causes for BMD discordance, including physiologic, pathological, anatomic, artifactual, and technical.[9] Various studies have analyzed the prevalence, risk factors, and impact of such discordance on the management of osteoporosis.[9–13] However, only a few studies have addressed the issue of discordance.

T-score discordance in which the LS is worse than the FN can lead to uncertainty in the decision-making process and fracture risk assessment. Several studies have estimated that a lower LS than FN *T*-score may lead to an increase in fracture risk, with this risk ranging between 10% and 30% depending on the way the fracture risk was calculated.[14,15] However, the impact of low LS BMD on fracture risk remains controversial and warrants further prospective assessment.

Therefore, the aim of this study was to comprehensively examine the impact of LS BMD on fracture risk in individuals with lower LS *T*-score than FN *T*-score.

Received in original form June 2, 2015; revised form July 29, 2015; accepted August 2, 2015. Accepted manuscript online August 4, 2015.
Address correspondence to: Jacqueline R Center, MBBS, MS, PhD, Garvan Institute of Medical Research, 384 Victoria St Darlinghurst NSW 2010 Australia. E-mail: j.center@garvan.org.au

Journal of Bone and Mineral Research, Vol. 31, No. 2, February 2016, pp 274–280
DOI: 10.1002/jbmr.2611

Subjects and Methods

Study population and design

This study was carried out as part of the Dubbo Osteoporosis Epidemiology Study, as reported.[16,17] In brief, The Dubbo Osteoporosis Epidemiology Study started in 1989 and is an ongoing study of community-dwelling women and men aged >60 years residing in the regional city of Dubbo, approximately 400 km northwest of Sydney, Australia. The study has been approved by the St Vincent's Hospital Human Research Ethics committee. In 1989, the semi-urban city of Dubbo had a population of 32,000 people, of whom 98.6% were white. Dubbo was chosen for its relative isolation, centralized health services, stable population, and age and sex distribution similar to the Australian population.

The current study included all participants who were ≥60 years and had bone density measurements at both LS and FN regions at the time of their first clinic visit. The study period extended from April 1989 to December 2014. Participants were followed until the study end or until they sustained their initial minimal trauma fracture, or died.

Fracture ascertainment and mortality data

Fracture events occurring from April 1989 onward were identified through radiological services in Dubbo. Circumstances of the fracture were obtained through direct interview. Only minimal trauma fractures (following a fall from standing height or less) were included. High-trauma fractures, pathological fractures (eg, cancer, Paget's disease), as well as fractures of the head, fingers, and toes were excluded. Fractures were also classified according to initial fracture type: hip, vertebral, and nonhip nonvertebral fracture. Vertebral fractures were those coming to clinical attention (symptomatic fractures) without systematic screening for vertebral deformities, or where a new vertebral fracture was identified on X-rays for other reasons.

Mortality status of study participants was identified from systematic searches of funeral lists, local newspapers, and Dubbo media reports, and was verified by death certificates from the New South Wales Registry of Births, Deaths and Marriages.

BMD measurements and WHO *T*-score classification

BMD (g/cm^2) was measured at the site of FN and LS by DXA using a GE LUNAR Densitometer (Madison, WI, USA). BMD was analyzed in three categories: normal, osteopenia, and osteoporosis, based on the WHO *T*-score classification. (*T*-score ≤ 2.5 SD osteoporotic, *T*-score > –2.5 and <1.0 osteopenic and *T*-score ≥ –1.0 normal. *T*-score reference ranges were calculated using the female and male BMD reference ranges provided by the GE LUNAR Densitometer, using the Australian Spine reference population for LS BMD measurements and the Australian Femur reference population for FN BMD measurements. Those reference ranges are similar to the most up-to-date BMD reference ranges generated from the Geelong Osteoporosis Study and recommended by the Australia and New Zealand Bone and Mineral Society and Osteoporosis Australia for use Australia-wide.[18] Absolute *T*-score difference was calculated by subtracting FN *T*-score from LS *T*-score.

Least significant change and study groups

Least significant change (LSC) is the least amount of BMD change that can be considered statistically significant. It is normally used to compare the difference between two BMD measurements at the same site. If the difference is the same or greater than the LSC, then the change is considered to be statistically significant.[19] In order to determine whether LS BMD was significantly different from FN BMD, the LSC was calculated using the SD of measurement error within subjects for LS BMD (0.027 g/cm^2) and for FN BMD (0.035 g/cm^2)[20] and the following formulas:

$$\text{Combined BMD SD} = \sqrt[2]{\left(0.035\right)^2 + \left(0.027\right)^2}$$

$$\text{LSC} = 2 \times \sqrt[2]{2 \times \text{BMDSD}}$$

$$\text{LSC} = 0.6\text{SD}$$

Accordingly, individuals were divided into three groups: (1) "Low LS" group (LS *T*-score – FN *T*-score ≤ –0.6); (2) "No difference" group (LS *T*-score – FNT –score > –0.6 and < +0.6); and (3) "High LS" group (LS *T*-score – FN *T*-score ≥ +0.6). There was no significant difference in fracture risks between the "No difference" and "High LS" groups in both men and women (hazard ratio [HR] 1.02; 95% CI, 0.76 to 1.38; $p = 0.9$ versus HR 0.98; 95% CI, 0.73 to 1.32; $p = 0.9$) in men and (HR 1.05; 95% CI, 0.88 to 1.25; $p = 0.6$ versus HR 0.96; 95% CI, 0.80 to 1.14; $p = 0.6$) in women. Therefore, those two groups were combined into one group: the "non-low LS" group, to which the "low LS" group was compared.

Clinical characteristics

Information on falls, postural stability, and osteoporosis medication history was collected through a direct interview by a study coordinator. Falls were analyzed according to fall history in the 12 months before the first clinic visit (yes/no). Postural stability was analyzed using two measurements: sway (using a sway meter that measures displacements of the body at the level of the waist) and quadriceps strength (using a spring gauge), which were assessed by the study coordinator at the time of the first clinic visit.

Statistical analysis

All statistical analyses were performed using SAS software, version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Estimation of fracture risk

Absolute fracture risk

Fracture risk for the "low LS" group compared with the rest of the cohort (non-low LS) was restricted to women because of the limited number of fractures ($n = 19$) in the "low LS" group in men. The incidence of fracture was calculated as the number of fractures per 1000 person-years of follow-up, assuming a Poisson distribution. Follow-up time was calculated from the beginning of the study to first low-trauma fracture, or death, or end of the study. Fracture rates were expressed relative to age at baseline visit. The estimation of five-year fracture risk according to continuous FN *T*-score was performed using an age and FN *T*-score–adjusted Cox proportional hazards model. Five-year fracture risk according to LS and FN *T*-scores was also estimated according to BMD classes based on WHO classification.

Relative fracture risk

Multivariate analyses of the contributors to fracture risk were performed for the "low LS" group using Cox proportional hazards models. Variables analyzed included: FN *T*-score, *T*-score difference, age, weight, height, quadriceps strength, sway, falls (yes/no), prior fracture (fracture after the age of 50 years and before the entry to the study), and prior treatment (history of osteoporosis medication including hormone replacement or other antiresorptive therapy).

Results

Study population characteristics

The study included 2270 women and 1373 men. The mean age was 69 ± 6.8 years in women and 70 ± 6.0 years in men, The mean LS *T*-score was –1.2 ± 1.7 in women and +0.2 ± 1.8 in men. Women had 726 incident fractures over 23,614 person-years and men had 222 fractures over 14,751 person-years. The average interval between the baseline visit and initial fracture was 6.5 years (IQR, 3 to 11 years) for women and 7 years (IQR, 2 to 12 years) for men. The average interval between baseline visit and initial fracture according to fracture type was 8 years (IQR, 3 to 15 years) for hip fracture in women and 11 years (IQR, 3 to 15 years) in men, 8 years (IQR, 4 to 13 years) for vertebral fracture in women and 6 years (IQR, 2 to 12 years) in men, 5 years (IQR, 2 to 10 years) for non-hip non-vertebral fracture in women and 7 years (IQR, 3 to 11 years) in men.

There were 573 (25%) women and 131 (10%) men with LS *T*-score in the "low LS" group, 855 (38%) women and 343 (25%) men in the "no difference group" and 842 (37%) women and 899 (65%) men in the "high LS" group. "Low LS" women were younger and reported fewer falls than other women. "Low LS" men were more likely to be treated than other men. Fracture type was different between the two groups, with more vertebral fractures but fewer hip fractures in the "low LS" women compared with the rest of the women (Table 1).

Fracture rates

"Low LS" women comprised 29% ($n = 404$), 21% ($n = 139$), and 15% ($n = 30$) of women in the 60 to 69 years, 70 to 79 years, and >80 years age-groups, respectively. "Low LS" women had a higher fracture rate compared to other women (35/1000 person-years [95% CI, 32 to 40] versus 29/1000 person-years [95% CI, 27 to 32], respectively) (Table 2).

Fracture rate difference between the two groups was age-dependent. It was increased 1.2-fold in the 60 to 69 years age group (27/1000 person-years [95% CI, 23 to 32] in "low LS" women versus 24/1000 person-years [95% CI, 21 to 27] in "non-low LS" women). The difference was more apparent with increasing age, with a 1.5-fold and 2.0-fold higher fracture rates in the "low LS" compared to the "non-low LS" women in the 70 to 79 years and >80 years age-groups, respectively. In the 70 to 79 years age-group it was 57/1000 person-years (95% CI, 45 to 73) versus 35/1000 person-years (95% CI, 30 to 41), respectively. In the >80 years age-group it was 126/1000 person-years (95% CI, 79 to 203) versus 63/1000 person-years (95% CI, 49 to 80), respectively (Table 2).

Five-year absolute fracture risk according to continuous FN *T*-score and age-groups

As expected, five-year fracture risk for women increased with decreasing FN *T*-score independent of LS *T*-score. However, "low LS" women had a higher fracture risk for every level of FN *T*-score in all age-groups, but this risk was more evident in older age (Fig. 1). For example, at a FN *T*-score of –2 in the 60 to 69 years age-group, "low LS" women had 3% higher absolute fracture risk than "non-low LS" women. For the same *T*-score in the 70 to 79 years age-group, "low LS" women had 10% higher absolute fracture risk compared to "non-low LS" women, whereas in the >80 years age-group, "low LS" women had 23% higher absolute fracture risk. As FN *T*-score approached normal levels, fracture risks for the younger but not older age-groups converged. Even for an FN *T*-score of zero, five-year absolute fracture risk was significantly

Table 1. Characteristics of "Low LS" and "Non-Low LS" Groups

	Women		Men	
	Non-low LS ($n = 1697$)	Low LS ($n = 573$)	Non-low LS ($n = 1242$)	Low LS ($n = 131$)
Age (years)[a]	70 (7)	**68 (6)**	70 (6)	69 (6)
Weight (kg)[a]	68 (14)	67 (14)	81 (13)	80 (17)
Height (cm)[a]	160 (6)	160 (6)	173 (7)	173 (8)
Body mass index (kg/m^2)[a]	27 (5)	26 (5)	27 (4)	27 (5)
Lumbar spine *T*-score[a]	–0.7 (1.6)	**–2.5 (1.2)**	0.4 (1.8)	**–1.8 (1.3)**
Femoral neck *T*-score[a]	–1.5 (1.1)	**–1.2 (1.1)**	–1.1 (1.1)	**–0.6 (1.4)**
Quadriceps strength (kg)[a]	21 (8)	21 (8)	35 (10)	36 (10)
Sway (mm^2)[b]	735 (480–1178)	754 (483–1147)	700 (437–1056)	676 (437–1178)
Falls[c]	603 (36)	**166 (29)**	415 (33)	42 (32)
Treated[c]	434 (26)	169 (30)	44 (4)	**13 (10)**
Prior fracture[c]	278 (16)	97 (17)	134 (11)	20 (15)
Initial fractures[c]	509 (30)	217 (38)	203 (16)	19 (15)
Fracture type[c]				
Hip	91 (18)	**13 (6)**	36 (18)	–
Vertebral	152 (30)	**101 (47)**	78 (38)	10 (53)
Nonhip nonvertebral	266 (52)	103 (47)	89 (44)	9 (47)

Values in bold are significant differences at $p \leq 0.05$ between "low LS" and "non-low LS" groups for the same gender.
LS = lumbar spine.
[a]Values represent means (SD) for continuous variables.
[b]Values represent median (interquartile range: 25%–75%) for continuous variables.
[c]Values represent number (%) for categorical variables.

Table 2. Initial Fracture Rates for "Low LS" and "Non-Low LS" Women According to Age-Group

	Non-low LS			Low LS		
	Individuals (*n*)	Fracture (*n*)	Initial fracture rates per 1000 person-years (95% CI)	Individuals (*n*)	Fracture (*n*)	Initial fracture rates per 1000 person-years (95% CI)
Women						
All	1697	509	29 (27–32)	573	217	**35 (32–40)**
60–69 years[a]	1006	271	24 (21–27)	404	130	27 (23–32)
70–79 years[a]	517	172	35 (30–41)	139	70	**57 (45–73)**
>80 years[a]	174	66	63 (49–80)	30	17	**126 (79–203)**

Values in bold are significant at $p \leq 0.05$.
LS = lumbar spine.
[a]Age at baseline.

increased in the older age groups of "low LS" women compared to "non-low LS" women (5% in the 70 to 79 years age-group and 15% in the 80+ years age-group) (Fig. 1).

Five-year absolute fracture risk according to LS and FN *T*-scores WHO classification

Given the common clinical use of the WHO classification of osteoporosis in the diagnosis and decision-making process, the fracture risk according to LS and FN WHO classification was examined. Women with osteoporosis at both LS and FN had the highest fracture risk (32%). Women with osteopenic LS and normal FN had a similar fracture risk to women with normal LS and osteopenic FN (8% versus 10%, respectively). Similarly, women with osteoporotic LS and osteopenic FN had a similar fracture risk to women with osteopenic LS and osteoporotic FN (24% versus 25%, respectively). However, having an osteoporotic LS with a normal FN or an osteopenic FN increased absolute fracture risk by 10% and 13%, respectively (Fig. 2).

Relative fracture risk

In "low LS" women, adjusting for FN *T*-score and *T*-score difference demonstrated that for every 1 SD LS *T*-score lower than FN *T*-score fracture risk increased by 32% (HR 1.32; 95% CI, 1.13 to 1.47; $p = 0.002$). In multivariate modeling, this risk was essentially unchanged at 30% (HR 1.30; 95% CI, 1.11 to 1.45; $p = 0.004$).

In "low LS" men, adjusting for FN *T*-score and *T*-score difference demonstrated that for every 1 SD LS *T*-score lower than FN *T*-score was associated with 16% increase in fracture risk, although this was not significant (HR 1.16; 95% CI, 0.19 to 1.61; $p = 0.65$). This risk remained nonsignificant in multivariate modeling (HR 1.20; 95% CI, 0.10 to 1.67; $p = 0.61$).

Sensitivity analyses (fracture risk excluding individuals with prior treatment)

The analyses were repeated after excluding women with prior treatment (hormone therapy [HT] only, $n = 368$; bisphosphonates [BP] or other osteoporosis medication, $n = 160$; HT + BP or

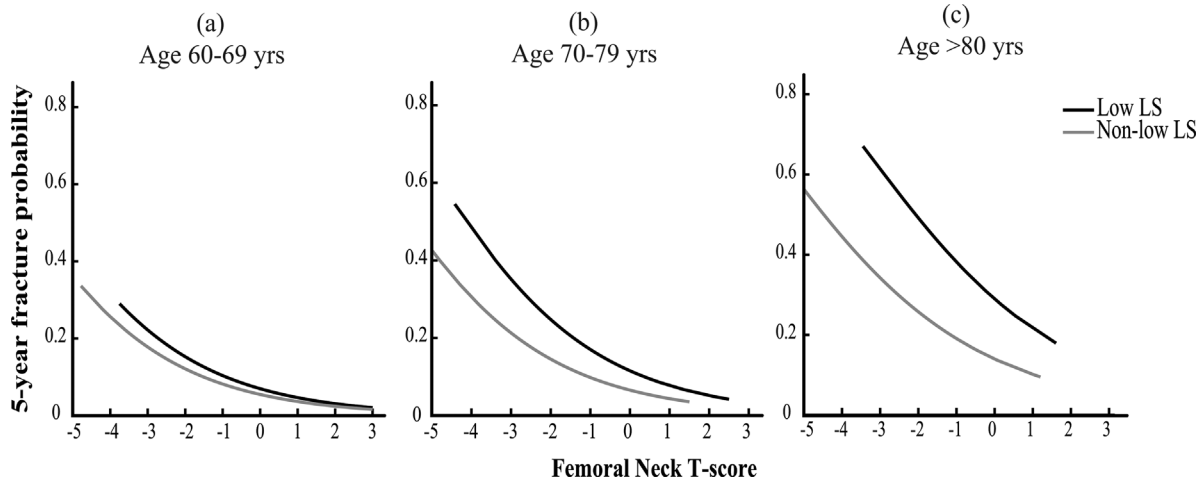

Fig. 1. Five-year absolute fracture risks for "low LS" and "non-low LS" women according to continuous femoral neck *T*-scores and age (60–69 years, 70–79 years, and 80+ years).

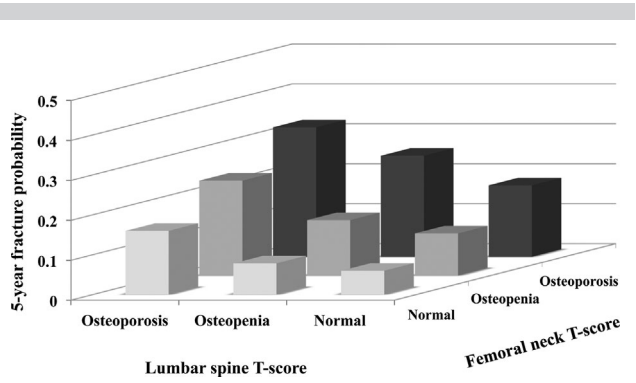

Fig. 2. Five-year absolute fracture risks for women according to osteoporosis, osteopenia, and normal WHO classification at the lumbar spine and femoral neck.

other osteoporosis medication, $n = 75$). The significant increase in fracture risk remained for every 1 SD lower LS *T*-score than FN in "low LS" women (30% [HR 1.30; 95% CI, 1.08 to 1.47; $p = 0.01$] after adjusting for FN *T*-score and *T*-score difference and 29% [HR 1.29; 95% CI, 1.07 to 1.46; $p = 0.01$] after adjusting for all variables).

After excluding men with prior treatment (testosterone only, $n = 12$; BP or other, $n = 45$), there was still a nonsignificant increase in fracture risk for every 1 SD lower LS than FN *T*-score in "low LS" men (36% [HR 1.36; 95% CI, 0.49 to 1.72; $p = 0.3$] after adjusting for FN *T*-score and *T*-score difference and 42% [HR 1.42; 95% CI, 0.5 to 1.77; $p = 0.3$] after adjusting for all variables).

Discussion

This is the first study, to our knowledge, to comprehensively examine the impact of low LS BMD on fracture risk while accounting for different age-groups and different levels of FN *T*-score. In women with significantly lower LS than FN *T*-score (low LS group), there was a significant 30% increase in fracture risk for each 1 SD lower LS than FN *T*-score. Low LS women had a higher absolute fracture risk for all levels of FN BMD, which was more marked in the osteopenic and osteoporotic ranges of FN BMD and in older age-groups. In low LS men, every 1 SD lower LS than FN *T*-score increased fracture risk by 20%; however, this was not significant because of the limited number of fractures in men with a lower LS *T*-score than FN *T*-score.

In this cohort, 25% of women had a significantly lower LS *T*-score than FN *T*-score (0.6 SD) compared to 10% of men. Consequently, men were under-represented in the "low LS" group, in which there were only 19 men with a fracture. Therefore, a meaningful analyses of fracture risk for low LS men was not achievable. The low numbers of men with significantly lower LS *T*-score than FN *T*-score may be explained by the increased bone loss at LS associated with loss of estrogen at menopause, especially in the first ten years post-menopause.[21,22] Indeed menopause was found to be strongly associated with *T*-score discordance, where LS BMD was lower than FN BMD in a couple of studies.[12,23] Moreover, it is noted that men have a higher mean LS BMD than women overall. This could be explained by the higher frequency of spine degenerative changes including ligamental calcifications and osteophyte formation that occur particularly in older men, which is why LS BMD measurements are generally ignored in both older men and women.

Currently, FN BMD is considered the gold standard for diagnosis of osteoporosis and assessment of fracture risk.[1,3,24,25] FN BMD has the highest predictive value for all major osteoporotic fractures, particularly for hip fractures, which are considered the most severe fracture type.[1,3,5,26] In part, this is considered to be due to the confounding of LS BMD values by degenerative changes that spuriously elevate the measured LS BMD values. Moreover, the gradient of risk of FN BMD for fracture at any given FN BMD in men seems to be similar to that in women.[5,27,28] Additionally, the predictive value of FN BMD is not significantly attenuated with time, suggesting it can be used in assessing long-term fracture probabilities.[5,25]

However, lower BMD measured at sites other than the FN, such as the LS, has been shown to indicate increased fracture risk.[26,29,30] Two studies have reported that women with LS *T*-score lower by 1 SD than FN *T*-score had increased fracture risk.[14,15] In one cross-sectional retrospective study, women with LS *T*-score lower by 1 SD than FN *T*-score had a 14% increased risk of fracture.[15] Another group reported a 10% increase in fracture risk per 1 SD lower LS *T*-score compared to FN *T*-score.[14] This was similar to the findings in a recent meta-analysis, which concluded that a 9% increase in fracture risk was associated with each 1 SD decrease in LS *T*-score compared to FN.[6] The difference between those findings and the current study is that the current study focused on fracture risk in those individuals with a statistically significant lower LS *T*-score than FN, based on the LSC (0.6 SD). This is the group of interest where the impact of low LS may be expected to increase fracture risk, and women demonstrated an increase of 30% in fracture risk for each 1 SD lower LS *T*-score compared to FN.

A novelty of this study is its investigation of the impact of low LS *T*-score, specifically in women who had significantly lower LS *T*-score than FN *T*-score, taking into account different age-groups and different FN *T*-score levels. When FN BMD was analyzed as a continuous variable, "low LS" women had higher five-year absolute fracture risks for all FN *T*-score levels and across all age-groups, which was more pronounced in the lower FN *T*-score levels and in older age. For example, for a *T*-score of –2.0, "low LS" women in the 60 to 69 years age-group had a 3% increased five-year fracture risk, a 10% increase in women in the 70 to 79 years age-group, and and a 23% increase in women in the 80+ years age-group compared to "non-low LS" women. Even at a FN *T*-score of zero, five-year absolute fracture risk was significantly increased in the older age-groups of "low LS" women compared to "non-low LS" women (5% in the 70 to 79 years age-group, and 15% in the 80+ years age-group).

Comparatively, when women of all ages were grouped according to the WHO classification at the LS and FN, women with a LS *T*-score that was one or two WHO classes below their FN *T*-score had a higher five-year absolute fracture risk. Overall fracture risk has been reported to be increased by 30% when the LS *T*-score was one or two WHO classes below the FN *T*-score.[15] In the present study, the addition of an osteoporotic LS to a normal or osteopenic FN, increased absolute fracture risks by 10% and 13%, respectively.

T-score discordance creates uncertainty over how to interpret bone density measurements, especially when LS *T*-score is much lower than FN *T*-score. Some suggest using the lowest *T*-score of the two measurements.[31] The National Osteoporosis Foundation recommends treatment for an LS *T*-score in the

osteoporotic range regardless of the estimated risk.[32] Other studies including a set of Canadian guidelines suggested substituting the minimum *T*-score obtained from sites other than the FN for the FN *T*-score.[33–36] However, this did not improve fracture risk prediction and was reported as systematically overestimating fracture risk.[34,35,37] Some of those studies, which focused on use of multiple sites for the diagnosis of osteoporosis, have proposed combining LS and FN measurements to enhance the accuracy for risk characterization.[34,35,38] A report from the Manitoba cohort and a meta-analysis of ten international cohorts have investigated the impact of low LS BMD in light of the Fracture Risk Assessment Tool (FRAX) estimated risks and it was suggested that a procedure based on the difference (offset) between the LS and FN *T*-scores could enhance fracture risk prediction with FRAX.[6,14] However, in clinical practice this is not a simple practical solution.

The present study provides further evidence about the significant contribution of a lower LS BMD than FN BMD to fracture risk in people with *T*-score discordance. The novelty of this study is the comparisons of absolute changes in fracture risk over time in individuals with a 0.6 SD lower LS *T*-score than FN *T*-score. However, this also means that those estimates would be even higher in an individual with a LS *T*-score that is more than 0.6 SD lower than FN *T*-score (eg, 1 SD). The findings highlight the importance of incorporating into the management process the low LS *T*-score especially for women $>$70 years old with a normal or osteopenic FN who are generally considered in the low fracture risk category and may not necessarily require treatment. In these groups, at least, fracture risks should be assessed based on both FN and LS *T*-scores to provide a more accurate risk estimate.

Although BMD is one of the major determinants of bone strength and fracture risk,[5] there is considerable overlap in BMD values between individuals who develop fractures and those who do not.[39] The trabecular bone score (TBS), a new measurement using the grayscale variation in DXA images, has been shown to add value to BMD in fracture risk assessment.[40–42] This could be of particular importance when BMD is in the non-osteoporotic range and is not sufficient for risk stratification. One study reported that spine TBS predicted fracture almost as well as LS BMD, and that the combination was superior to either measurement alone.[43] Their relevant contributions remain to be studied where both TBS and LS BMD are available.

This study has a number of strengths. It is a large population-based prospective study of men and women followed for more than 20 years. The large number of fracture events that were recorded enabled meaningful analyses of fracture risk according to different levels of BMD in women. This study evaluated the impact of low LS BMD on fracture risk by providing a comprehensive comparison of fracture outcomes among different levels of FN BMD. However, this study has some limitations. The cohort is predominantly white, and the results may not be the same in other ethnic groups. There were fewer men than women with lower LS *T*-score than FN *T*-score and with much fewer fractures; therefore, meaningful analyses could not be conducted. All LS BMD measurements were included; the presence of any pathology that could potentially increase BMD such as osteoarthritis or sclerosis was not examined. However, this could only result in the number of people with lower LS *T*-scores being underestimated, because they would have been misclassified as having higher LS *T*-scores. Baseline measurements for risk factors were used for fracture risk assessment; therefore, any changes over the period of follow-up (improvement or deterioration) in risk factors such as falls status and postural stability measures were not included.

In conclusion, this study provides valuable information about the contribution of LS BMD to fracture risk. Women with significantly lower LS *T*-scores than FN *T*-scores (at least $\geq$0.6 SD) demonstrated consistently higher absolute fracture risks regardless of their FN *T*-scores. The findings clearly suggest that a low LS BMD should not be ignored. The effect of having a lower LS BMD was not uniform across age-groups and FN BMD levels, with an increasing effect for older age-groups and lower FN BMD levels. For these women, in particular, LS discordance is likely to affect treatment decision thresholds. Guidelines that emphasize the use of LS BMD in addition to FN BMD, for the diagnosis of osteoporosis, assessment of fracture risk, and treatment decision and monitoring need to be implemented. Ultimately, a clinically practical method that incorporates LS BMD in the fracture risk prediction and accurately reflects the contribution of both FN and LS BMD to fracture risk is warranted.

Disclosures

JAE has consulted for and/or received research funding from Amgen, Decode, Eli Lilly, Merck Sharp & Dohme, Novartis, Sanofi-Aventis, and Servier. JRC has been supported by and/or given educational talks for, Merck Sharp & Dohme, Amgen, and Sanofi-Aventis. DB, DA, and TVN report no conflicts of interest.

Acknowledgments

This work was supported by the National Health Medical Research Council Australia (NHMRC project ID; DB 1073430, JRC 1008219, DA, TVN, JRC, and JAE 1070187). The authors are solely responsible for the contents of this work, and do not reflect the views of the NHMRC. Other funding bodies are Osteoporosis Australia-Amgen grant; the Bupa Health Foundation (formerly MBF Foundation); the Ernst Heine Foundation; and untied grants from Amgen, Merck Sharp & Dohme, sanofi-Aventis, Servier, and Novartis. The study sponsors had no role in the study design; collection, analyses and interpretation of the data; the writing of this report; or the decision to submit this manuscript for publication.

Authors' roles: Study design: DA, DB, TVN, JRC, and JAE. Data Collection: DA, DB, and JAE. Analysis and interpretation of data: DA, DB, JAE, and JRC. Drafting of the manuscript: DA, JAE, and DB. Revising manuscript content: DB, TVN, JRC, and JAE. Approving final version of manuscript: DA, DB, TVN, JRC, and JAE.

References

1. Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. BMJ. 1996;312(7041):1254–9.
2. El Maghraoui A, Roux C. DXA scanning in clinical practice. QJM. 2008;101(8):605–17.
3. Kanis JA. Diagnosis of osteoporosis and assessment of fracture risk. Lancet. 2002;359(9321):1929–36.
4. Kanis JA, McCloskey EV, Johansson H, Oden A, Melton LJ 3rd, Khaltaev N. A reference standard for the description of osteoporosis. Bone. 2008;42(3):467–75.
5. Johnell O, Kanis JA, Oden A, et al. Predictive value of BMD for hip and other fractures. J Bone Miner Res. 2005;20(7):1185–94.

6. Johansson H, Kanis JA, Oden A, et al. Impact of femoral neck and lumbar spine BMD discordances on FRAX probabilities in women: a meta-analysis of international cohorts. Calcif Tissue Int. 2014;95(5): 428–35.
7. Ahmed AI, Blake GM, Rymer JM, Fogelman I . Screening for osteopenia and osteoporosis: do the accepted normal ranges lead to overdiagnosis? Osteoporos Int. 1997;7(5):432–8.
8. Faulkner KG, von Stetten E, Miller P. Discordance in patient classification using T-scores. J Clin Densitom. 1999;2(3):343–50.
9. Woodson G. Dual X-ray absorptiometry T-score concordance and discordance between the hip and spine measurement sites. J Clin Densitom. 2000;3(4):319–24.
10. Mulder JE, Michaeli D, Flaster ER, Siris E. Comparison of bone mineral density of the phalanges, lumbar spine, hip, and forearm for the assessment of osteoporosis in postmenopausal women. J Clin Densitom. 2000;3(4):373–81.
11. Abrahamsen B, Stilgren LS, Hermann AP, et al. Discordance between changes in bone mineral density measured at different skeletal sites in perimenopausal women—implications for assessment of bone loss and response to therapy: The Danish Osteoporosis Prevention Study. J Bone Miner Res. 2001;16(7):1212–9.
12. Moayyeri A, Soltani A, Tabari NK, Sadatsafavi M, Hossein-Neghad A, Larijani B. Discordance in diagnosis of osteoporosis using spine and hip bone densitometry. BMC Endocr Disord. 2005;5(1):3.
13. El Maghraoui A, Mouinga Abayi DA, Ghozlani I, et al. Prevalence and risk factors of discordance in diagnosis of osteoporosis using spine and hip bone densitometry. Ann Rheum Dis. 2007;66(2): 271–2.
14. Leslie WD, Lix LM, Johansson H, Oden A, McCloskey E, Kanis JA. Spine-hip discordance and fracture risk assessment: a physician-friendly FRAX enhancement. Osteoporos Int. 2011;22(3):839–47.
15. Blackburn TD, Howard DB, Leib ES. Utility of spine bone mineral density in fracture prediction within FRAX. J Clin Densitom. 2013;16(1):81–6.
16. Jones G, Nguyen T, Sambrook PN, Kelly PJ, Gilbert C, Eisman JA. Symptomatic fracture incidence in elderly men and women: the Dubbo Osteoporosis Epidemiology Study (DOES). Osteoporos Int. 1994;4(5):277–82.
17. Center JR, Nguyen TV, Schneider D, Sambrook PN, Eisman JA. Mortality after all major types of osteoporotic fracture in men and women: an observational study. Lancet. 1999;353(9156):878–82.
18. Pasco JA, Nicholson GC, Kotowicz MA. Cohort profile: Geelong Osteoporosis Study. Int J Epidemiol. 2012;41(6):1565–75.
19. Baim S, Wilson CR, Lewiecki EM, Luckey MM, Downs RW Jr, Lentle BC. Precision assessment and radiation safety for dual-energy X-ray absorptiometry: position paper of the International Society for Clinical Densitometry. J Clin Densitom. 2005;8(4):371–8.
20. Nguyen TV, Sambrook PN, Eisman JA. Sources of variability in bone mineral density measurements: implications for study design and analyses of bone loss. J Bone Miner Res. 1997;12(1):124–35.
21. Eastell R. Treatment of postmenopausal osteoporosis. N Engl J Med. 1998;338(11):736–46.
22. Vokes TJ, Gillen DL, Lovett J, Favus MJ. Comparison of T-scores from different skeletal sites in differentiating postmenopausal women with and without prevalent vertebral fractures. J Clin Densitom. 2005;8(2):206–15.
23. Mounach A, Abayi DA, Ghazi M, et al. Discordance between hip and spine bone mineral density measurement using DXA: prevalence and risk factors. Semin Arthritis Rheum. 2009;38(6):467–71.
24. Arabi A, Baddoura R, Awada H, et al. Discriminative ability of dual-energy X-ray absorptiometry site selection in identifying patients with osteoporotic fractures. Bone. 2007;40(4):1060–5.
25. Kanis JA, Oden A, Johnell O, Jonsson B, de Laet C, Dawson A. The burden of osteoporotic fractures: a method for setting intervention thresholds. Osteoporos Int. 2001;12(5):417–27.
26. Stone KL, Seeley DG, Lui LY, et al. BMD at multiple sites and risk of fracture of multiple types: long-term results from the Study of Osteoporotic Fractures. J Bone Miner Res. 2003;18(11):1947–54.
27. Melton LJ 3rd, Orwoll ES, Wasnich RD. Does bone density predict fractures comparably in men and women? Osteoporos Int. 2001; 12(9):707–9.
28. O'Neill TW. The relationship between bone density and incident vertebral fracture in men and women. J Bone Miner Res. 2002;17(12): 2214–21.
29. Lippuner K, Johansson H, Kanis JA, Rizzoli R. FRAX assessment of osteoporotic fracture probability in Switzerland. Osteoporos Int. 2010;21(3):381–9.
30. Melton LJ 3rd, Atkinson EJ, O'Fallon WM, Wahner HW, Riggs BL. Long-term fracture prediction by bone mineral assessed at different skeletal sites. J Bone Miner Res. 1993;8(10):1227–33.
31. Rochmis PG, Sheridan MJ, Perry L. Is the NHANES III femoral neck database discordant with the total hip and trochanteric region databases? J Clin Densitom. 2009;12(2):224–8.
32. Dawson-Hughes B, Looker AC, Tosteson AN, Johansson H, Kanis JA, Melton LJ 3rd. The potential impact of new National Osteoporosis Foundation guidance on treatment patterns. Osteoporos Int. 2010;21(1):41–52.
33. Siminoski K, Leslie WD, Frame H, et al. Recommendations for bone mineral density reporting in Canada: a shift to absolute fracture risk assessment. J Clin Densitom. 2007;10(2):120–3.
34. Kanis JA, Johnell O, Oden A, et al. The use of multiple sites for the diagnosis of osteoporosis. Osteoporos Int. 2006;17(4):527–34.
35. Leslie WD, Lix LM, Tsang JF, Caetano PA. Single-site vs multisite bone density measurement for fracture prediction. Arch Intern Med. 2007;167(15):1641–7.
36. Siminoski K, Leslie WD, Frame H, et al. Recommendations for bone mineral density reporting in Canada. Can Assoc Radiol J. 2005;56(3): 178–88.
37. Leslie WD, Lix LM. Absolute fracture risk assessment using lumbar spine and femoral neck bone density measurements: derivation and validation of a hybrid system. J Bone Miner Res. 2011;26(3):460–7.
38. Blake GM, Patel R, Knapp KM, Fogelman I. Does the combination of two BMD measurements improve fracture discrimination? J Bone Miner Res. 2003;18(11):1955–63.
39. Hordon LD, Raisi M, Aaron JE, Paxton SK, Beneton M, Kanis JA. Trabecular architecture in women and men of similar bone mass with and without vertebral fracture: I. Two-dimensional histology. Bone. 2000;27(2):271–6.
40. Rabier B, Heraud A, Grand-Lenoir C, Winzenrieth R, Hans D. A multicentre, retrospective case-control study assessing the role of trabecular bone score (TBS) in menopausal Caucasian women with low areal bone mineral density (BMDa): analysing the odds of vertebral fracture. Bone. 2010;46(1):176–81.
41. Winzenrieth R, Dufour R, Pothuaud L, Hans D. A retrospective case-control study assessing the role of trabecular bone score in postmenopausal Caucasian women with osteopenia: analyzing the odds of vertebral fracture. Calcif Tissue Int. 2010;86(2):104–9.
42. Leslie WD, Pahlavan PS, Tsang JF, Lix LM. Prediction of hip and other osteoporotic fractures from hip geometry in a large clinical cohort. Osteoporos Int. 2009;20(10):1767–74.
43. Hans D, Goertzen AL, Krieg MA, Leslie WD. Bone microarchitecture assessed by TBS predicts osteoporotic fractures independent of bone density: the Manitoba study. J Bone Miner Res. 2011;26(11): 2762–9.