Factors Associated with Low Trabecular Bone Score in Patients Receiving Maintenance Hemodialysis

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Abstract

Background: Low bone mineral density (BMD) is common among maintenance hemodialysis (MHD) patients and associated with increased fracture risk and mortality. However, BMD does not provide information on bone quality. The dual-energy X-ray absorptiometry (DXA)-derived lumbar spine trabecular bone score (TBS) facilitates the assessment of bone quality. The present study examined BMD, TBS, and factors associated with low TBS in MHD patients.

Methods: This is a single-center, cross-sectional study of 132 MHD patients. Areal BMD and lumbar spine TBS were determined by DXA. The degree of abdominal aortic calcification (AAC) was evaluated in a lateral lumbar spine radiograph using Kauppila score.

Results: The median age was 67 years and 35.3% were women. The average dialysis vintage was 4.9±5.9 years. The prevalence of osteoporosis was 39.2%. Higher prevalence of osteoporosis was observed in women (women 59.6% vs. men 27.9%). The prevalence of low TBS (<1.31) was 33.8%. TBS was also significantly lower in women (women 1.29±0.12 vs. men 1.40±0.12; P<0.001). The group of patients with low TBS showed higher percentage of female and higher serum cholesterol, alkaline phosphatase, and homocysteine compared with the group with normal TBS. Serum calcium, phosphate, magnesium, parathyroid hormone, 25-hydroxyvitamin D, and beta-2-microglobulin were comparable between the two groups. The prevalence of severe AAC (Kauppila scores ≥6) was 52.6%. There were no correlations between AAC score with BMD or TBS. In multivariate analysis, female sex was the only independent predictor of low TBS.

Conclusions: Low TBS was observed in approximately one-third of MHD patients. Female sex was the only independent predictor of low TBS. There were no correlations between mineral parameters and AAC with TBS. Whether low TBS could predict fracture risk will require further study.

Keywords: dialysis; kidney failure; ESKD; ESRD; osteopenia; vascular calcification

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ปัจจัยที่มีความสัมพันธ์กับความบกพร่องของคุณภาพกระดูกในผู้ป่วยฟอกเลือดด้วยเครื่องไตเทียม

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บทคัดย่อ

บทนำ: มวลกระดูก (bone mineral density หรือ BMD) ต่ำพบได้บ่อยในผู้ป่วยที่ได้รับการฟอกเลือดด้วยเครื่องไตเทียมและเพิ่มความเสี่ยงต่อการเกิดกระดูกหักและการเสียชีวิต อย่างไรก็ตามการตรวจมวลกระดูกไม่สามารถบอกคุณภาพของกระดูกได้ การตรวจดัชนีคุณภาพกระดูก (trabecular bone score หรือ TBS) ด้วยเครื่องตรวจวิเคราะห์ความหนาแน่นของกระดูก (dual-energy X-ray absorptiometry หรือ DXA) สามารถช่วยประเมินคุณภาพของกระดูกได้ งานวิจัยนี้ต้องการศึกษามวลกระดูกและดัชนีคุณภาพกระดูก รวมไปถึงปัจจัยที่เกี่ยวข้องกับดัชนีคุณภาพกระดูกในผู้ป่วยที่ได้รับการฟอกเลือดด้วยเครื่องไตเทียม

วิธีการวิจัย: การศึกษานี้เป็นการศึกษาในสถาบันเดียว ณ.จุดเวลาใดเวลาหนึ่งในผู้ป่วยฟอกเลือดด้วยเครื่องไตเทียมจำนวน 132 ราย โดยมีการตรวจวิเคราะห์ BMD และ TBS ของกระดูกสันหลังด้วยเครื่อง DXA นอกจากนี้ยังมีการประเมินปริมาณของแคลเซียมที่เกาะในหลอดเลือดแดงเอออร์ตา (abdominal aortic calcification หรือ AAC) จากภาพเอกซเรย์กระดูกสันหลังส่วนเอวโดยใช้คะแนน Kauppila

ผลการวิจัย: อายุของผู้เข้าร่วมวิจัยมีค่ามัธยฐานอยู่ที่ 67 ปี เป็นเพศหญิงร้อยละ 35.3 ระยะเวลาเฉลี่ยที่ได้รับการฟอกเลือดคือ 4.9±5.9 ปี พบว่ามีความชุกของภาวะกระดูกพรุนร้อยละ 39.2 โดยพบในเพศหญิงมากกว่าเพศชาย (59.6% เทียบกับ 27.9%) ค่าเฉลี่ยของ TBS คือ 1.36±0.13 พบความชุกของภาวะ TBS ต่ำร้อยละ 33.8 โดยเพศหญิงมีค่า TBS ต่ำกว่าเพศชายอย่างมีนัยสำคัญทางสถิติ (1.29±0.12 เทียบกับ 1.4±0.12; P<0.001) กลุ่มผู้ป่วยที่มีค่า TBS ต่ำ (<1.3) พบว่าส่วนใหญ่เป็นผู้หญิง มีระดับโคเลสเตอรอล อัลคาไลน์ ฟอสฟาเตส และโฮโมซิสเทอีนสูงกว่าผู้ป่วยที่มีค่า TBS ปกติ อย่างไรก็ตามไม่พบความแตกต่างของซีรั่มแคลเซียม ฟอสเฟต แมกนีเซียม พาราไทรอยด์ฮอร์โมน วิตามินดี และเบต้าทูไมโครโกลบูลิน ในทั้ง 2 กลุ่ม ร้อยละ 52.5 ของผู้ป่วยมีภาวะ AAC ที่รุนแรง (คะแนน Kauppilla ≥6) ในขณะที่ไม่พบความสัมพันธ์ระหว่าง AAC กับ BMD หรือ TBS จากการวิเคราะห์แบบพหุตัวแปรพบว่าเพศหญิงเป็นปัจจัยเดียวที่มีความสัมพันธ์อย่างอิสระกับ TBS ต่ำ

สรุป: ประมาณ 1 ใน 3 ของผู้ป่วยที่ได้รับการฟอกเลือดด้วยเครื่องไตเทียมมีค่า TBS ต่ำ โดยเพศหญิงเป็นปัจจัยเดียวที่มีความสัมพันธ์อย่างเป็นอิสระกับ TBS ต่ำ นอกจากนี้ไม่พบความสัมพันธ์ระหว่างฮอร์โมนและเกลือแร่ที่เกี่ยวข้องกับกระดูกและ AAC กับ TBS ยังจำเป็นต้องทำการศึกษาเพิ่มเติมเพื่อประเมินความสามารถของ TBS ในการพยากรณ์กระดูกหักในอนาคต

คำสำคัญ: กระดูกผุ; บำบัดทดแทนไต; ไตวายเรื้อรังระยะสุดท้าย; ฟอกไต

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Introduction

Mineral and bone disorders (MBD) in chronic kidney disease (CKD) which encompass abnormalities of mineral metabolites and hormones, bone diseases and cardiovascular calcification contribute to the risk of cardiovascular disease, mortality, and fracture. The 2017 Kidney Disease Improving Global Outcomes (KDIGO) guidelines suggested that bone mineral density (BMD) may be used to evaluate fracture risk in CKD patients.[1] However, the predictive ability of BMD diminishes substantially in patients receiving dialysis compared with general population.[2] BMD can be used to determine the quantity of the bone but gives limited information on the bone quality. The microarchitecture of trabecular bone, one of the important components of bone strength, cannot be assessed by BMD testing. As the risk of fracture increases with progression of CKD, it may be important to assess both the quality and the quantity of the bone. Bone microarchitecture may be evaluated by high-resolution peripheral quantitative computed tomography (HR-pQCT) and bone biopsy, but the use of both modalities is limited due to high cost of the HR-pQCT and the need for specialized laboratory equipment to process and the specialist to read the bone biopsy specimen. Measurement of trabecular bone score (TBS) has emerged as a new tool for assessing bone microarchitecture based on dual-energy X-ray absorptiometry (DXA) images of the lumbar spine. Low TBS indicates degraded and weakened bone microarchitecture which is associated with an increase in fracture risk.

According to the prior study in patients with CKD, TBS correlated with both cortical and trabecular bone microarchitecture evaluated by HR-pQCT and bone histomorphometry.[3] The previous research in Caucasian population with CKD and end-stage kidney disease (ESKD) revealed the association between lower TBS and increased fracture risk.[4-8] Only few studies on TBS in Asian ESKD population have been published. The present study examined the prevalence of osteoporosis and low TBS in patients receiving maintenance hemodialysis (MHD). Factors associated with low TBS and the relationship between TBS and abdominal aortic calcification (AAC) were also examined.

Methods

Study design and population

This is a single-center, cross-sectional study that included MHD patients from Srinagarind Hospital, Khon Kaen University, Thailand between April 2022 to March 2023. The Inclusion criteria were age ≥18 years and receiving HD for ≥3months. The exclusion criteria were history of organ transplantation, receiving concurrent peritoneal dialysis or palliative care, presence of active malignancy or psychiatric disorders, pregnancy, and history of using or currently receiving anti-resorptive agents including bisphosphonate, denosumab, and aromatase inhibitors. The Khon Kaen University Ethics Committee for Human Research (IRB00001189) approved the research protocol. All participants provided written informed consent. The study was performed according to the Declaration of Helsinki.

Biochemical data

The data on demographic, underlying diseases, CKD-MBD medications (vitamin D, phosphate binders, and cinacalcet), and laboratory data including serum calcium, phosphate, 25-hydroxyvitamin D, parathyroid hormone (PTH), total alkaline phosphatase, beta2-microglobulin, and homocysteine levels were collected. All patients underwent lateral lumbar spine radiograph in a standing position using standard radiographic equipment. The severity of AAC was graded using the previously validated Kauppila score.[9] Areal BMD was assessed using DXA (Lunar Prodigy, GE Lunar, Madison, Wisconsin, United States) at the lumbar spine (L1-L4), total hip, femoral neck, and distal third of the radius. Osteopenia (-2.5 < T-score < -1) and osteoporosis (T-score < -2.5) were determined using the World Health Organization (WHO) T-score threshold values.[10] DXA images of the L1-L4 vertebrae and TBS iNsight software (version 2.1, Med-Imaps, Pessac, France) were used to evaluate and calculate TBS. The patients were divided into two groups based on TBS as follow: low TBS group, TBS <1.31; normal TBS group, TBS ≥1.31. The TBS cut-off of 1.31 was used because the previous study reported the association between TBS <1.31 and increased fracture risk.[11]

Statistical analysis

Continuous variables were presented as mean ± standard deviation (SD) or median (interquartile range (IQR)). For categorical variables, the data were presented as proportions. The Shapiro-Wilk test was used to determine the normal distribution of the data. Comparisons between two continuous variables were performed using the Student's T-test or Mann-Whitney U test. For categorial variables, Chi-square test or Fisher's exact test was applied. The relationship between the two variables was analyzed by Pearson or Spearman correlation. Factors associated with low TBS were evaluated using logistic regression analysis. P-value <0.05 was regarded as statistically significant. All statistical analyses were performed using STATA Version 17 (Texas, USA).

Results

Two hundred and one patients were screened, and 132 (66%) completed the study (**Figure 1**). The median age was 67 (57-72) years, and 47 (35.3%) patients were female. The median dialysis vintage was 3.1 (1.2-5.4) years. The median body mass index was 21.2 (19.1-23.6) kg/m^2. Eighty-two (61.7%) patients had type 2 diabetes. Forty (30.1%) patients received calcium-containing phosphate binders, 33 (24.8%) received calcitriol or alfacalcidol, and 16 (12%) received cinacalcet. The comparisons of biochemical parameters between the group of patients with low TBS and normal TBS are shown in **Table 1**. The group with low TBS showed higher percentage of female and higher serum total cholesterol, alkaline phosphatase, and homocysteine but lower serum albumin levels.

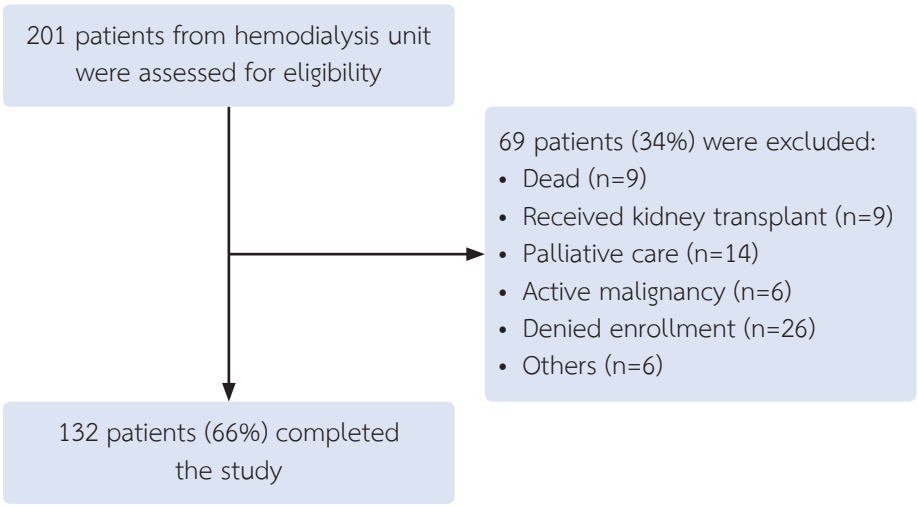

Figure 1. Study Flowchart

Fifty-five (41.7%) patients had osteopenia and 52 (39.4%) had osteoporosis. The prevalence of osteoporosis was higher in female (female 59.6% vs. male 27.9%) (**Figure 2**). The average TBS was 1.36±0.13. Female showed significantly lower TBS (female 1.29±0.12 vs. male 1.40±0.12; P <0.001). The prevalence of low TBS (<1.31) was 33.8%. The average TBS was lower in the group of patients with osteoporosis compared with the group with normal BMD (1.30±0.10 vs. 1.40±0.13; P <0.01). There was no difference in the TBS between the groups of patients with and without DM or with and without AAC. TBS were also comparable among the groups of patients with PTH below, within, or above the target range (2 to 9 times the upper normal limit) (**Figure 3**).

Table 1. Comparisons of biochemical parameters between the group of patients with low and normal trabecular bone score

Parameters	Low TBS <1.31 N=45	Normal TBS ≥1.31 N=87	*P* value
Age (years)	65.5±14.7	62.9±12.0	0.29
Female (%)	27 (60%)	20 (23%)	<0.01
Dialysis vintage (years)	3.8 (1.5-5.2)	3 (1.0-5.5)	0.53
Type 2 diabetes (%)	29 (64.4%)	53 (60.9%)	0.22
Body mass index (kg/m^2)	21.8±3.7	21.9±3.9	0.43
Hemoglobin (g/dL)	10.4±1.5	10.7±1.6	0.24
BUN (mg/dL)	58.1±17.6	61.5±21.3	0.36
Creatinine (mg/dL)	9.27±2.48	9.92±2.94	0.21
Fasting plasm glucose (mg/dL)	145±90	131±65	0.29
Bicarbonate (mEq/L)	23.3±2.7	23.4±2.7	0.87
Uric acid (mg/dL)	6.9±1.6	6.8±1.9	0.75
Cholesterol (mg/dL)	159±44	141±33	0.01
Calcium (mg/dL)	8.61±0.69	8.80±0.70	0.07
Phosphate (mg/dL)	3.67±1.49	3.82±1.51	0.29
Magnesium (mg/dL)	2.28±0.35	2.38±0.36	0.07
Albumin (g/dL)	3.9±0.4	4.1±0.4	0.04
Alkaline phosphatase (IU/L)	178±143	127±70	<0.01
25-hydroxyvitamin D (ng/mL)	38.8±12.5	41.8±14.3	0.12
Parathyroid hormone (pg/mL)	280.9±227.7	317.1±289.2	0.23
C-reactive protein (mg/L)	6.4±9.0	5.7±10.9	0.64
Beta2-microglobulin (mg/L)	26.4±8.6	24.3±8.5	0.09
Homocysteine (µmol/L)	26.8±8.0	23.5±6.4	0.01

TBS, trabecular bone score

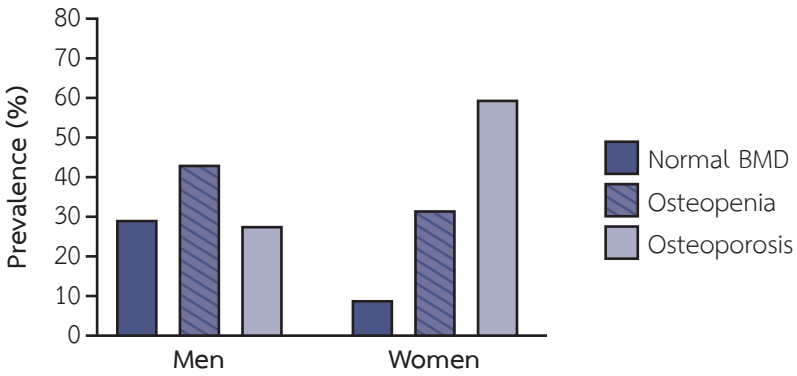

Figure 2. Prevalence of osteopenia and osteoporosis
BMD, bone mineral density

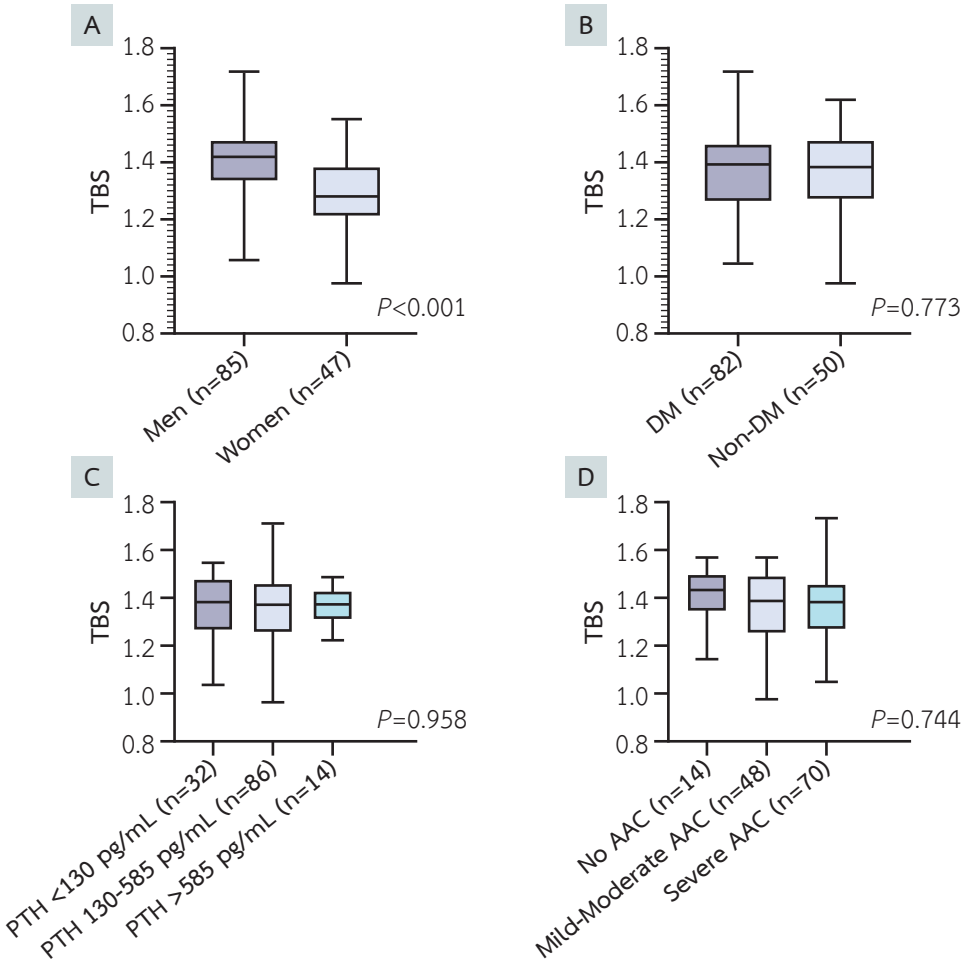

Figure 3. Comparisons of trabecular bone score according to different parameters
A, sex; B, diabetes; C, parathyroid hormone levels and D, abdominal aortic calcification
TBS, trabecular bone score; DM, diabetes mellitus; PTH, parathyroid hormone; AAC, abdominal aortic calcification

AAC was present in 119 (89.5%) patients. The median Kauppila score was 6 (2-10). There were 70 (52.6%) patients with severe AAC (Kauppila score ≥6) (**Figure 4**). The patients with DM showed higher prevalence of AAC (77 (93.9%) vs. 42 (84%); P = 0.035). There was no difference in the prevalence of AAC between the group of patients with PTH level within or outside the target range (78 (89%) vs. 41 (91.1%); P = 0.92).

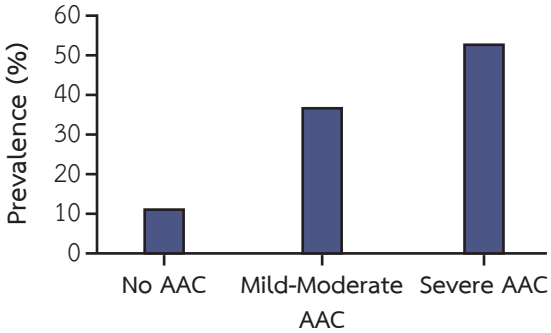

Figure 4. Prevalence of abdominal aortic calcification according to severity
AAC, abdominal aortic calcification; mild to moderate AAC, Kauppila score 1-5; severe AAC, Kauppila score ≥6

TBS correlated positively with the BMD at the lumbar spine (L1-L4), total hip, femoral neck, and distal third of the radius (**Figure 5**). There was no relationship between TBS and the severity of AAC. In univariate logistic regression analysis, female sex, higher alkaline phosphatase, and homocysteine levels were associated with low TBS. In multivariate analysis, female sex was the only independent predictor of low TBS (**Table 2**).

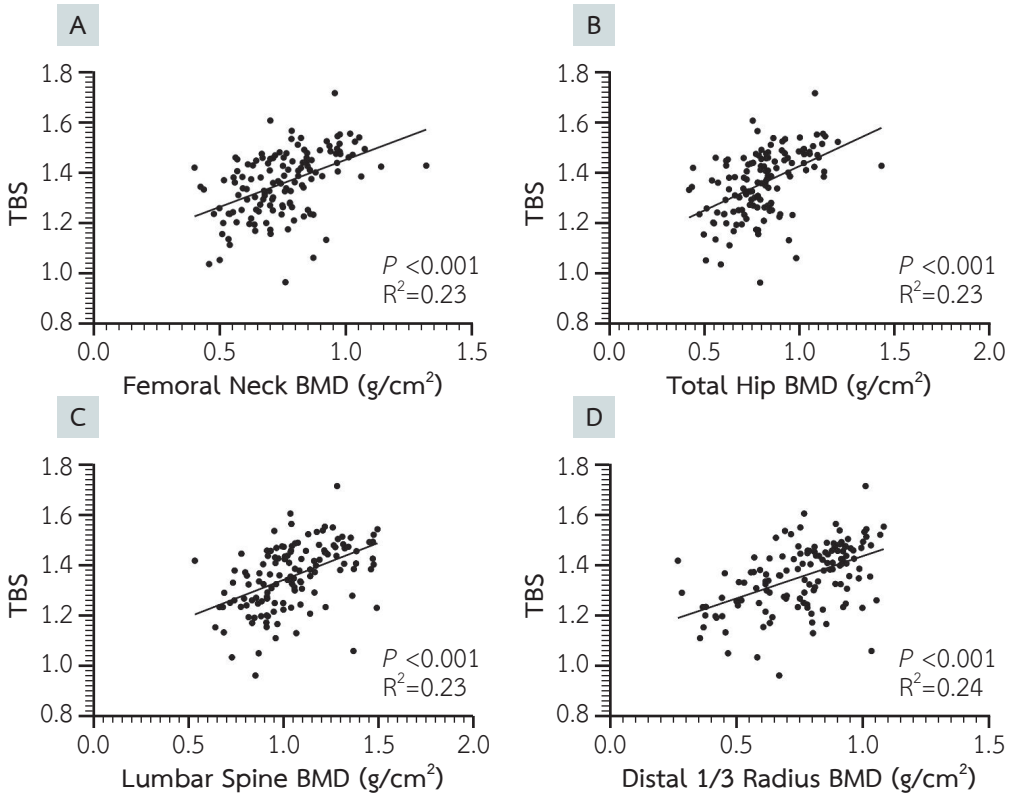

Figure 5. Relationship between trabecular bone score and bone mineral density at all sites
TBS, trabecular bone score; BMD, bone mineral density

Table 2. Logistic regression analyses of factors associated with low trabecular bone score

	Univariate			Multivariate		
Variables	OR	95% CI	*P*	OR	95% CI	*P*
Age (5 years)	1.08	0.94, 1.25	0.292	1.18	0.96, 1.45	0.125
Female sex	5.10	2.34, 11.1	<0.001	5.88	2.39, 14.44	<0.001
BMI (kg/m^2)	0.99	0.90, 1.09	0.863	0.96	0.85, 1.09	0.510
DV (months)	1.00	0.99, 1.00	0.321	1.00	0.99, 1.01	0.295
Diabetes	1.20	0.57, 2.52	0.636	1.39	0.50, 3.83	0.524
BUN (mg/dL)	0.99	0.97, 1.01	0.354	0.99	0.97, 1.03	0.939
Creatinine (mg/dL)	0.92	0.80, 1.05	0.213	1.14	0.89, 1.46	0.280
Calcium (mg/dL)	0.67	0.39, 1.15	0.150	0.92	0.43, 1.96	0.835

	Univariate			Multivariate		
Variables	OR	95% CI	*P*	OR	95% CI	*P*
Phosphate (mg/dL)	0.93	0.73, 1.19	0.573	1.03	0.73, 1.46	0.847
Magnesium (mg/dL)	0.46	0.16, 1.30	0.142	0.45	0.09, 2.12	0.312
ALP (IU/L)	1.01	1.00, 1.01	0.017	1.00	0.99, 1.01	0.220
25-OH-D (ng/mL)	0.98	0.96, 1.01	0.243	0.98	0.95, 1.02	0.402
PTH (pg/mL)	0.99	0.99, 1.00	0.467	0.99	0.99, 1.00	0.159
CRP (mg/L)	1.01	0.97, 1.04	0.713	1.00	0.96, 1.05	0.993
β2-M (mg/L)	1.03	0.99, 1.07	0.182	1.01	0.96, 1.07	0.654
Homocysteine (μmol/L)	1.12	1.05, 1.20	0.023	0.95	0.89, 1.02	0.151

OR, odds ratio; CI, confidence interval; BMI, body mass index; DV, dialysis vintage; ALP, alkaline phosphatase; 25-OH-D, 25-hydroxyvitamin D; PTH, parathyroid hormone; CRP, C-reactive protein; β2-M, beta2-microglobulin

Discussion

The present study revealed the prevalence of osteoporosis of 39.2% and low TBS of 33.8%. The group of patients with low TBS were more likely to be female, had higher serum cholesterol, alkaline phosphatase, and homocysteine levels compared with the group of patients with normal TBS. TBS correlated well with BMD at all sites. There were no correlations between AAC score with BMD or TBS. In multivariate analysis, female sex was the only independent predictor of low TBS.

BMD testing has been the gold standard for diagnosis of osteoporosis. However, BMD does not provide the information on bone quality. Lumbar spine TBS could be added to BMD for additional information on bone microarchitecture and bone quality.[12] The current KDIGO guidelines recommend BMD test in patients with CKD.[1] Several studies in dialysis patients have confirmed the ability of total BMD in predicting cardiovascular and all-cause mortality.[13] Not only reduced bone mass was associated with increased fracture risk and mortality, poor bone quality also contributed to the risk of fracture.[14,15] HR-pQCT is another modality that can provide information on bone microarchitecture which can predict fracture risk. However, HR-pQCT is not available in most dialysis facilities due to high cost. TBS is a more economical alternative because the images can be obtained by DXA at the same time as BMD test. Previous studies have demonstrated lower TBS among CKD patients compared with general population, and lower TBS was associated with higher fracture risk.[4-8, 16-18] Based on the data from the meta-analysis of TBS database for estimating the risk of fracture in 17,809 subjects from 14 prospective cohorts across diverse regions, the TBS value of 1.31 has been proposed as a cut-off for both males and females. TBS >1.31 is regarded as normal, 1.23 - 1.31 as having partially degraded microarchitecture, and <1.23 as degraded microarchitecture.[11] By applying this cut-off value to the MHD patients from the present study, approximately one-third showed partially degraded or degraded microarchitecture.

The patients with low TBS showed higher serum alkaline phosphatase and homocysteine levels than those with normal TBS. Alkaline phosphatase is secreted by osteoblasts, and elevated alkaline phosphatase levels could indicate osteoblast dysfunction predisposing to impaired bone microarchitecture. Homocysteine is a protein-bound uremic toxin, and the evidence from previous studies suggest that elevated homocysteine levels could modulate osteoclastogenesis by inducing deleterious effects on bone via various mechanisms.[19] Similar to BMD, female had lower TBS than male. This finding was likely due to the same reasons for lower BMD

in females in general population, which include hypogonadism, estrogen deprivation, and other unidentified intrinsic factors that may influence trabecular microarchitecture in females. However, the present study did not find the relationship between increasing age and low TBS. It is possible that the impact of age on TBS is attenuated in patients receiving MHD due to the complexities of uremic milieu. Similar to other studies, TBS correlated well with BMD at all sites. Overall, these data confirmed the presence of reduced bone mass and impaired bone quality in MHD patients.

It is well established that the degree of vascular calcification is associated with an increase in cardiovascular events and mortality in dialysis patients.[20] The pathophysiologic mechanisms of vascular calcification are complex involving both traditional and CKD-related risk factors.[21] Abnormal bone-vascular interactions result in a reduced capability of the bone to buffer calcium and phosphate leading to calcium deposition in the blood vessels.[22] The previous study in MHD patients has revealed an inverse relationship between impaired bone microarchitecture by HR-pQCT and the degree of coronary artery calcification by multi-slice computed tomography.[23] The improvement in bone turnover could slow the progression of coronary artery calcification in both low and high turnover bone disease.[24] Despite the previous report of an inverse relationship between TBS and AAC score among young dialysis patients, there was no relationship between TBS and AAC score in the present study.[25] This could be due to the more advanced age and the higher prevalence of diabetes of the patients in the present study.

The strength of the present study includes the study population was relatively large and consisted of a homogeneous cohort of MHD patients. The parameters of interest were BMD, TBS, and other MBD-related factors that were relevant to day-to-day clinical practice. The limitation of this study was the lack of longitudinal follow-up which could help provide additional information on the ability of TBS to predict fracture in dialysis population.

In conclusion, low TBS was observed in approximately one-third of MHD patients. Female sex was the only independent predictor of low TBS. There were no correlations between any of the mineral parameters and AAC with TBS. Whether low TBS could predict fracture risk will require further study.

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