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RESEARCH ARTICLE

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Contributions of Clinical and Technical Factors to Longitudinal Change in Trabecular Bone Score and Bone Density: A Registry-Based Individual-Level Analysis

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ABSTRACT

Lumbar spine trabecular bone score (TBS), a gray-level texture measure derived from spine dual-energy X-ray absorptiometry (DXA) images, is a bone mineral density (BMD)-independent risk factor for fracture. An unresolved question is whether TBS is sufficiently responsive to change over time or in response to widely used osteoporosis therapy at the individual level to serve as a useful biomarker. Using the Manitoba DXA Registry, we identified 11,643 individuals age 40 years and older with two fan-beam DXA scans performed on the same instrument within 5 years (mean interval 3.2 years), of whom 6985 (60.0%) received antiresorptive osteoporosis medication (majority oral bisphosphonate) between the scans. We examined factors that were associated with a change in lumbar spine TBS, lumbar spine BMD, and total hip BMD exceeding the 95% least significant change (LSC). Change exceeding the LSC was identified in 23.0% (9.3% increase, 13.8% decrease) of lumbar spine TBS, 38.2% (22.1% increase, 16.1% decrease) lumbar spine BMD, and 42.5% (17.6% increase, 24.9% decrease) total hip BMD measurement pairs. From regression models, the variables most strongly associated with significant change in TBS (decreasing order) were tissue thickness change, acquisition mode change, weight change, and spine percent fat change. Consistent with the insensitivity of TBS to oral antiresorptive therapies, use of these agents showed very little effect on TBS change. In contrast, for both spine BMD change and total hip BMD change, osteoporosis medication use was the most significant variable, whereas tissue thickness change, acquisition mode change, and weight change had relatively weak effects. In summary, change in spine TBS using the present algorithm appears to be strongly affected by technical factors. This suggests a limited role, if any, for using TBS change in untreated individuals or for monitoring response to antiresorptive treatment in routine clinical practice with the current version of the TBS algorithm. © 2023 The Authors. *Journal of Bone and Mineral Research* published by Wiley Periodicals LLC on behalf of American Society for Bone and Mineral Research (ASBMR).

KEY WORDS: OSTEOPOROSIS; DXA; BONE MINERAL DENSITY; TRABECULAR BONE SCORE

Introduction

The World Health Organization (WHO) defines osteoporosis conceptually as a systemic skeletal disease characterized by low bone mass (decreased quantity) and microarchitectural deterioration of bone tissue (decreased quality) resulting in susceptibility to fracture.[1] Most fractures occur in individuals who have a bone mineral density (BMD) *T*-score better than the threshold for osteoporosis; thus, factors other than BMD influence bone strength and fracture risk.[2,3] This has stimulated development of new methods for skeletal assessment. Lumbar spine trabecular bone score (TBS), a gray-level texture measure derived from spine dual-energy X-ray absorptiometry (DXA) images, is a BMD-independent risk factor for fracture.[4] TBS has

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been integrated into the fracture risk assessment (FRAX) algorithm as an adjustment to the calculated risk score.[5] The use of TBS for guiding patient management is supported by guidelines from several organizations.[6-8]

An unresolved question is whether TBS is sufficiently responsive to change in bone status over time in treated and untreated individuals to serve as a useful biomarker at the individual level.[9,10] Antiresorptive medications, such as oral bisphosphonates, decrease bone remodeling, which favors refilling of resorption cavities and secondary mineralization, leading to a modest increase in BMD and preservation of existing bone structure.[11] Change in BMD, particularly at the total hip, is a good indicator of antifracture effect of osteoporosis medications and has been proposed as a surrogate for fracture outcomes in drug development trials.[12,13] Moreover, total hip BMD can be assessed in clinical practice at the individual level with sufficiently high reproducibility and responsiveness that a change in BMD exceeding the 95% least significant change (LSC) predicts fracture outcomes.[14] The increase in TBS from antiresorptive therapies is smaller than the increase in BMD, consistent with the mechanism of action noted above, and change in TBS does not appear to be associated with fracture outcomes.[15] Anabolic therapies produce a larger increase in TBS, though this remains smaller than the increase in spine BMD.[9,10] Technical factors can also impact serial TBS and BMD measurements. For example, with TBS, greater abdominal soft tissue creates image noise that must be distinguished from abnormal bone texture.[16] The current TBS algorithm uses body mass index (BMI) to adjust for this effect, but BMI does not fully capture other variations in body composition.[17] Additionally, scan acquisition parameters can also affect TBS.[18]

The current individual-level analysis was undertaken to explore technical and clinical factors associated with change in TBS and BMD exceeding the LSC among treated and untreated patients using a large clinical registry that includes all DXA tests for the Province of Manitoba, Canada. The data set provides results applicable to the clinical practice setting.

Materials and Methods

Study population

In Canada, health services including DXA testing are provided to nearly all residents through a single public health care system.[19] DXA testing through the Manitoba Density Program has been managed as an integrated program since 1997.[20] Criteria for testing are informed by national guidelines and include but are not limited to women aged 65 years or older without additional risk factors, as well as men and younger women with additional risk factors (eg, low-trauma fracture, radiologic evidence of osteoporosis, high-risk medication use, clinical conditions associated with BMD loss) or other indications with physician justification (www.gov.mb.ca/health/primarycare/providers/chronicdisease/bonedensity/). The recommended BMD retesting interval is 3 years, but a shorter interval is accepted for high-risk medication use, and a 5-year interval is recommended for those with normal BMD or low fracture risk. The Manitoba Density Program maintains a database of all DXA results that can be linked with other population-based databases through an anonymous personal identifier. The associated database exceeds 99% in terms of completeness and accuracy.[21] For the current analysis, we identify to all individuals aged 40 years and older with two fan-beam DXA scans performed on the same scanner within 5 years. We excluded individuals whose first DXA scan used a pencil-beam scanner, where scans were performed on different DXA instruments, where the interval between scans exceeded 5 years, or where administrative data linkage was not available were excluded. The index date was taken to be the date of the second DXA scan because this reflects the clinical scenario facing practitioners regarding how to interpret observed change in TBS in light of prior information, including treatment history. The study was approved by the Research Ethics Board of the University of Manitoba and the Health Information Privacy Committee of Manitoba Health.

Bone densitometry and trabecular bone score

All spine and hip DXA scans were performed with fan-beam DXA scanners (GE Lunar Prodigy before November 2012, GE iDXA from November 2012 onward, GE Healthcare, Madison, WI, USA) and analyzed in accordance with manufacturer recommendations. Hip *T*-scores were calculated using the NHANES III white female reference values; spine *T*-score used manufacturer white female reference values.[22] All densitometers were BMD cross-calibrated using anthropomorphic phantoms and no clinically significant differences were identified (*T*-score differences ≤0.1). Lumbar spine TBS (L_1 to L_4) measurements were performed in the Bone Disease Unit at the University of Lausanne, Switzerland (TBS iNsight Software, version 3.03, Medimaps Group, Geneva, Switzerland), using anonymized spine DXA files to ensure blinding of the Swiss investigators to all clinical parameters and outcomes. Information on lumbar spine BMD (L_1 to L_4), soft tissue thickness, and fat percent was derived from the same spine DXA image and regions of interest. No TBS phantom was available for scanner calibration given the retrospective study design, which is a regulatory requirement for clinical use. Weight and height were measured at the time of each DXA. We excluded those with body mass index (BMI) outside the range 15–37 kg/m^2 as recommended by the TBS manufacturer.

Outcomes

A significant change in lumbar spine TBS, either an increase or decrease exceeding the 95% LSC, was the primary outcome measure with the referent category an absolute difference in TBS measurements that did not exceed the 95% LSC (no change). The pooled spine TBS LSC was 0.080 based upon short-term (different day, mean 1 week) test–retest measurements in 96 Prodigy and 50 iDXA spine DXA scan-pairs that involved all DXA technologists. In the same data set pooled LSC was 0.050 g/cm^2 for L_1 to L_4 spine BMD and 0.030 g/cm^2 for single total hip BMD.

Explanatory variables

We considered clinical and technical factors that could impact TBS and BMD. Use of osteoporosis medication between the two scans was categorized according to medication persistence ratio (MPR) as low (MPR <0.50), moderate (MPR 0.50–0.79), and high (MPR >0.80) with the referent being none (MPR 0). Medication use was obtained from the provincial pharmacy system.[23] Among the other clinical factors, we examined age, sex, time interval between scans, glucocorticoid exposure (greater than 3 months total use between scans), aromatase inhibitor exposure (greater than 3 months total use between the two scans), smoking status, high alcohol intake, rheumatoid arthritis, and other causes of secondary osteoporosis (androgen deprivation

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therapy, hyperthyroidism, ankylosing spondylitis, celiac disease, chronic pancreatitis, chronic liver disease, inflammatory bowel disease, cerebrovascular disease, multiple sclerosis, muscular dystrophy, Parkinson disease, and solid organ or bone marrow transplantation) captured from a combination of self-report, hospital discharge abstracts, and physician billing claims as previously described.[24] Among the technical factors, we considered change in DXA scan mode (from thinner to thicker or from thicker to thinner), change in weight, change in average percent fat derived from the spine DXA image, or change in average tissue thickness derived from the spine DXA image. Before 2010, scans were performed with one of three provincial Prodigy instruments and subsequently with one of three iDXA instruments. The scan mode used was based upon body size (standard, thin, thick) following manufacturer recommendations. We also examined the presence versus absence of lumbar vertebral exclusions as an indicator of structural artifact in the spine (eg, degenerative changes).

Table 1. Study Population Characteristics on the Index Date (Second DXA Scan)

Characteristic	$N = 11,643$
Age (years)	65.3 ± 10.0
Sex (male)	746 (6.4)
Weight (kg)	66.5 ± 12.4
Spine fat (%)	30.8 ± 10.4
Spine tissue thickness (cm)	17.8 ± 2.7
Weight change (kg)	−0.1 ± 4.9
Spine fat change (%)	0.8 ± 4.8
Spine tissue thickness change (cm)	0.2 ± 1.2
Spine vertebral exclusions	4413 (38.0)
Time between scans (years)	3.2 ± 1.0
Glucocorticoid use	999 (8.6)
Smoking	952 (8.2)
Rheumatoid arthritis	403 (3.5)
Secondary osteoporosis	2481 (21.3)
High alcohol use	30 (0.3)
Aromatase inhibitor use	871 (7.5)
Osteoporosis medication persistence ratio	
None	4658 (40.0)
Low, MPR <0.50	2246 (19.3)
Moderate, MPR 0.50–0.79	1590 (13.7)
High, MPR ≥0.80	3149 (27.0)
Scanner type	
Prodigy	10,519 (90.3)
iDXA	1124 (9.7)
Scan acquisition mode	
Standard	10,609 (91.1)
Thin	50 (0.4)
Thick	984 (8.5)
Change in acquisition mode	
No change	11,211 (96.3)
Change to thinner	98 (0.8)
Change to thicker	334 (2.9)
Lumbar spine TBS (L_1 to L_4)	1.247 ± 0.115
Lumbar spine BMD *T*-score (L_1 to L_4)	−1.4 ± 1.3
Total hip BMD *T*-score	−1.2 ± 1.0

Abbreviation: DXA = dual-energy X-ray absorptiometry; MPR = medication persistence ratio; BMD = bone mineral density; TBS = trabecular bone score.

Note: Data are Mean ± SD, or *n* (%).

Statistical analyses

Statistical analyses were performed with IBM SPSS for Windows (version 28; IBM Corp., Armonk, NY, USA). Descriptive statistics for demographic and baseline characteristics are presented as mean ± SD for continuous variables or number (%) for categorical variables. Bivariate correlations between TBS, BMD, and relevant continuous variables were examined. We also examined change in TBS and BMD in relation to osteoporosis medication MPR category. Change exceeding the LSC was classified as discordant or concordant between measurement sites. Analyses were performed to study effect of interval weight change, change in average spine tissue thickness, and change in average spine fat using 5 categories based on cut-offs that were approximately equal to ±1 SD and ±2 SD. Multinomial logistic regression was then performed to study factors independently contributing to a significant increase or decrease (versus no change) in TBS and BMD. Although there were significant correlations between some of the variables, none showed a high level of multicollinearity (all variance inflation factors less than 8). However, because acquisition mode change is usually performed in response to change in body composition, odds ratios (ORs) were conservatively estimated after excluding weight change, fat change, and tissue thickness change. To identify those factors most strongly associated with change in TBS and BMD, we use the chi-square from the likelihood ratio test (difference in −2 log-likelihoods between the final model and a reduced model formed by omitting the variable of interest from the final model).[25] Although the absolute chi-square values do not have a direct interpretation, they provide a useful way to rank the relative importance of the candidate variables when measured from the same model. We also performed multiple sensitivity analyses, including stratification by age and sex. We also analyzed results in individuals according to treatment category (none versus high MPR). We also examined effects of using the same or a different acquisition mode or assuming different LSC cut-offs. For individuals with more than two DXA scans, we also repeated analyses for third versus second DXA, or higher-order DXA (fourth or greater) versus the immediate prior DXA. Finally, we compared results in those without versus with any potential technical factors (different scan mode, change in weight ≥5 kg or spine fat ≥5%, or change spine tissue thickness ≥1 cm).

Results

Study population

The study population used for the primary analysis consisted of 11,643 individuals with two DXA assessments of TBS and BMD, with study population characteristics on the index date (second DXA scan) summarized in Table 1. Mean age was 65.3 ± 10.0 years, with the vast majority female (746 [6.4%] men), and a mean time interval between scans of 3.2 ± 1.0 years. At the second scan (index date), mean spine TBS was 1.247 ± 0.115, spine BMD *T*-score −1.4 ± 1.3 and total hip BMD *T*-score −1.2 ± 1.0. The first and second measurements were highly correlated (spine TBS $r = 0.79$, spine BMD $r = 0.92$, total hip BMD $r = 0.85$). Most scans were performed with a Prodigy instrument (90.3%) and used standard acquisition mode (91.1%). Although the mean interval changes in weight, spine fat, and spine tissue thickness were small, there was significant individual variation as found in the SD values. A substantial

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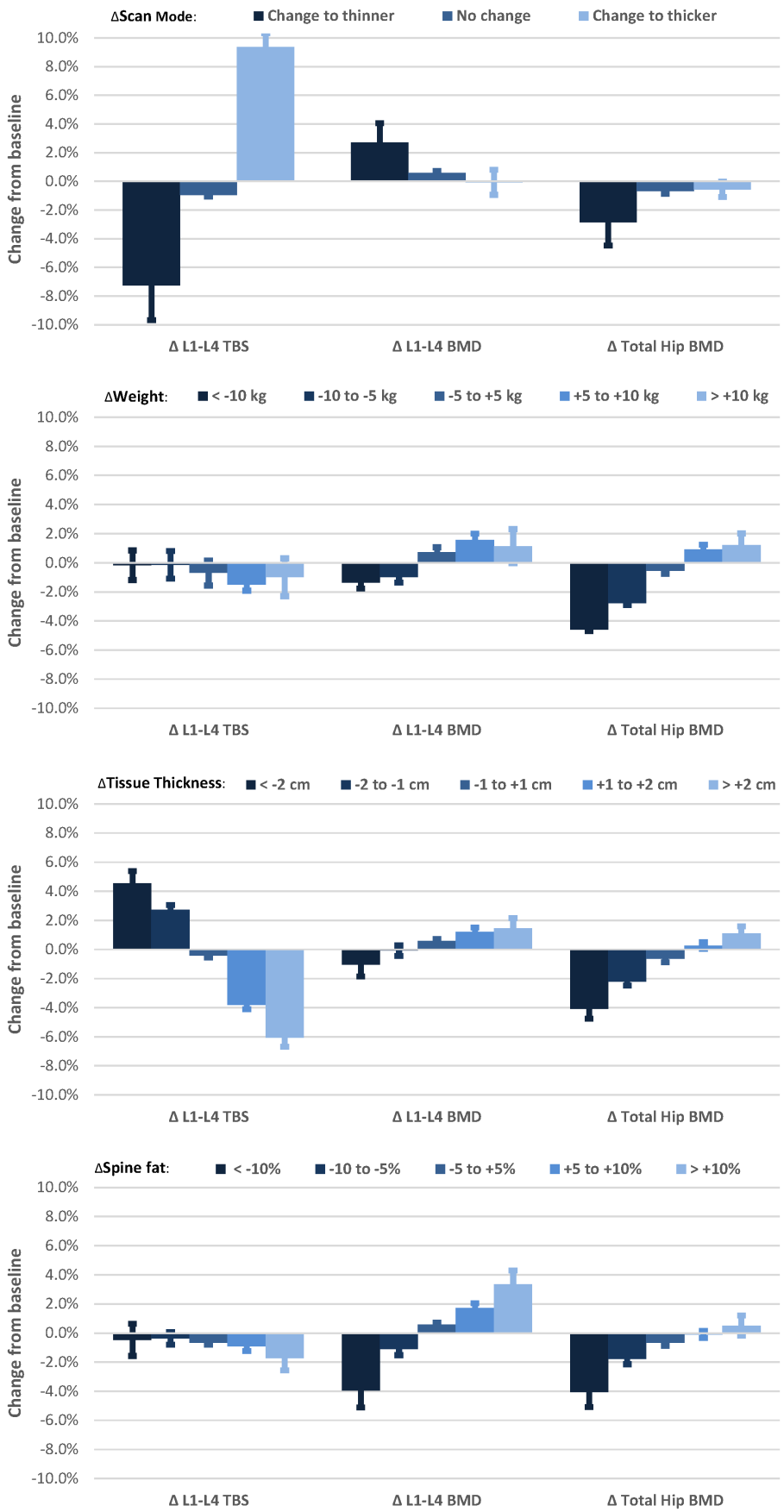

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fraction of these individuals had significant glucocorticoid exposure (8.6%) or aromatase inhibitor use (8.2%).

Medication use and change in TBS and BMD

Exposure to osteoporosis medication between the two scans was identified in 6985 (60.0%), among whom 27.0% had high MPR (≥0.80) (Table 1). Oral bisphosphonate therapy accounted for the majority of osteoporosis medication use (78.3%), followed by systemic estrogen (12.0%) and raloxifene (6.2%). The mean interval between scans for medication users (3.3 ± 0.9 years) and non-users (3.1 ± 1.0 years) was similar. Mean changes in TBS and BMD over time according to MPR category are summarized in Supplemental Table S1. Among untreated individuals, there was a decrease in mean TBS and BMD. Increasing treatment MPR was associated with attenuated decreases in TBS and BMD. Among those with a high MPR, TBS was essentially unchanged, whereas there was an increase in BMD at both the spine and total hip. Among untreated individuals, the proportion with a significant decrease in BMD (spine 24.1%, total hip 37.8%) was greater than the proportion with a significant decrease in TBS (16.9%); conversely, the proportion with a significant increase among treated individuals with high MPR was greater for BMD (spine 33.6, total hip 38.6%) than for TBS (10.5%). The ratio of significant increase to decrease, as an index of treatment response, was steeper for BMD than TBS.

Unadjusted associations with change in TBS and BMD

There were lower cross-sectional (index date) correlations between TBS and BMD measurements (r = 0.22–0.28) than between spine and total hip BMD measurements (r = 0.62) (Supplemental Table S2). There were weak but significant negative correlations between TBS and weight ($r = -0.13$), spine percent fat ($r = -0.16$), and spine tissue thickness ($r = -0.38$), whereas these were all positively correlated with BMD. Change in TBS and change in BMD showed very low correlations (r = 0.05–0.14), with slightly higher correlation between change in spine and change in total hip BMD measurements (r = 0.30) (Supplemental Table S2). Increasing spine tissue thickness was negatively correlated with change in TBS ($r = -0.42$) but showed weak positive correlations with change in BMD (r = 0.07–0.10). Change in BMD was weakly but positively correlated with increasing weight (r = 0.09–0.12) and increasing spine percent fat (r = 0.07–0.19); both parameters showed very weak but significant negative correlations with change in TBS.

Table 2. Adjusted Odds Ratios (OR) for a Significant Decrease in Spine TBS (L_1 to L_4), Spine BMD (L_1 to L_4), and Total hip BMD

Characteristic	Spine TBS OR (95% CI)	*p* Value	Spine BMD OR (95% CI)	*p* Value	Total hip BMD OR (95% CI)	*p* Value
Age (per 10-year increase)	**0.90 (0.83–0.96)**	0.002	**0.62 (0.58–0.66)**	<0.001	**0.92 (0.88–0.97)**	0.002
Sex (male versus female)	**3.82 (3.00–4.88)**	<0.001	**0.44 (0.33–0.60)**	<0.001	**0.52 (0.41–0.65)**	<0.001
Weight change (per 5 kg increase)	**0.16 (0.14–0.18)**	<0.001	1.00 (0.91–1.10)	0.989	**0.75 (0.69–0.82)**	<0.001
Spine fat change (per 5% increase)	**0.55 (0.50–0.60)**	<0.001	**0.66 (0.61–0.71)**	<0.001	1.00 (0.93–1.06)	0.844
Spine tissue thickness change (per cm increase)	**15.5 (13.5–17.8)**	<0.001	1.07 (0.99–1.15)	0.093	**0.91 (0.85–0.97)**	0.004
Vertebral exclusions	1.10 (0.96–1.27)	0.167	**0.80 (0.71–0.90)**	<0.001	0.97 (0.87–1.07)	0.506
Scan interval (per year increase)	**1.12 (1.04–1.20)**	0.002	**1.44 (1.36–1.53)**	<0.001	**1.42 (1.35–1.50)**	<0.001
Glucocorticoid use	**1.33 (1.04–1.70)**	0.024	**1.39 (1.12–1.71)**	0.002	**1.50 (1.25–1.80)**	<0.001
Smoking	0.95 (0.75–1.21)	0.682	0.85 (0.70–1.02)	0.080	**1.37 (1.17–1.60)**	<0.001
Rheumatoid arthritis	1.13 (0.79–1.60)	0.514	**1.30 (0.99–1.72)**	0.060	**1.31 (1.03–1.68)**	0.031
Secondary osteoporosis	1.05 (0.87–1.27)	0.588	1.12 (0.96–1.31)	0.154	**1.42 (1.24–1.63)**	<0.001
High alcohol use	1.30 (0.42–4.00)	0.647	1.10 (0.40–3.04)	0.857	0.89 (0.37–2.14)	0.787
Aromatase inhibitor use	**1.60 (1.21–2.12)**	0.001	**2.09 (1.68–2.60)**	<0.001	**1.75 (1.44–2.13)**	<0.001
Osteoporosis medication use, MPR 0.01–0.49	0.86 (0.72–1.03)	0.097	0.96 (0.84–1.09)	0.500	**0.72 (0.64–0.81)**	<0.001
Osteoporosis medication use, MPR 0.50–0.79	**0.62 (0.50–0.77)**	<0.001	**0.40 (0.32–0.48)**	<0.001	**0.38 (0.32–0.44)**	<0.001
Osteoporosis medication use, MPR ≥0.80	**0.47 (0.40–0.57)**	<0.001	**0.26 (0.22–0.31)**	<0.001	**0.22 (0.19–0.25)**	<0.001
Osteoporosis medication use, none	1 (REF)		1 (REF)		1 (REF)	
Acquisition mode change, to thinner[a]	**8.56 (5.51–13.3)**	<0.001	0.51 (0.25–1.04)	0.064	1.08 (0.65–1.80)	0.764
Acquisition mode change, to thicker[a]	0.75 (0.43–1.32)	0.318	**1.67 (1.24–2.26)**	<0.001	1.26 (0.95–1.66)	0.107
Acquisition mode, no change	1 (REF)		1 (REF)		1 (REF)	

Abbreviation: TBS = trabecular bone score; BMD = bone mineral density; CI = confidence interval; MPR = medication persistence ratio.
Note: Data are from multinomial logistic regression. Boldface indicates $p < 0.05$.
[a]Model excluding weight change, fat change, and tissue thickness change.

(Figure legend continued from previous page.)

Fig. 1. Unadjusted percent change in spine trabecular bone score (TBS; L_1 to L_4), spine bone mineral density BMD (L_1 to L_4), and total hip BMD according to change in scan mode, weight change, spine tissue thickness change, and spine percent fat change.

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Fig. 1 shows that change in scan mode was strongly associated with TBS change, with a mean decrease of −0.091 when switching to a thinner scan mode and mean increase of 0.120 when switching to a thicker scan mode, both exceeding the TBS LSC. In contrast, change in scan mode had little effect on lumbar spine or total hip BMD change. Categories of increasing weight were negatively associated with TBS change but positively associated with BMD change, especially for the total hip. Categories of increasing tissue thickness were negatively associated with TBS change but positively associated with BMD change.

Discordant change in TBS and BMD

Based upon 95% LSC limits, a significant decrease in TBS was found for 13.8% and a significant increase in 9.3% for all patients in this cohort. Higher rates of change were found for spine BMD (significant decrease in 16.1% and significant increase in 22.0%) and total hip BMD (significant decrease in 24.9% and significant increase in 17.6%). Major change discordance (significant increase in one measurement with a significant decrease for another) was most common for spine TBS versus total hip BMD (3.7%) followed by spine TBS versus spine BMD (3.4%), and least common for spine BMD versus total hip BMD (1.5%) (Supplemental Table S3). Change concordance (significant increase or decrease in both measurements) was greater for spine BMD versus total hip BMD (20.1%) compared with TBS versus BMD (6.2–6.5%). Among cases with spine TBS and BMD change both exceeding the LSC, the fraction with major discordance was 0.36, whereas the major discordance fraction between spine and total hip BMD change was 0.07.

Significant decrease in TBS or BMD

Multivariable-adjusted ORs for a significant decrease in TBS or BMD are summarized in Table 2. Variables positively associated with a decrease in TBS included increased tissue thickness (per cm OR = 15.5, 95% confidence interval [CI] 13.5–17.8) and change to a thinner acquisition mode (OR = 8.56, 95% CI 5.51–13.3). These variables were not associated with spine BMD loss; there was lower likelihood for total hip BMD loss as tissue thickness increased (per cm OR = 0.91, 95% CI 0.85–0.97) but no significant association with acquisition mode. Prior glucocorticoid use (OR = 1.33, 95% CI 1.04–1.70) and aromatase inhibitor use (OR = 1.60, 95% CI 1.21–2.12) were both associated with an increased likelihood of a significant decrease in TBS, but the corresponding ORs for decrease in spine BMD and total hip BMD were slightly greater. A longer interval between scans tended to be associated with greater likelihood of detecting a significant decrease in spine and total hip BMD (per year ORs = 1.44 and 1.42, respectively) but was only weakly associated with a significant decrease in spine TBS (per year OR = 1.12, 95% CI 1.04–1.20). Men were much more likely to show a significant decrease in spine TBS (OR = 3.82, 95% CI 3.00–4.88) but less likely to show a decrease in spine BMD (OR = 0.44, 95% CI 0.33–0.60) or total hip BMD (OR = 0.52, 95% CI 0.41–0.65).

Significant increase in TBS or BMD

ORs for significant increase in TBS and BMD are summarized in Table 3. Variables positively associated with an increase in TBS included weight gain (per 5 kg OR = 5.51, 95% CI 4.70–6.45),

Table 3. Adjusted Odds Ratios (OR) for a Significant Increase in Spine TBS (L_1 to L_4), Spine BMD (L_1 to L_4), and Total Hip BMD

Characteristic	Spine TBS OR (95% CI)	*p* Value	Spine BMD OR (95% CI)	*p* Value	Total hip BMD OR (95% CI)	*p* Value
Age (per 10-year increase)	**1.10 (1.02–1.21)**	0.020	**1.31 (1.23–1.37)**	<0.001	1.01 (0.95–1.07)	0.694
Sex (male versus female)	**1.71 (1.24–2.35)**	<0.001	**3.59 (2.95–4.37)**	<0.001	**1.61 (1.31–2.00)**	<0.001
Weight change (per 5 kg increase)	**5.51 (4.70–6.45)**	<0.001	0.95 (0.87–1.04)	0.254	**1.18 (1.07–1.29)**	<0.001
Spine fat change (per 5% increase)	**2.08 (1.85–2.34)**	<0.001	**1.88 (1.75–2.02)**	<0.001	1.04 (0.97–1.12)	0.287
Spine tissue thickness change (per cm increase)	**0.06 (0.05–0.08)**	<0.001	**0.89 (0.83–0.96)**	0.002	**1.09 (1.01–1.17)**	0.023
Vertebral exclusions	**1.21 (1.02–1.43)**	0.029	**1.53 (1.38–1.69)**	<0.001	1.04 (0.93–1.16)	0.541
Scan interval (per year increase)	1.00 (0.91–1.09)	0.979	**1.12 (1.06–1.19)**	<0.001	**1.10 (1.04–1.17)**	0.001
Glucocorticoid use	1.32 (0.99–1.77)	0.056	**0.77 (0.63–0.93)**	0.008	0.81 (0.66–1.00)	0.054
Smoking	0.87 (0.64–1.17)	0.346	0.87 (0.72–1.06)	0.168	0.83 (0.67–1.02)	0.078
Rheumatoid arthritis	1.02 (0.66–1.56)	0.934	0.88 (0.66–1.18)	0.405	0.89 (0.65–1.22)	0.469
Secondary osteoporosis	1.20 (0.95–1.50)	0.122	1.09 (0.95–1.27)	0.222	**1.28 (1.10–1.48)**	0.002
High alcohol use	0.63 (0.08–4.89)	0.659	1.67 (0.64–4.32)	0.293	0.86 (0.28–2.69)	0.795
Aromatase inhibitor use	0.79 (0.54–1.15)	0.214	**0.58 (0.43–0.78)**	<0.001	**0.68 (0.49–0.93)**	0.016
Osteoporosis medication use, MPR 0.01–0.49	1.12 (0.88–1.41)	0.357	**2.05 (1.75–2.40)**	<0.001	**2.21 (1.84–2.65)**	<0.001
Osteoporosis medication use, MPR 0.50–0.79	**1.45 (1.13–1.86)**	0.004	**4.36 (3.73–5.10)**	<0.001	**4.52 (3.80–5.39)**	<0.001
Osteoporosis medication use, MPR ≥0.80	**1.58 (1.29–1.93)**	<0.001	**5.51 (4.82–6.30)**	<0.001	**5.83 (5.01–6.78)**	<0.001
Osteoporosis medication use, none	1 (REF)		1 (REF)		1 (REF)	
Acquisition mode change, to thinner[a]	**2.34 (1.11–4.90)**	0.025	**2.82 (1.71–4.65)**	<0.001	**1.89 (1.01–3.53)**	0.045
Acquisition mode change, to thicker[a]	**24.1 (18.7–31.1)**	<0.001	0.88 (0.65–1.19)	0.403	1.01 (0.74–1.39)	0.949
Acquisition mode, no change	1 (REF)		1 (REF)		1 (REF)	

Abbreviation: TBS = trabecular bone score; BMD = bone mineral density; CI = confidence interval; MPR = medication persistence ratio.
Note: Data are from multinomial logistic regression. Boldface indicates $p < 0.05$.
[a]Model excluding weight change, fat change, and tissue thickness change.

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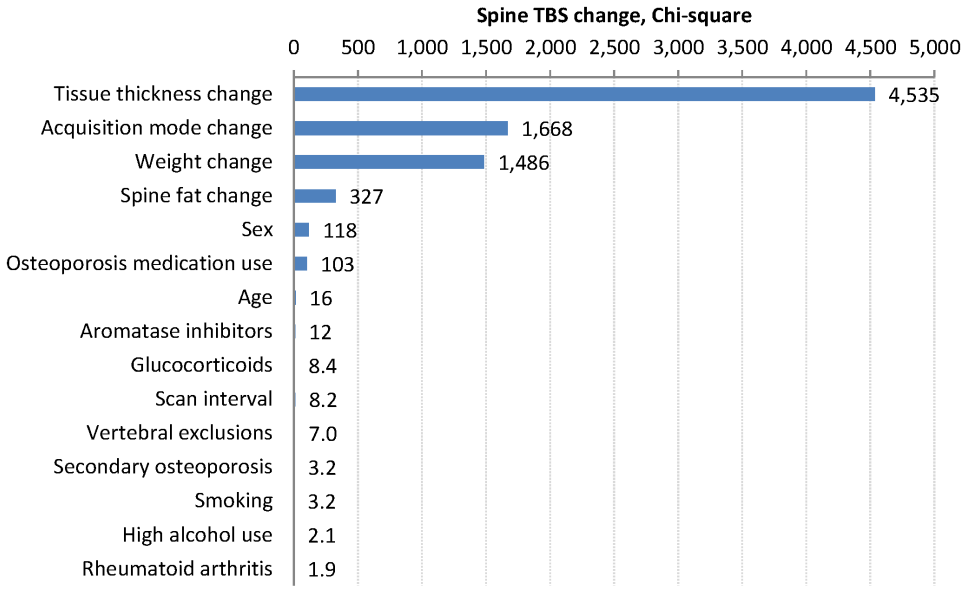

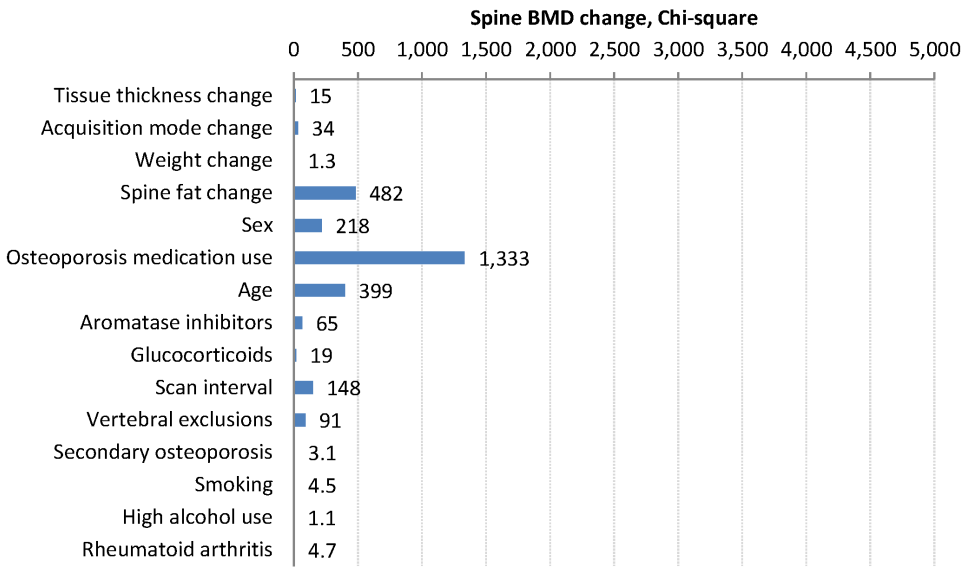

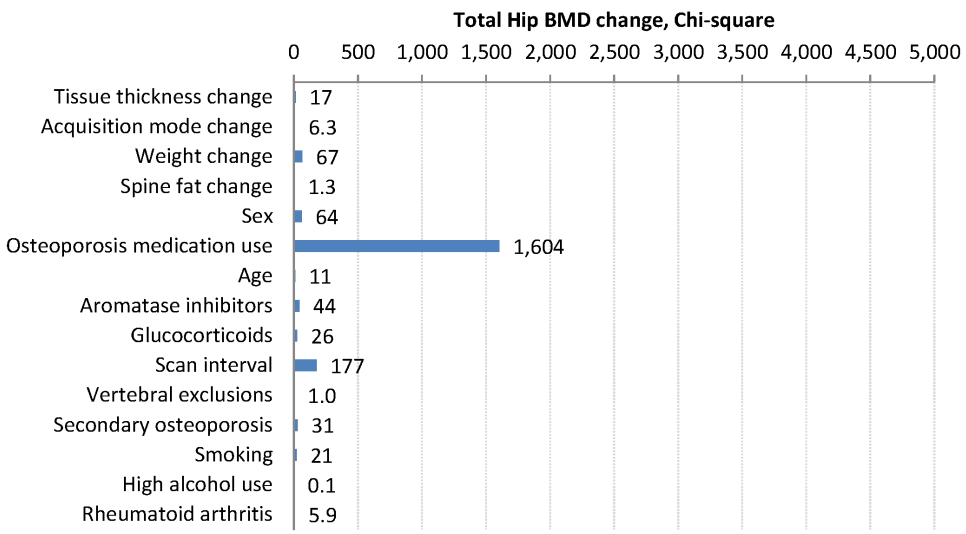

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increasing abdominal spine fat (per 5% OR = 2.08, 95% CI 1.85–2.34), change to a thinner acquisition mode (OR = 2.34, 95% CI 1.11–4.90), and change to a thicker acquisition mode (OR = 24.1, 95% CI 18.7–31.1). These showed variable effects on spine BMD change (significant for increasing spine fat and change to a thinner acquisition mode) and total hip BMD change (significant for weight gain and change to a thinner acquisition mode). Older age tended to be associated with a greater likelihood of observing an increase in spine TBS and spine BMD but did not affect total hip BMD. Men were more likely to show a significant increase in spine TBS (OR = 1.71, 95% CI 1.24–2.35), spine BMD (OR = 3.59, 95% CI 2.95–4.37), and total hip BMD (OR = 1.61, 95% CI 1.31–2.00). Compared with untreated patients, prior osteoporosis medication use was associated with a greater likelihood of seeing a significant increase in TBS (for MPR ≥ 0.80, OR = 1.58, 95% CI 1.29–1.93), but this was much less than change in BMD (OR = 5.51, 95% CI 4.82–6.30 for spine BMD; OR = 5.83, 95% CI 5.01–6.78 for total hip BMD).

Rank-ordering explanatory variables

The rank-ordered chi-square statistics from the multinomial logistic regression models demonstrated that the four variables most strongly associated with significant change in TBS (decreasing order) were tissue thickness change, acquisition mode change, weight change, and spine fat change (Fig. 2). Other variables, including antiresorptive medication use, glucocorticoids, aromatase inhibitors, and vertebral exclusions, had a much smaller impact on TBS change. In contrast, spine BMD change and total hip BMD change were much more responsive to antiresorptive medication use, which was the most significant variable, whereas tissue thickness change, acquisition mode change, and weight change had very weak effects. Spine fat change and vertebral exclusions affected spine BMD change but had little effect on total hip BMD change.

Sensitivity analyses

Similar importance and ranking of explanatory variables was found when analyses of TBS change were stratified by age (Supplemental Fig. S1) or by sex (Supplemental Fig. S2); among untreated individuals versus individuals with high MPR for osteoporosis therapy (Supplemental Fig. S3); for different acquisition modes (Supplemental Fig. S4); for different TBS LSC cut-offs (Supplemental Fig. S5); and when change was assessed at the third DXA visit or at fourth and later visits (Supplemental Fig. S6). Finally, we saw similar results in those without (n = 6030, 51.8%) versus with (n = 5613, 48.2%) any identifiable potential technical factor (different acquisition mode, change in weight ≥5 kg, change in spine fat ≥5%, or change in tissue thickness >1 cm) (Supplemental Fig. S7). In those without versus with any identifiable potential technical factors, change in TBS exceeding the LSC cut-off was found in 13.3% versus 33.4% (absolute difference 20.1%). In contrast, there was a much smaller impact on BMD change exceeding the LSC for both the lumbar spine (36.1% versus 40.4%, respectively, absolute difference 4.3%) and total hip (38.6% versus 46.6%, respectively, absolute difference 8.0%).

Discussion

This large registry-based analysis was able to identify technical and clinical factors associated with finding a significant (ie, greater than the LSC) change in spine TBS (iNsight Software, version 3.03), and contrast this with significant changes in spine BMD and total hip BMD. Some of these results are expected given the inability of antiresorptive therapies to alter trabecular bone structure, rendering TBS a relatively insensitive biomarker for response assessment as reported previously.[15] Thus, although there was a dose response between medication exposure and change in TBS, this was much less than that found with BMD. In those with change exceeding the LSC in both measurements, major discordance between TBS and BMD change was found in more than one-third of cases but between spine and total hip BMD was found in less than one-tenth. The major drivers for change in TBS were other clinical or technical factors including tissue thickness change, acquisition mode change, weight change, and abdominal fat percent change. Technical factors of a magnitude that could affect assessment of TBS change were common and found in almost half of the population. In general, factors associated with a greater likelihood of a decrease in TBS were associated with a lower likelihood of detecting a significant increase in TBS, and vice versa, with some exceptions (male sex and change to a thinner acquisition mode were associated with both an increased likelihood of decrease and increase in TBS). Some factors showed opposite effects for TBS and BMD, such as the effect of male sex (greater likelihood for a decrease with TBS but reduced likelihood for decreased BMD) and increasing tissue thickness (greater likelihood for a decrease with TBS but reduced likelihood for total hip BMD).

These analyses help to inform considerations about reporting of TBS change in clinical practice and its possible role as a surrogate for antifracture effect from antiresorptive osteoporosis treatment. Although previously reported group level changes in TBS from treatment provide some general insight into bone response,[15,26,27] as observed with the dose response in TBS within our study, at the individual patient level, these are unlikely to be clinically meaningful and should be interpreted with caution. The impact of scan mode, BMI, and body composition changes on TBS have been noted by others. Chen and colleagues[28] found a mean TBS difference of 0.24 (20%) when patients were scanned on both GE Prodigy standard versus thick mode (same day with repositioning), which is even larger than the longitudinal effect of scan mode change that we observed. Hologic scanners appear to be less sensitive to changing scan mode (fast array, array, high definition).[29,30] In a cross-sectional analysis from the Canadian Multicentre Osteoporosis Study (CaMos), increasing BMI was associated with lower TBS on Hologic scanners but not on GE scanners.[17] Our larger study found that greater weight was associated with lower TBS when using GE scanners and that interval weight gain was associated with a decrease in TBS. In the MrOS cohort that used Hologic scanners,

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Fig. 2. Characteristic importance for significant change in spine trabecular bone score (TBS; decreasing rank), spine bone mineral density (BMD), and total hip BMD.

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weight loss >10% was strongly associated with an increase in TBS but a decrease in total hip BMD; other predictors of discordance in longitudinal changes for TBS and BMD were observed, including baseline BMI, walking speed, and use of ACE inhibitor medication.[18]

Results from this study and previous reports highlight the importance of ongoing efforts to understand the relative contributions of technical factor and bone structure to the grayscale measure that is TBS. Preliminary data show that a modification to the TBS algorithm that directly uses information about tissue thickness is less sensitive to change in weight and increases fracture prediction compared with the current algorithm.[31] Importantly, our findings are specific to longitudinal change in TBS; a single TBS measurement, which implicitly integrates soft tissue and bone structural effects, is a well-documented BMD-independent predictor of fracture risk.[4,5] Therefore, our results do not alter the clinical use of TBS for fracture prediction, treatment initiation, or as a validated adjustment to both the FRAX score or BMD *T*-score.[4-8] Our findings support the 2015 and 2019 official positions from the International Society for Clinical Densitometry (ISCD) that the role of TBS in monitoring antiresorptive therapy is unclear.[9,10]

Strengths to the current report include the large and diverse nature of the clinical registry, which is reflective of the kinds of patients routinely encountered in clinical practice. This includes the predominance of women but with substantial numbers of higher-risk men, high rates of osteoporosis medication use, and high rates of risk factors for rapid bone loss, including glucocorticoids and aromatase inhibitors. The mean testing interval (mean 3.2 years) follows local clinical practice.[20] This is at the upper end of most clinical guidelines, though others have noted that DXA monitoring ≤3 yearly is unlikely to provide clinically meaningful data given the slow average change in BMD relative to measurement error.[32] Longer monitoring intervals (over 5 years) can mitigate the effect of measurement error but become less useful for short- and medium-term clinical decision making.[33] Limitations are also acknowledged. There was very little anabolic therapy in our cohort (<0.1%), and therefore results may not be applicable to this class of treatments, which are able to robustly improve trabecular architecture. We evaluated BMD and TBS change over a relatively short interval (<5 years); treatment up to 10 years can produce a larger increase, especially from denosumab.[34,35] We used a small number of carefully monitored DXA scanners. Although these instruments were not calibrated with a TBS phantom because of the retrospective study design, the observed average differences between scanners were relatively small (less than 2%), and we restricted our analysis to comparisons performed on the same scanner. All analysis were performed on GE scanners and may not be applicable to Hologic scanners. Spine TBS and BMD results and change were based upon L_1 to L_4 without vertebral exclusions. This aligns with the current practice for using L_1 to L_4 TBS to adjust FRAX scores and the insensitivity of TBS to degenerative artifact.[5,36] However, it could have adversely impacted spine BMD monitoring. Finally, the LSC used for TBS was relatively large compared with spine BMD and total hip BMD. However, this is within the range of LSC values that have previously been reported[9,37] and reflects the larger variability from performing test–retest scanning on different days rather than the same day.[38] Moreover, our findings were unchanged when we assumed much smaller TBS LSC values. We used a single LSC for men and women as there were insufficient men to compute sex-specific LSC values. Some of the findings in men (greater likelihood for both a significant decrease and increase in TBS versus women) may reflect larger TBS measurement error in men, but this could not be tested.

In summary, we found that change in spine TBS, unlike change in spine and hip BMD, was relatively insensitive to antiresorptive treatment (predominantly oral bisphosphonate) but was strongly affected by technical factors related to body composition. Change in TBS should be interpreted in light of the limitations and technical factors identified in this study. Our findings suggest a limited role, if any, for using TBS change in untreated individuals or for monitoring response to antiresorptive treatment in routine clinical practice with the current version of the TBS algorithm.

Disclosures

WDL and HG declare no conflicts of interest. NB: Nothing to declare for the context of this paper; research funding from Radius; consultant for Amgen. EVM: Nothing to declare for FRAX and the context of this paper, but numerous ad hoc consultancies/speaking honoraria and/or research funding from Amgen, Bayer, General Electric, GSK, Hologic, Lilly, Merck Research Labs, Novartis, Novo Nordisk, Nycomed, Ono, Pfizer, ProStrakan, Roche, Sanofi-Aventis, Servier, Tethys, UBS, and Warner-Chilcott. DH: Co-ownership in the TBS patent; stock options or royalties: Medimaps group; research grants: Amgen and Agnovos.

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Peer Review

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Data Availability Statement

Data sharing is not permitted under the Researcher Agreement with Manitoba Health and Seniors Care (MHASC). However, researchers may apply for data access through the Health Research Ethics Board for the University of Manitoba and the Health Information and Privacy Committee of MHASC.

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