Osteoporosis International (2020) 31:1905–1912
https://doi.org/10.1007/s00198-020-05458-1

ORIGINAL ARTICLE

Trabecular bone score in patients with chronic kidney disease

C. Rampersad[1] · R. H. Whitlock[1,2] · W. D. Leslie[1] · C. Rigatto[1,2] · P. Komenda[1,2] · C. Bohm[1,2] · D. Hans[3] · N. Tangri[1,2]

Received: 14 November 2019 / Accepted: 7 May 2020 / Published online: 21 May 2020

Abstract

Summary Patients with chronic kidney disease have high risk of osteoporotic fractures. Lower trabecular bone score (TBS) was associated with poorer kidney function and higher fracture risk when kidney function was normal. Addition of TBS to The Fracture Risk Assessment Tool with bone mineral density did not improve fracture risk prediction.

Introduction We sought to determine whether trabecular bone score (TBS) either independently or adjusted for The Fracture Risk Assessment Tool (FRAX) could predict risk of major osteoporotic fractures (MOFs) in a large population-based sample of patients with all stages of chronic kidney disease (CKD).

Methods We used population-based administrative databases to identify patients above age 20 years who had dual-energy X-ray absorptiometry (DXA) scan and serum creatinine measured within 1 year, during the years 2005 to 2010. Patients were excluded if they were on dialysis or had a functioning renal transplant. We stratified patients by estimated glomerular filtration rate (eGFR). We collected femoral neck bone mineral density (BMD), lumbar spine TBS, incident major osteoporotic fractures (MOF) and hip fractures, and other clinical characteristics.

Results Among 8289 patients, there were 6224 (75.1%) with eGFR ≥ 60 mL/min/1.73 m^2, 1624 (19.6%) with eGFR 30–60 mL/min/1.73 m^2, and 441 (5.3%) with eGFR < 30 mL/min/1.73 m^2. There were 593 patients (7.2%) with MOFs and 163 (2.0%) with hip fractures. Lower TBS score was associated with increased risk of MOF and hip fractures across all eGFR strata in unadjusted Cox proportional hazards models but after adjusting for FRAX with BMD, lower TBS was only statistically significant for MOF prediction for eGFR ≥ 60 mL/min/1.73 m^2.

Conclusion Lower TBS scores were associated with lower eGFR and increased fracture risk in patients with eGFR ≥ 60 mL/min/1.73 m^2. However, the addition of TBS to the FRAX score with BMD did not significantly improve fracture risk prediction in patients with CKD.

Keywords Bone mineral density · Chronic kidney disease · Fracture · FRAX · Trabecular bone score

Introduction

Chronic kidney disease (CKD) has a global prevalence of 11–13% and is about three times more common in adults over 65 years and older [1]. In older individuals, CKD is consistently associated with increasing medical comorbidities including osteoporosis [2]. In the general population, the lifetime risk of osteoporotic fracture is one in five men and one in three women and nearly 1.5- to 3-fold higher in patients with CKD [3–10]. This is due in part to the association between CKD and mineral bone disorder (MBD), which begins as early as CKD stage 2 and is universal by CKD stage 5 [11].

Due to high prevalence of osteoporotic fractures, their associated morbidity and mortality, cost to the patient and healthcare system, and availability of effective treatments to decrease fracture risk, national and international guidelines recommend screening for osteoporosis in the at-risk

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00198-020-05458-1) contains supplementary material, which is available to authorized users.

✉ C. Rampersad
umrampec@myumanitoba.ca

[1] Rady Faculty of Health Sciences, University of Manitoba, GF324–820 Sherbrook Street, Winnipeg, Manitoba R3A 1R9, Canada

[2] Seven Oaks General Hospital, Chronic Disease Innovation Centre, Winnipeg, Manitoba, Canada

[3] Center of Bone Diseases, Bone and Joint Department, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland

population [12]. The 10-year risk of major osteoporotic fracture (MOF) can be estimated by the WHO Fracture Risk Assessment Tool (FRAX®) [13, 14]. FRAX is the reference standard in fracture risk stratification in the general population and incorporates multiple variables including age, sex, clinical factors, and optionally, femoral neck bone mineral density (BMD). BMD as measured by dual-energy X-ray absorptiometry (DXA) scan is accurate in patients with CKD stages 1–3 and is associated with fracture risk [15]. We have recently validated both BMD and FRAX in the CKD population [16].

However, CKD is also thought to affect bone microarchitecture, which is an important factor in fracture risk not captured by BMD [17–19]. Non-invasive assessment of bone architecture can be performed by calculating the trabecular bone score (TBS) which measures gray-level texture variations in bone that can be obtained from lumbar spine DXA [4]. TBS is increasingly recognized as a useful component of fracture risk assessment and has been implemented into FRAX, with lower TBS being associated with increased fracture risk [20–23]. This association has been demonstrated in kidney transplant recipients and in smaller cohort studies of patients with early stages of CKD [23–27]. We hypothesized that TBS, either independently or adjusted for FRAX, is able to predict risk of MOFs in a large population-based sample of patients with varying stages of CKD.

Methods

Study design and population

We retrospectively studied a cohort consisting of all patients in the Canadian province of Manitoba above age 20 years who had a dual-energy X-ray absorptiometry (DXA) scan and a serum creatinine level measured within 1 year, during the years 2005 to 2010. Patients were excluded if they were on dialysis or had a functioning renal transplant at the time of DXA scan, which was used as the index date.

Data was obtained from anonymously linked health databases from the Data Repository from the Manitoba Centre for Healthy Policy at the University of Manitoba. Serum creatinine values were obtained from the Diagnostic Services of Manitoba laboratory database, which captures laboratory data of more than 70% of the Manitoban population. The lowest serum creatinine value over the study's duration was used to calculate the estimated glomerular filtration rate (eGFR) as per the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Patients were stratified into groups based on their eGFR: eGFR ≥ 60 mL/min/1.73 m^2 (normal kidney function or CKD stages 1 or 2), eGFR 30–60 mL/min/1.73 m^2 (CKD stage 3), and eGFR < 30 mL/min/1.73 m^2 (CKD stages 4 and 5).

Fracture risk assessment

All spine and hip DXA scans were performed using Prodigy scanners (GE-Healthcare, Madison, WI, USA) and analyzed in accordance with manufacturer recommendations (enCore Software 14.x, GE Healthcare, Madison, WI, USA). BMD measurements were derived for the femoral neck and lumbar spine (L1-L4 with exclusion of levels affected by artifact). Vertebral exclusions were determined by International Society for Clinical Densitometry (ISCD)-certified physicians using a standardized clinical procedure: visual inspection of the scan for localized artifact, T-score discordances between adjacent vertebral levels exceeding 1 SD, and correlation with additional imaging where available. Femoral neck BMD T-scores were calculated using the NHANES III white female reference values [28]. For the lumbar spine, manufacturer reference data for white US women were used. Instruments were cross-calibrated using anthropomorphic phantoms. All three instruments used for this study exhibited stable long-term performance (coefficient of variation (CV) < 0.5%).

All TBS measurements were performed in the Bone Disease Unit at the University of Lausanne, Switzerland (TBS iNsight Software, Version 3.03, Med-Imaps, Pessac, France), using anonymized spine DXA files to ensure blinding of the Swiss investigators to all clinical parameters and outcomes [29]. For each region used in the lumbar spine BMD measurement, TBS was evaluated based on gray-level analysis of the DXA images as the slope at the origin of the log-log representation of the experimental variogram [30]. In the current analysis, we used a research version of the TBS iNsight software that allows for large-batched analyses from a workstation and provides outputs identical to the commercially available software. No significant calibration differences in mean TBS levels were seen for the three DXA scanners used. Short-term reproducibility (CV) for TBS calculated from all three instruments used for this study and from multiple technicians was 2.1% in 92 individuals with repeat spine DXA scans. The Canadian FRAX tool (version 3.11, FRAX Desktop Multi-Patient Entry) was used to calculate 10-year risk of MOF and hip fracture. This risk is calculated using clinical risk factors, and can also be adjusted for BMD, and both BMD and TBS using a previously defined algorithm [31]. Femoral neck BMD, height, weight, and body mass index (BMI) were extracted from the Manitoba BMD database. Family history of parental fractures was self-reported by patients. The Manitoba Health Insurance Registry was used to obtain patients' age and sex. The Drug Prescription Information Network (DPIN) captures province-wide drug dispensing and was used to identify prolonged glucocorticoid use that lasted more than 90 days. Physicians claims databases and hospital abstracts were accessed using previously described methods to obtain information on previous fractures, diagnosis of rheumatoid arthritis, diagnosis of COPD (as a

proxy for smoking use) and diagnosis of alcohol/substance abuse (as a proxy for high alcohol intake) [14].

Clinical outcomes of interest

Outcomes of interest were MOFs encompassing fractures of the hip, vertebra (clinical), forearm, and humerus, which occurred within 5 years from the index date. MOFs were identified by codes from hospital discharge summaries and physician billing codes using previously described methods. [32, 33] Hip fracture was identified if it was the primary diagnosis code for a hospital stay. Clinical vertebral fracture was identified if it was the primary diagnosis code for a hospital stay or physician visit. Forearm and humerus fractures were identified if it was a primary diagnosis code for a hospital stay or two physician visits within 90 days. Fractures were excluded if a similar type of fracture occurred in the preceding 6 months, or if the diagnosis code for the fracture was accompanied by a high trauma code.

Data analysis

Statistical analysis was done using SAS 9.4 (SAS Institute, Inc., Cary, NC, USA). Descriptive statistics included baseline demographic information, risk factors for MOF, FRAX scores, TBS, and MOFs. We presented categorical variables with their frequency and percentage and compared them using the Chi-square test. We presented continuous variables with their mean and standard deviation and compared them using analysis of variance (ANOVA) or Mann-Whitney *U* test. We tested whether kidney function was a predictor of TBS with a multivariable linear regression model adjusting for clinical risk factors.

We used Cox proportional hazards models in all groups stratified by eGFR to assess whether there was an association between our outcomes of interest and TBS and whether that association was consistent irrespective of kidney function. Hazard ratios of TBS were expressed per SD decrease and were modeled: (1) without adjusting for covariates, (2) adjusting for age and sex, (3) adjusting for FRAX without BMD, and (4) adjusting for FRAX with BMD. Each of these models was also conducted for the entire cohort while adding CKD, either as a continuous variable (eGFR) or categorical variable (CKD stage), and an interaction term between CKD and TBS.

Supplementary analyses

We also used Cox proportional hazards models to compare the magnitudes of the associations of both FRAX with BMD and TBS-adjusted FRAX with BMD with our outcomes of interest in all groups stratified by eGFR. The hazard ratios of FRAX were expressed per SD increase and we examined the interaction of kidney function (categorical) and TBS-adjusted FRAX. FRAX was log-transformed for all Cox models. Hip fractures and MOF outcomes were modeled separately with their corresponding FRAX scores.

We calculated concordance statistics (*c*- statistics) among kidney disease groups as an alternative measure of the ability of TBS-adjusted FRAX to discriminate fracture risk. Additionally, we assessed the association between TBS and MOF or hip fracture in a subgroup of females only.

Results

Baseline characteristics

The study cohort consisted of 8289 patients who had both a DXA scan and serum creatinine measured within 12 months. Baseline characteristics of these patients, including fracture risk assessment scores, are presented in Table 1. There were 6224 (75.1%) patients with eGFR ≥ 60 mL/min/1.73 m^2, 1624 (19.6%) patients with eGFR 30–60 mL/min/1.73^2, and 441 (5.3%) patients with eGFR < 30 mL/min/1.73 m^2. Patients with eGFR < 60 mL/min/1.73 m^2, compared to those with eGFR ≥ 60 mL/min/1.73 m^2, were more likely to be male, older, overweight, have recent glucocorticoid exposure, or have comorbidities like diabetes, hypertension, chronic obstructive pulmonary disorder (COPD), or substance abuse. TBS and BMD were lower, and all FRAX scores were higher in patients with eGFR < 60 mL/min/m^2. There was no difference in history of previous fractures among groups.

As a continuous variable, eGFR was independently associated with TBS (− 0.003 per 10 mL/min/1.73 m^2 decrease; 95% CI, − 0.004 to − 0.002) and eGFR < 30 mL/min/1.73 m^2 was also an independent predictor of TBS compared to eGFR ≥ 60 mL/min/1.73 m^2 (− 0.037; 95% CI, − 0.049 to − 0.026) with a similar trend for eGFR 30–60 mL/min/1.73 m^2 (− 0.007; 95% CI − 0.013 to 0.0001) (Supplementary Table 1).

Outcomes of interest

Over the follow-up period of 5 years, there were 593 patients (7.2%) with MOFs and 163 patients (2.0%) with hip fractures across all groups. Compared to patients with eGFR ≥ 60 mL/min/1.73 m^2 (6.7%) and eGFR 30–60 mL/min/1.73 m^2 (8.4%), those with eGFR < 30 mL/min/1.73^2 (9.1%) were more likely to have MOFs ($p = 0.017$) (Table 1).

Patients with eGFR 30–60 mL/min/1.73 m^2 (3.4%) had more hip fractures than patients with eGFR < 30 mL/min/1.73 m^2 (2.9%) and patients with ≥ 60 mL/min/1.73 m^2 (1.5%) ($p < 0.001$) (Table 1).

Table 1 Patient characteristics

	eGFR ≥ 60 (n = 6224)	eGFR 30–60 (n = 1624)	eGFR < 30 (n = 441)	p value
Baseline				
Sex (male)	658 (10.6%)	305 (18.8%)	109 (24.7%)	< 0.001
Age	61.0 ± 12.6	69.2 ± 12.8	64.3 ± 15.6	< 0.001
Body mass index (kg/m^2)	26.9 ± 5.5	27.5 ± 5.4	27.8 ± 5.8	< 0.001
Rheumatoid arthritis	377 (6.1%)	70 (4.3%)	20 (4.5%)	0.015
COPD	557 (8.9%)	190 (11.7%)	59 (13.4%)	< 0.001
Alcohol or substance abuse diagnosis	215 (3.5%)	28 (1.7%)	11 (2.5%)	0.001
Recent glucocorticoid use	565 (9.1%)	327 (20.1%)	124 (28.1%)	< 0.001
Prior fracture	1016 (16.3%)	288 (17.7%)	75 (17.0%)	0.39
Parental hip fracture	707 (11.4%)	184 (11.3%)	36 (8.2%)	0.118
Lumbar spine TBS (L1-L4)	1.320 ± 0.125	1.294 ± 0.129	1.279 ± 0.135	< 0.001
Lumbar spine T-score	− 0.86 ± 1.36	− 1.15 ± 1.39	− 1.33 ± 1.43	< 0.001
Femoral neck T-score	− 1.26 ± 1.01	− 1.46 ± 1.05	− 1.60 ± 1.09	< 0.001
FRAX predicted probability of hip fracture (without BMD)	2.8 ± 5.1	5.6 ± 7.0	4.4 ± 6.3	< 0.001
FRAX predicted probability of hip fracture (with BMD)	2.1 ± 4.2	4.1 ± 5.8	4.1 ± 7.0	< 0.001
FRAX predicted probability of hip fracture (with BMD and TBS)	2.2 ± 4.1	4.1 ± 5.5	4.3 ± 7.0	< 0.001
FRAX predicted probability of MOF (without BMD)	9.8 ± 8.1	14.6 ± 10.3	12.2 ± 10.0	< 0.001
FRAX predicted probability of MOF (with BMD)	9.4 ± 7.2	13.0 ± 9.1	12.5 ± 10.2	< 0.001
FRAX predicted probability of MOF (with BMD and TBS)	9.6 ± 7.3	13.1 ± 8.8	12.9 ± 10.2	< 0.001
eGFR (mL/min/1.73 m^2)	85 ± 15	47 ± 8	17 ± 8	< 0.001
Diabetes	1026 (16.5%)	459 (28.3%)	185 (42.0%)	< 0.001
Hypertension	3920 (63.0%)	1433 (88.2%)	423 (95.9%)	< 0.001

BMD bone mineral density, *COPD* chronic obstructive pulmonary disease, *eGFR* estimated glomerular filtration rate, *MOF* major osteoporotic fracture, *TBS* trabecular bone score

Association of TBS with MOFs and hip fractures

We examined the effect of lower lumbar spine TBS on fractures at each strata of kidney function in unadjusted analyses and after adjustment for the FRAX score at BMD (Table 2). In unadjusted analyses, each standard deviation decrease in TBS resulted in a 27% higher risk of MOF in patients with eGFR ≥ 60 mL/min/1.73 m^2 (95% CI 1.19–1.36), 30% in patients with eGFR 30–60 mL/min/1.73 m^2 (95% CI 1.15–1.46), and 24% in patients with eGFR < 30 mL/min/1.73 m^2 (95% CI 1.01–1.53). When adjusted for age-sex or FRAX without BMD, lower TBS remained a significant risk for MOF in subgroups with eGFR ≥ 60 mL/min/1.73 m^2 and < 60 mL/min/1.73 m^2 but not the subgroup with eGFR < 30 mL/min/1.73 m^2. When TBS was adjusted for FRAX with BMD, the HR for MOF was only statistically significant in the subgroup with eGFR ≥ 60 mL/min/1.73

Table 2 Hazard ratios for lumbar spine trabecular bone score to predict MOF stratified by kidney function

HR per SD decrease (95% CI)	eGFR ≥ 60 (n = 6224)	eGFR < 60 (n = 2065)	eGFR 30–60 (n = 1624)	eGFR < 30 (n = 441)	Interaction (TBS*CKD)
TBS unadjusted	*1.27 (1.19–1.36)*	*1.29 (1.16–1.42)*	*1.30 (1.15–1.46)*	*1.24 (1.01–1.53)*	0.94
TBS adjusted for age and sex	*1.19 (1.10–1.28)*	*1.19 (1.07–1.33)*	*1.18 (1.04–1.33)*	1.19 (0.95–1.50)	0.53
TBS adjusted for FRAX MOF without BMD	*1.16 (1.08–1.25)*	*1.17 (1.05–1.31)*	*1.17 (1.03–1.32)*	1.14 (0.91–1.43)	0.58
TBS adjusted for FRAX MOF with BMD	*1.12 (1.04–1.20)*	1.10 (0.98–1.23)	1.10 (0.97–1.25)	1.07 (0.85–1.35)	0.77
Total MOF	416	177	137	40	

Italics denotes statistical significance

CKD chronic kidney disease, *eGFR* estimated glomerular filtration rate, *MOF* major osteoporotic fracture, *TBS* trabecular bone score, *95% CI* 95% confidence interval, *HR* hazard ratio, *SD* standard deviation

m^2, but all 95% CIs for the hazard ratios overlapped and no significant interactions between TBS and eGFR (p = 0.06) or CKD stage (p = 0.77) were detected.

For hip fractures, the HR for each standard deviation decrease in TBS was 1.47 in patients with eGFR ≥ 60 mL/min/1.73 m^2 (95% CI 1.28–1.69), 1.38 in patients with eGFR 30–60 mL/min/1.73 m^2 (95% CI 1.15–1.67), and 1.34 in patients with eGFR < 30 mL/min/1.73 m^2 (95% CI 0.93–1.91) in unadjusted analyses (Table 3). Lower TBS remained significant for hip fracture in subgroups defined as eGFR ≥ 60 mL/min/1.73 m^2 or eGFR < 60 mL/min/1.73 m^2 (but not the subgroup with eGFR < 30 mL/min/1.73 m^2) when adjusted for age-sex or FRAX without BMD. The risk for hip fracture was not significant at any eGFR when TBS was adjusted for FRAX with BMD. Interactions between TBS and eGFR (p = 0.92) and TBS and CKD stage (p = 0.91) were again non-significant. The associations between TBS and fractures did not qualitatively change when restricted to a female-only subgroup (Supplementary Table 2).

The hazard ratios for incident MOFs and hip fractures per standard deviation increase in FRAX (with BMD) and FRAX (with BMD and TBS) are presented in Supplementary Table 3. Hazard ratios were significant at all eGFR categories, with small increases in magnitude when FRAX with BMD was adjusted for TBS for all CKD stages. The interaction between FRAX with TBS and CKD stage (p = 0.021) was significant for MOF probability (higher hazard ratios in the eGFR 30–60-mL/min subgroup), but not for hip fractures (p = 0.40).

Discrimination

TBS-adjusted FRAX with BMD showed very good discrimination for predicting hip fractures (c-statistic = 0.83) and good discrimination for predicting MOF (c-statistic = 0.68) (Supplementary Table 4) but was nearly identical to FRAX alone with BMD across all eGFR strata.

Discussion

In this prospective study of more than 8000 participants with DXA testing, we found that the addition of trabecular bone score to the FRAX score with BMD did not meaningfully improve prediction of fracture outcomes in patients with CKD. Although TBS was independently associated with eGFR, and the hazard ratios for FRAX with TBS were marginally higher than FRAX alone, the incremental improvement declined at lower levels of eGFR, and the addition of TBS did not improve discrimination. These findings suggest that the addition of TBS may not improve fracture risk assessment in older patients with CKD which was not consistent with our hypothesis.

Previous studies have examined the role of TBS in fracture risk assessment in elderly patients with CKD. Recently, Naylor et al. conducted a retrospective analysis of the Canadian Multicentre Osteoporosis Study (CaMos) study and found that lower TBS was independently associated with 60% higher risk of MOFs in patients with reduced renal function [4]. These authors studied 1426 patients but had only 199 patients with eGFR < 60 mL/min/1.73 m^2, and only 5 of those patients had eGFR < 30 mL/min/1.73 m^2. Based on a larger population sample size with a larger number of patients with eGFR < 60 mL/min/1.73 m^2, and particularly with eGFR < 30 mL/min/1.73 m^2, our study did not find a clinically meaningful association between TBS and fracture risk. We believe that differences in baseline characteristics, as well as the lack of patients with reduced levels of kidney function, may explain the differences in our findings. In contrast to the CaMos study which was a random population-based sample, our study included patients who had DXA tests ordered by physicians for screening or clinical indications. These differences likely contributed to a high incidence rate of fracture events observed in our study, and possibly the differences in the association.

The ability of TBS to predict fracture risk has also been studied in patient populations with comorbid illnesses other than CKD. A 2014 review of the utility of TBS in various causes of secondary osteoporosis, including diabetes mellitus,

Table 3 Hazard ratios for lumbar spine trabecular bone score to predict hip fractures stratified by kidney function

HR (95% CI)	eGFR ≥ 60 (n = 6224)	eGFR < 60 (n = 2065)	eGFR 30–60 (n = 1624)	eGFR < 30 (n = 441)	Interaction (TBS*CKD)
TBS unadjusted	*1.47 (1.28–1.69)*	*1.38 (1.17–1.62)*	*1.39 (1.15–1.67)*	1.34 (0.93–1.91)	0.42
TBS adjusted for age and sex	*1.25 (1.07–1.45)*	*1.24 (1.04–1.48)*	1.19 (0.98–1.46)	1.29 (0.87–1.90)	0.89
TBS adjusted for FRAX hip without BMD	*1.18 (1.01–1.38)*	*1.24 (1.04–1.47)*	1.21 (1.00–1.48)	1.26 (0.86–1.84)	0.83
TBS adjusted for FRAX hip with BMD	1.08 (0.93–1.26)	1.11 (0.93–1.32)	1.11 (0.91–1.36)	1.08 (0.72–1.61)	0.91
Total hip fractures	95	68	55	13	

Italics denotes statistical significance

CKD chronic kidney disease, *eGFR* estimated glomerular filtration rate, *TBS* trabecular bone score, *95% CI* 95% confidence interval, *HR* hazard ratio

hyperparathyroidism, autoimmune conditions, patients receiving prolonged glucocorticoid therapy, and patients with breast cancer receiving hormonal therapy, found that TBS was able to predict increased risk of fractures [34]. However, patients with non-transplant CKD were not included in this review. TBS has been shown to be useful in predicting fracture risk in kidney transplant recipients both at the time of transplant and at post-operative follow-up [23, 25, 27, 35, 36]. These patients often have considerable glucocorticoid exposure, and their findings may not be generalizable to the non-dialysis, non-transplant CKD population.

It is important to note that we found a significant positive association between TBS adjusted for FRAX with BMD and both incident MOFs and hip fractures in patients with eGFR > 60 mL/min/1.73 m^2. Interestingly, this association was not observed in patients with CKD. No significant interactions between TBS and CKD stage were detected. Moreover, there was a small increase in hazard ratios across all categories of eGFR when FRAX was adjusted for TBS, compared to FRAX alone. However, the strength of association between TBS and fracture risk in our subjects with normal eGFR was not as high as that seen in previous studies for the general population. This may in part reflect selection biases in the population undergoing eGFR assessment or limited power to detect small effect sizes in the different subgroups since confidence intervals overlapped between the various CKD subgroups.

Fracture risk is influenced by both bone density and quality, with the latter involving bone microarchitecture, mineralization, turnover, properties of collagen, and accumulated damage [37, 38]. Bone density is assessed by DXA scan, while the gold standard in assessing bone quality is bone biopsy [38]. TBS has been utilized as a convenient method of non-invasively assessing bone microarchitecture and has shown promise as a method for non-invasively assessing bone quality in CKD [25]. However, CKD also predisposes patients to multiple factors affecting other aspects of bone quality which may not be captured by TBS. These include hyperparathyroidism, phosphate imbalances, decreased calcitriol activity, and elevated fibroblast growth factor 23 (FGF23) [37, 39]. FGF23 is a peptide that influences serum phosphate concentration. It is found in elevated concentrations in patients with CKD and may be one of the earliest detectable biomarkers of MBD. Although TBS as an indicator of bone quality is an important influence on fracture risk in individuals with normal eGFR, these additional features unique to patients with CKD may be more impactful than TBS and could thereby weaken the association between TBS and fracture risk.

Strengths of our study include the large sample size, which incorporated a significant proportion of individuals with CKD and the high number of primary outcome events accrued over the study period. To our knowledge, ours is the largest study of patients with DXA scans and CKD, and a significant proportion of the individuals had eGFR < 30 mL/min/1.73 m^2. There was also a high incidence of MOFs which were the main outcome of interest. In addition, due to universal healthcare coverage in the province of Manitoba, the provincial sources from which we obtained data were complete and there was minimal loss to follow-up in the study.

Limitations of our study include limited power in specific CKD subgroups, particularly those with eGFR < 30 mL/min/1.73 m^2 due to a small number of patients and low number of fracture events, resulting in wide confidence intervals for hazard ratios that included unity (null effect). However, the absence of significant interactions between TBS and CKD stage is consistent with the possibility that TBS works as well in CKD patients as in those with preserved eGFR. Our predominantly female cohort is likely due to the inclusion criteria of having a DXA scan ordered by a physician as part of clinical care and is reflective of the higher prevalence of osteoporosis in females who are often preferentially screened compared to male counterparts. It is not known whether our findings are applicable to male patients, and this requires further investigation. In addition, patients were also placed into categories based on eGFR calculated using the single lowest value of serum creatinine within 1 year from the DXA scan. This may not accurately reflect their baseline renal function and may have influenced our conservative results. Finally, data for baseline characteristics in our cohort did not include measurements of serum parathyroid hormone (PTH) or vitamin D levels, which may be important contributors in mineral bone disorder (MBD) seen in CKD.

In conclusion, our study found that TBS is independently associated with reduced kidney function as measured by a single eGFR, but does not seem to improve prediction of fracture risk in patients with CKD in our study. Alternative measures of bone health may be needed to improve fracture risk prediction in the CKD population.

Acknowledgments Data used in this study are from the Population Health Research Data Repository housed at the Manitoba Centre for Health Policy, University of Manitoba and were derived from data provided by Manitoba Health, Winnipeg Regional Health Authority and Diagnostic Services Manitoba. This article has been reviewed and approved by the members of the Manitoba Bone Density Program Committee. All authors contributed to review of data results and drafting of the manuscript.

Funding information This work was supported through funding provided by the Department of Health of the Province of Manitoba to the University of Manitoba (HIPC# 2015/2016-12). The results and conclusions are those of the authors and no official endorsement by Manitoba Health was intended or should be inferred.

Compliance with ethical standards

Conflicts of interest Dr. Hans is a co-owner of the TBS patent and holds stock options and royalties in the Medimaps group. Dr. Tangri reports grants and personal fees from Astra Zeneca Inc, personal fees from Otsuka Inc, personal fees from Janssen, personal fees from Boehringer

Ingelheim/Eli LIlly, grants, personal fees and other from Tricida Inc, outside the submitted work.

References

1. Hill NR, Fatoba ST, Oke JL, Hirst JA, O'Callaghan CA, Lasserson DS, Hobbs F (2016) Global prevalence of chronic kidney disease - a systematic review and meta-analysis. PLoS One 11(7):e0158765. https://doi.org/10.1371/journal.pone.0158765
2. Najar MS, Mir MM, Muzamil M (2017) Prevalence of osteoporosis in patients with chronic kidney disease (stages 3-5) in comparison with age- and sex-matched controls: a study from Kashmir Valley Tertiary Care Center. Saudi J Kidney Dis Transpl 28(3):538–544
3. Canada O (2016) Better Bone Health 2015-2016 Annual Report. https://osteoporosis.ca/wp-content/uploads/Osteo-Annual-Report-2015-2016-Web-Version.pdf
4. Naylor KL, McArthur E, Leslie WD, Fraser L, Jamal SA, Cadarette SM, Pouget JG, Lok CE, Hodsman AB, Adachi JD, Garg A (2014) The three-year incidence of fracture in chronic kidney disease. Kidney Int 86(4):810–818
5. Dukas L, Schacht E, Stahelin H (2005) In elderly men and women treated for osteoporosis a low creatinine clearance of <65 ml/min is a risk factor for falls and fractures. Osteoporos Int 16:1683–1690
6. Kinsella S, Chavrimootoo S, Molloy MG, Eustace J (2010) Moderate chronic kidney disease in women is associated with fracture occurrence independently of osteoporosis. Nephron Clin Pract 116(3):c256–c262
7. Fried LF, Biggs ML, Shlipak MG, Seliger S, Kestenbaum B, Stehman-Breen C, Sarnak M, Siscovick D, Harris T, Cauley J, Newman AB, Robbins J (2007) Association of kidney function with incident hip fracture in older adults. J Am Soc Nephrol 18(1):282–286
8. Dooley AC, Weiss NS, Kestenbaum B (2008) Increased risk of hip fracture among men with CKD. Am J Kidney Dis 51(1):38–44
9. Ensrud KE, Lui LY, Taylor BC, Ishani A, Shlipak MG, Stone KL, Cauley JA, Jamal SA, Antoniucci DM, Cummings SR, Group OFR (2007) Renal function and risk of hip and vertebral fractures in older women. Arch Intern Med 167(2):133–139
10. Nickolas TL, McMahon DJ, Shane E (2006) Relationship between moderate to severe kidney disease and hip fracture in the United States. J Am Soc Nephrol 17(11):3223–3232
11. Fang Y, Ginsberg C, Sugatani T, Monier-Faugere M, Malluche H, Hruska K (2014) Early chronic kidney disease-mineral bone disorder stimulates vascular calcification. Kidney Int 85(1):142–150
12. Papaioannou A, Morin S, Cheung AM, Atkinson S, Brown JP, Feldman S, Hanley DA, Hodsman A, Jamal SA, Kaiser SM, Kvern B, Siminoski K, Leslie WD, Canada SACoO (2010) 2010 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada: summary. CMAJ 182(17):1864–1873
13. Fraser LA, Langsetmo L, Berger C, Ioannidis G, Goltzman D, Adachi JD, Papaioannou A, Josse R, Kovacs CS, Olszynski WP, Towheed T, Hanley DA, Kaiser SM, Prior J, Jamal S, Kreiger N, Brown JP, Johansson H, Oden A, McCloskey E, Kanis JA, Leslie W (2011) Fracture prediction and calibration of a Canadian FRAX tool: a population-based report from CaMos. Osteoporos Int 22(3):829–837
14. Leslie WD, Lix LM, Johansson H, Oden A, McCloskey E, Kanis J (2010) Independent clinical validation of a Canadian FRAX tool: fracture prediction and model calibration. J Bone Miner Res 25(11):2350–2358
15. Connelly K, Collister D, Tangri N (2018) Fracture risk and treatment in chronic kidney disease. Curr Opin Nephrol Hypertens 27(3):221–225
16. Whitlock RH, Leslie WD, Shaw J, Rigatto C, Thorlacius L, Komenda P, Collister D, Kanis JA, Tangri N (2019) The Fracture Risk Assessment Tool (FRAX®) predicts fracture risk in patients with chronic kidney disease. Kidney Int 95(2):447–454. https://doi.org/10.1016/j.kint.2018.09.022
17. Burt LA, Bhatla JL, Hanley DA, Boyd S (2017) Cortical porosity exhibits accelerated rate of change in peri- compared with postmenopausal women. Osteoporos Int 28(4):1423–1431
18. Samelson EJ, Broe KE, Xu H, Yang L, Boyd S, Biver E, Szulc P, Adachi J, Amin S, Atkinson E, Berger C, Burt L, Chapurlat R, Chevalley T, Ferrari S, Goltzman D, Hanley DA, Hannan MT, Khosla S, Liu CT, Lorentzon M, Mellstrom D, Merle B, Nethander M, Rizzoli R, Sornay-Rendu E, Van Rietbergen B, Sundh D, Wong AKO, Ohlsson C, Demissie S, Kiel DP, Bouxsein M (2019) Cortical and trabecular bone microarchitecture as an independent predictor of incident fracture risk in older women and men in the Bone Microarchitecture International Consortium (BoMIC): a prospective study. Lancet Diabetes Endocrinol 7(1):34–43
19. Ramchand SK, Seeman E (2018) The influence of cortical porosity on the strength of bone during growth and advancing age. Curr Osteoporos Rep 16(5):561–572
20. Boutroy S, Hans D, Sornay-Rendu E, Vilayphiou N, Winzenrieth R, Chapurlat R (2013) Trabecular bone score improves fracture risk prediction in non-osteoporotic women: the OFELY study. Osteoporos Int 24:77–85
21. Rabier B, Heraud A, Grand-Lenoir C, Winzenrieth R, Hans D (2010) A multicentre, retrospective case-control study assessing the role of trabecular bone score (TBS) in menopausal Caucasian women with low areal bone mineral density (BMD): analysing the odds of vertebral fracture. Bone 46:176–181
22. Hans D, Goertzen AL, Krieg MA, Leslie W (2011) Bone microarchitecture assessed by TBS predicts osteoporotic fractures independent of bone density: the Manitoba study. J Bone Miner Res 26:2762–2769
23. Naylor KL, Lix LM, Hans D, Garg AX, Rush DN, Hodsman AB, Leslie W (2016) Trabecular bone score in kidney transplant recipients. Osteoporos Int 27(3):1115–1121
24. Aleksova J, Kurniawan S, Elder G (2018) The trabecular bone score is associated with bone mineral density, markers of bone turnover and prevalent fracture in patients with end stage kidney disease. Osteoporos Int 29(6):1447–1455
25. Shevroja E, Lamy O, Hans D (2018) Review on the utility of trabecular bone score, a surrogate of bone micro-architecture, in the chronic kidney disease spectrum and in kidney transplant recipients. Front Endocrinol (Lausanne) 9:561
26. Ramalho J, Marques IDB, Hans D, Dempster D, Zhou H, Patel P, Pereira RMR, Jorgetti V, Moyses RMA, Nickolas T (2018) The trabecular bone score: relationships with trabecular and cortical microarchitecture measured by HR-pQCT and histomorphometry in patients with chronic kidney disease. Bone 116:215–220
27. Sharma AK, Toussaint ND, Elder GJ, Rajapakse CS, Holt SG, Baldock P, Robertson PL, Ebeling PR, Sorci OR, Masterson R (2018) Changes in bone microarchitecture following kidney transplantation-beyond bone mineral density. Clin Transpl 32(9):e13347
28. Looker AC, Wahner HW, Dunn WL, Calvo MS, Harris TB, Heyse SP, Johnston CC Jr, Lindsay R (1998) Updated data on proximal femur bone mineral levels of US adults. Osteoporos Int 8(5):468–489
29. Silva BC, Broy SB, Boutroy S, Schousboe JT, Shepherd JA, Leslie WD (2015) Fracture risk prediction by non-BMD DXA measures: the 2015 ISCD Official Positions Part 2: Trabecular Bone Score. J Clin Densitom 18(3):309–330. https://doi.org/10.1016/j.jocd.2015.06.008

30. Pothuaud L, Barthe N, Krieg MA, Mehsen N, Carceller P, Hans D (2009) Evaluation of the potential use of trabecular bone score to complement bone mineral density in the diagnosis of osteoporosis: a preliminary spine BMD-matched, case-control study. J Clin Densitom 12(2):170–176. https://doi.org/10.1016/j.jocd.2008.11.006
31. McCloskey EV, Odén A, Harvey NC, Leslie WD, Hans D, Johansson H, Kanis J (2015) Adjusting fracture probability by trabecular bone score. Calcif Tissue Int 96:500–509
32. Lix LM, Azimaee M, Osman BA, Caetano P, Morin S, Metge C, Goltzman D, Kreiger N, Prior J, Leslie W (2012) Osteoporosis-related fracture case definitions for population-based administrative data. BMC Public Health 12:301
33. O'Donnell S, Group CCDSSCOW (2013) Use of administrative data for national surveillance of osteoporosis and related fractures in Canada: results from a feasibility study. Arch Osteoporos 8:143
34. Ulivieri FM, Silva BC, Sardanelli F, Hans D, Bilezikian JP, Caudarella R (2014) Utility of the trabecular bone score (TBS) in secondary osteoporosis. Endocrine 47(2):435–438
35. Perez-Saez MJ, Herrera S, Prieto-Alhambra D, Vilaplana L, Nogues X, Vera M, Redondo-Pachon D, Mir M, Guerri R, Erespo M, Diez-Perez A, Pascual J (2017) Bone density, microarchitecture, and material strength in chronic kidney disease patients at the time of kidney transplantation. Osteoporos Int 28(9):2723–2727
36. Luckman M, Hans D, Cortez N, Nishiyama KK, Agarawal S, Zhang C, Nikkel L, Iyer S, Fusaro M, Guo EX, McMahon DJ, Shane E, Nickolas T (2017) Spine trabecular bone score as an indicator of bone microarchitecture at the peripheral skeleton in kidney transplant recipients. Clin J Am Soc Nephrol 12(4):644–652
37. McNerny EMB, Nickolas T (2015) Bone qualty in chronic kidney disease: definitions and diagnosis. Curr Osteoporos Rep 13(3):207–213
38. Jamal SA, Nickolas T (2015) Bone imaging and fracture risk assessment in kidney disease. Curr Osteoporos Rep 13(3):166–172
39. Nickolas TL, Jamal S (2015) Bone kidney interactions. Rev Endocr Metab Disord 16(2):157–163