Fibroblast Growth Factor 23 and Klotho Are Associated With Trabecular Bone Score but Not Bone Mineral Density in the Early Stages of Chronic Kidney Disease: Results of the Cross-Sectional Study

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Summary

This study evaluates bone mineral density (BMD) and trabecular bone score (TBS) in relationship with new markers of chronic kidney disease (CKD), fibroblast growth factor 23 (FGF23), and klotho. The patients in this cross-sectional study were divided as follows: group A -patients in stages G1-3; group B -patients in stages G4 – 5 according to KDIGO. Plasma levels of soluble klotho and FGF23 were determined by ELISA. Bone mineral density (BMD) and trabecular bone score (TBS) were measured. 74 patients with CKD (mean age 68.8 years) were included in the study. Higher levels of FGF23 were observed in group B (N=15) compared to group A (N=59; p=0.001) were observed. FGF23 was higher in group A compared to group B. Significant difference in TBS within the first 3 stages of CKD was observed (mean TBS in G1=1.375 vs. G2=1.340 vs. G3a=1.24; p<0.05) and negative correlation of FGF23 and TBS (R=-0.33; p=0.05) and positive correlation between klotho and TBS (R=0.419; p=0.04) was observed. This study confirmed that FGF23 and klotho are associated with TBS, but TBS reflects a decrease in kidney function only in the first 3 stages of CKD. Thus, FGF23 and klotho together with TBS are promising markers of early trabecular bone impairment in CKD.

Key words

FGF23 • Klotho • TBS • Kidney

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Introduction

Changes in mineral metabolism in chronic kidney disease (CKD) occur along with its onset. Low-energy fractures are very common in patients with CKD, but their development is not fully understood. Their development could be exacerbated by CKD-related changes, including sarcopenia or falls (Weisinger and Bellorin-Font 2004, Naylor *et al.* 2014, Avin and Moorthi 2015). Fracture risk in CKD has been reported to be at least two times higher than in healthy individuals of the same age (Alem *et al.* 2000. Nickolas *et al.* 2006). One of the most common risk factors for fragility fractures is a decrease in BMD. According to the most recent KDIGO guidelines (Isakova *et al.* 2017) BMD as a screening for increased fracture risk is useful in stages 3-5. Additionally, it seems that total hip BMD (TH) compared to lumbar spine BMD (L-spine) is more affected by CKD progression, particularly in subjects with eGFR< 60 ml/min/1.73 m^2 (Bezerra de Carvalho *et al.* 2019). However, CKD is also associated with impairment of bone microarchitecture. A trabecular bone score (TBS), a surrogate used in clinical settings to assess bone texture, could contribute to the estimate of fracture risk. The potential to use TBS in secondary osteoporosis was evaluated in several conditions such as primary hyperparathyrodisim (Muñoz-Torres *et al.* 2019), glucocorticoid induced osteoporosis (Sandru *et al.* 2020), acromegaly (Kužma *et al.* 2019) or diabetes (Jackuliak

et al. 2019), etc. In the recent study (Rampersad *et al.* 2020), the potential of TBS to estimate fracture risk was evaluated. TBS was associated with a lower estimated glomerular filtration rate (eGFR). Furthermore, eGFR less than 60ml/min/1.73m^2, which is considered borderline between grade 2 and 3a, was associated with a higher risk of fractures. It is plausible that TBS reflects bone status in early CKD grades. Low TBS values were observed in end-stage renal disease (ESRD) compared to healthy controls (Yavropoulou *et al.* 2017, Yoon *et al.* 2019) or predicitive of a prior vertebral fracture (Aleksova *et al.* 2018).

In addition, newer markers are used to detect early changes in kidney function. Fibroblast growth factor 23 (FGF23) and Klotho are potential regulators of mineral metabolism, and their levels change with the progression of renal failure (Muñoz-Castañeda and Rodelo-Haad 2020). The FGF23-Klotho complex in the kidney induces phosphaturia and suppresses the synthesis of 1.25-dihydroxyvitamin D. In patients with CKD, circulating FGF23 levels are progressively increased and lead to retention of phosphate, but this results in reduced renal production of 1.25-dihydroxyvitamin D and leads to secondary hyperparathyroidism (Komaba 2010). Excessive actions of FGF23 cause several types of hypophosphatemic osteomalacia characterized by impaired mineralization of the bone matrix. The association between FGF23 and impaired trabecular bone was confirmed by study using high resolution peripheral quanitative computed tomography (HR-pQCT) (Rupp *et al.* 2019). Thus, it is plausible that a possible relationship exists between newer laboratory markers, such as FGF23, klotho, and TBS, as the surrogate of trabecular bone microacrhitecture.

Patients and methods

A single-center cross-sectional study was conducted in CKD outpatients between 7/2018 and 7/2019. All study procedures were reviewed and approved by the local ethical committee. Each patient signed an informed consent before any study procedure.

The inclusion criteria were as follows:

- All patients with CKD diagnosis according to the KDIGO guidelines (Muñoz-Castañeda and Rodelo-Haad 2020) regardless of sex, age or CKD ethiology
    - eGFR categories according to KDIGO:
        - G1…90 ml/min/1.73m^2
        - G2… 60-89 ml/min/1.73m^2
        - G3a... 45-59 ml/min/1.73m^2
        - G3b... 30-44 ml/min/1.73m^2
        - G4... 15-29 ml/min/1.73m^2
        - G5 … < 15 ml/min/1.73m^2
- No history of specific treatment for osteoporosis other than vitamin D or calcium supplementation.

Exclusion criteria:

- Patients with acute illness (e.g. infection) or any exacerbated chronic disease, including acute exacerbation of CKD (defined as an absolute increase in serum creatinine more than 1.5 times the value of a previous examination)
- Hospitalized patients
- Immobile patients
- Patients with specific treatment for osteoporosis in addition to vitamin D and calcium supplementation
- Patients with a known diagnosis of secondary osteoporosis (such as glucocorticoid - induced osteoporosis, malabsorption, primary hyperparathyroidism, rheumatoid arthritis, etc.)

Methods

In all patients, laboratory parameters that evaluated the stage of CKD (eGFR, albumin / creatinine ratio of a single urine sample), calcium-phosphate metabolism (Ca, P, PTH), additional bone turnover parameters (25-OH-D3, CTx - C-terminal telopeptide fragment of collagen type I, P1NP - propeptide of type I procollagen, OC-osteocalcin) and common biochemical parameters were evaluated to assess the internal environment, liver function, lipid spectrum and blood count. At the same time, serum samples were taken to determine FGF23 and soluble klotho. In all patients, basic anthropometric measurements and determination of bone status using DXA and TBS.

Laboratory parameters

Conventional biochemical and urine tests were performed using commercial kits available. From the basic laboratory parameters: Na, K, Cl, Mg, Ca, P, urea, creatinine, eGF, PTH, ALP, AST, GMT, ALT, cholesterol, HDL, LDL, TAG, urine examination were determined. Estimated glomerular filtration (eGFR) was calculated using the Chronic Kidney Disease - Epidemiology Collaboration (CKD-EPI) formula. Furthermore, 25-OH-D3 levels were determined using an automated electrochemiluminescence system (Eclesys

Vitamin D Total II, 2019, Roche Diagnostics GmBH, Mannheim, Germany.

From bone turnover markers, CTx, OC, and P1NP were evaluated by ECLIA using the Roche Elecsys 1010/2010 kit.

Plasma levels of soluble klotho were determined using an ELISA with quantitative sandwich enzyme immunoassay. Its minimum detectable levels are 0.039 ng/ml. And the accuracy of the intra-assay was CV %<8 % and the accuracy of the inter-assay was CV %<10 %, while three samples of known concentration were tested 20 times on a plate.

Plasma levels of FGF23 were also determined by ELISA. For FGF23, the minimum detectable level is less than 6.3 pg / ml, and this assay has high sensitivity and specificity for the determination of FGF23. Intra-assay precision was CV<10 %, and inter-assay precision was CV<12 %, while 3 samples with low, medium and high levels of FGF23 were tested on 3 different plates, 8 replicates in each plate.

Bone measurements

BMD measurements at the L1-4 spine (LS), femoral neck (FN) and total hip (TH) were performed using DXA with a Hologic Horizon device with APEX software version 13.3 : 7.

TBS was performed from DXA lumbar spine scans using TBS iNsight® software (Medimaps SASU, Pessac, France) version 3.0.2.0.

Table 1. Study groups characteristics

Parameters	Group A (G1-3)	Group B (G4-5)	p-value
Number of patients	59	15	NS
Age (yrs)	70.5±11.4	68.5±11.1	NS
Weight (kg)	87.4±2.5	88.5±5.0	NS
Height (cm)	172±8.7	170.1±10.1	NS
Hypertension (Y/N)	49/10	14/1	0.05
Diabetes (Y/N)	34/25	11/4	0.05
eGF (ml/s)	1.11±0.37	0.31±0.12	0.0001
creatinine (umol/l)	96.89±28.8	278.97±105.2	0.0001
BUN (urea) (umol/l)	7.39±2.5	18.35±7.9	0.0001
Serum Ca (mmol/l)	2.35±0.15	2.43±0.2	NS
Phosphorus (mmol/l)	1.06±0.02	1.34±0.05	0.0001
vit D (ng/ml)	17.31±7.4	22.39±11.2	0.04
vit D suficiency (Y/N)	17/40	8/6	NS
iPTH (pmol/l)	4.63±2.4	5.90±4.3	NS
ALP (ukat/l)	1.12±0.32	1.21±0.33	NS
glucose (mmol/l)	7.02±2.2	7.3±2.04	NS
HbA1c DCCT (%)	7.07±1.1	6.59±0.6	NS
Haemoglobin (g/l)	135.8±16.9	119.6±23.7	0.005
Osteocalcin (ug/l)	19.38±8,1	39.61±28.1	0.0001
P1NP (ug/l)	44.58±17.3	68.28±31.3	0.0006
CTx (ng/l)	371.78±154.8	569.5±367.1	0.004
Klotho (ng/ml)	0.176±0.15	0.195±0.1	NS
FGF23 (ng/ml)	0.098±0.03	0.144±0.04	0.001
Previous fractures (Y/N)	6/53	1/14	NS
BMD L-spine (g/cm^2)	1.09±0.19	1.121±0.2	NS
BMD neck (g/cm^2)	0.828±0.17	0.845±0.15	NS
BMD total hip (g/cm^2)	0.984±0.15	0.972±0.17	NS
TBS	1.285±0.12	1.293±0.09	NS

* continuous variables are expressed as means ±SD, ** ordinal variables are expressed as absolute numbers

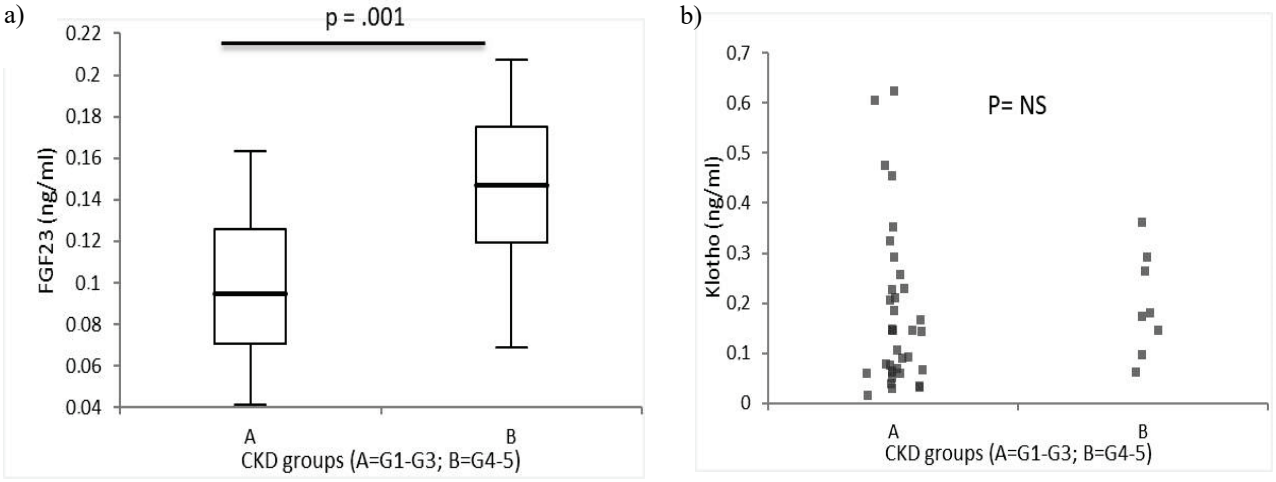

Fig. 1. Comparison between groups shows lower values of FGF23 in patients within group A (**a**) and no difference in levels of klotho between groups (**b**)

Statistical methods

For statistical analysis, Analyze-it® software version 4.91.3 (The Tannery, Leeds, United Kingdom) was used. Continuous variables were expressed as mean ± standard deviation (SD). Before statistical analysis, we excluded values that were greater / lesser than +/- 3 SD. The Shapiro-Franca test was used to assess the normality of the distribution of the monitored parameters. For individual comparisons between groups, we used Student's t-test and Mann-Whitney test depending on the normality of the distribution of specific data. For bone measurements (DXA and TBS) we used ANCOVA analysis to compare individual groups. We used univariate analysis and logistic regression to assess individual correlations. We consider $p < 0.05$ values to be significant differences.

Results

In total, 74 CKD patients (42 males/32 females, 68.8 years of average age) were included in the analysis, a number of 10; 25; 24; 10 and 5 patients in G1. G2, G3, G4, and G5, respectively. For better comparison, the patients were divided into two groups: group A, where we included patients in stages G1-G3 (N=59) and group B included patients in stage G4-5 (N=15). Patients in group A had significantly higher values of eGF, hemoglobin, and lower serum creatinine, urea, phosphorus, vitamin D, bone markers and a proportion of patients with arterial hypertension and diabetes mellitus, compared to patients in group B (see Table 1 for further details).

FGF23 levels were significantly higher in group B compared to group A. Klotho levels between groups did not reach statistical significance (Fig. 1). No differences in BMD and TBS were observed between the groups.

Early stages (G1-G3a) of CKD

Comparison of TBS between each stage of CKD showed a significant difference in G1 vs G2 (1.374 vs. 1.304; p=0.05); and G1 vs G3 (1.374 vs 1.24; p=0.03), but not in other stages. The significant difference in FN BMD between G1 and G2 (0.94 vs 0.81; p= 0.05) was observed. No differences were observed at other BMD sites in all stages (Table 2 and Fig. 2).

A negative relationship was observed between TBS and FGF23 (R=-0. 33; p=0.05) and a positive relationship between TBS and klotho (R=0.419; p=0.04) was observed. No association of FGF23 and klotho was observed between BMD (Fig. 3).

Discussion

CKD leads to significant comorbidities, quality of life impairment, and shortened survival (Carney 2020). One of the common complications of CKD is an increased risk of fragility fractures, especially in the elderly population (Klawansky *et al.* 2003). Current in comparison to former KDIGO guidelines (Muñoz-Castañeda and Rodelo-Haad 2020) resurrected measurement of BMD in case treatment of osteoporosis is considered. However, fragility fractures in CKD are associated with changes in bone structure, volume, and

remodeling. Thus, it is necessary to better define the risk of fracture, using tools that can be used in clinical settings. In addition, newer markers of kidney function are developed to capture early changes in kidney function and subsequently target management and treatment.

In this study, the relationship between bone measures, such as BMD and TBS, and newer markers of kidney function, FGF23 and klotho, was evaluated among patients with CKD G1-5. Levels of FGF23 levels were higher in CKD G4-5 compared to G1-3, but no differences in klotho levels were observed. Additionally, the TBS values, but not the BMD, were higher in the early stages of CKD, with the highest values in G1 and the lowest in G3. The correlation analysis showed a significant relationship between TBS and FGF23 and klotho, demonstrating that there is an association between the microarchitecture of the trabecular bone and FGF23, especially in the early stages of CKD. Given that, TBS seems more sensitive in the early detection of CKD patients at risk of fracture.

The FGF23–Klotho system has emerged as an endocrine axis required to maintain phosphate homeostasis and 'phosphatopathy' is a key factor in understanding its action. Despite substantial loss of nephron, hyperphosphatemia is observed only in patients with ESRD (CKD stage 4 or 5), indicating that phosphate homeostasis is maintained until stage 4 to 5 during the progression of CKD. This is because the decrease in

Table 2. Early stages (G1-G3a) of CKD – characteristics

Parameters	G1 (N=10)	G2 (N=25)	G3a (N=10)	p-value
age	54.3±8.9	66.4±8.7	76.8±6.4	****all <0.001
Gender (M/F)	8/2	15/10	6/4	NS
BMI (kg/m2)	29.5±5.5	30.9±4.3	28.1±4.2	NS
eGF (ml/s)	1.67±0.12	1.23±0.14	0.87±0.09	****all <0.0001
S-Ca (mmol/l)	2.29±0.1	2.32±0.12	2.39±0.19	NS
S-P (mmol/l)	1.135±0.16	1.03±0.15	1.08±0.2	NS
vitamin D (ng/ml)	18.8±4.6	15.5±8,1	19.7±8,1	NS
s-iPTH (pmol/l)	4.2±1.9	4.8±2.5	4.2±2.9	NS
P1NP	35.1±8	44,1±18	53,1±14	G1 vs G3a = 0.005
CTx	325.4±162	342±161	446±150	NS
P-klotho	0.13±0.07	0.13±0.1	0.18±0.21	G1 vs G3a = 0.06;
P-FGF23	0.073±0.012	0.103±0.04	0.108±0.028	G1 vs G2 =0.09; G1 vs G3a = 0.02
LS BMD	1.07±0.2	1.06±0.12	1.08±0.27	NS
FN BMD	0.94±0.2	0.81±0.15	0.75±0.06	G1 vs G2 = 0.05
TH BMD	1.06±0.2	0.98±0.13	0.91±0.07	NS
TBS	1.374±0.04	1.304±0.09	1.24±0.097	G1 vs G2 = 0.05; G1 vs G3a = 0.02

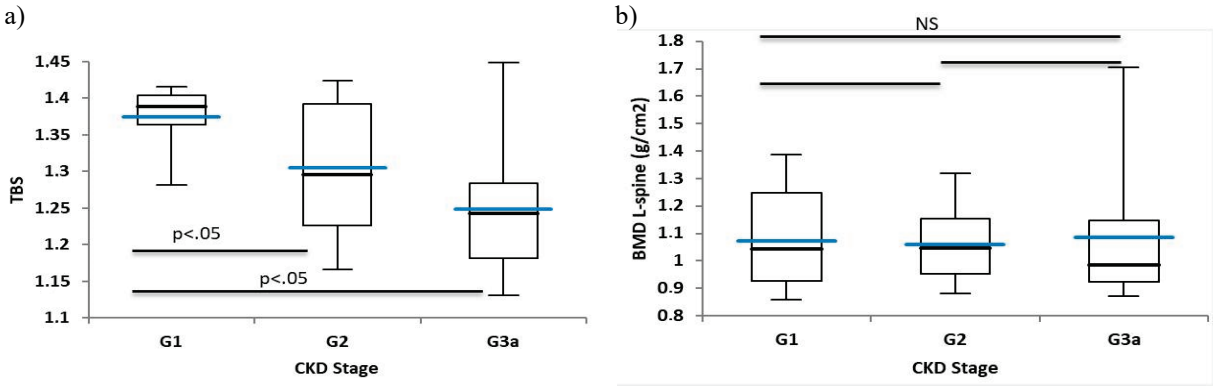

Fig. 2. Comparison of TBS (**a**) and BMD (**b**) in early stages of CKD

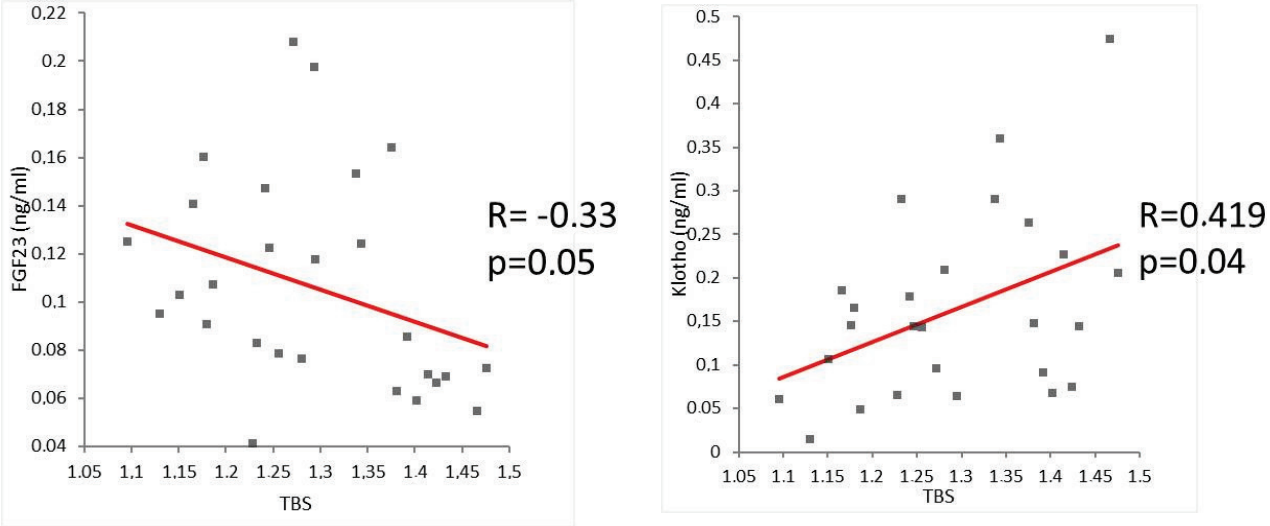

Fig. 3. Correlation analysis between (**a**) TBS - FGF23 and (**b**) TBS – klotho.

nephron number is compensated by an increase in phosphate excretion per nephron, which is achieved by an increase in FGF23. In fact, FGF23 starts to increase as early as stage 2 (Kuro-o 2017) before changes in calcium, phosphorus, and PTH concentrations after small kidney damage (Rodelo-Haad *et al.* 2019). FGF23 is one of the first markers of CKD-MBD, which has long been thought to regulate only vitamin D and phosphate metabolism. Levels of klotho levels in urine and plasma start to decline in the second stage of CKD, during the reduction of the glomerular filtration rate and the loss of functional nephrons (Zou *et al.* 2018). Decreased klotho levels lead to increased levels of FGF23 and suppress active vitamin D synthesis with all its consequences on bone metabolism.

This study shows that BMD at any site, except the difference in FN BMD in the stages G1 vs. G2, is not associated with the decrease in eGFR. Data on the relationship of CKD with BMD are contradictory. Previously, it was not recommended to perform BMD tests routinely, especially in stages 3-5D of CKD, because BMD does not predict fracture risk in a similar way to the general population (2009). More recently, low areal BMD measured by DXA in the forearm, hip, and spine can predict a future fracture in studies showing CKD, even in end-stage renal disease (Iimori *et al.* 2012, Yenchek *et al.* 2012, West *et al.* 2015, Isakova *et al.* 2017). As in the general population, the relevance of BMD is limited to overestimation by scoliosis, osteoarthritis, as well as vascular or joint calcifications. However, in patients with CKD, it has been suggested that both bone mass (BMD) and bone texture (TBS) should be determined to better estimate the risk of fracture (Pimentel *et al.* 2017). In our cohort, a difference in TBS values was observed in the first three stages, with the highest TBS values observed in G1 and the lowest in G3. This difference was not observed in BMD at any site (L-spine, neck or total hip). At the same time, a significant association of TBS with FGF23 was observed. It is therefore likely that a relationship between decreased renal function and degradation of the trabecular bone microarchitecture exists. The average value of TBS in stage G3a was 1.24, representing the borderline cutoff value of 1.23 for high trabecular degradation and risk of fractures according to meta-analysis (McCloskey *et al.* 2016). This also confirms that TBS is a suitable tool for assessing bone microarchitecture in clinical settings to estimate fracture risk in patients with CKD. In a cohort that included 1.426 CKD patients (199 of whom had CKD G3a and worse) followed for an average of 4.7 years, TBS was independently (age, sex, FRAX, and BMD) associated with fracture risk (Naylor *et al.* 2016). This was supported by a recent study by Rampersad *et al.* (2020) where they found a gradual decrease in TBS with a decrease in eGFR. Similar findings were confirmed in patients with end-stage renal disease (ESRD), where patients on hemodialysis had significantly lower TBS than healthy controls. Furthermore, those who had diagnosed osteoporosis with DXA had even lower TBS compared to those who did not have osteoporosis (Yavropoulou *et al.* 2017). Another study of 59 ESRD patients confirmed that TBS is significantly correlated with qCT parameters (Brunerova *et al.* 2016).

This study has few limitations, such as cross-sectional design and small sample size with disproportionate number of subjects in each stage of

CKD. However, the early stages G1-3a showed significant results and the number of patients in these stages is optimal for performing statistical analysis. It would be interesting to screen for vertebral asymtpomatic fractures between groups. There was a significant difference in age between the groups, but this follows from the fact that eGFR decreases with age.

To conclude, this pilot study shows that among patients with CKD, FGF23, as the novel marker of kidney function, is higher in patients with stages 4-5 of CKD according to KDIGO. TBS, but not BMD, is gradually decreasing in the early stages of CKD. FGF23 and klotho are associated with TBS showing that early changes in kidney function are associated with impairment of bone microstructure. This study confirms that TBS is a suitable tool to assess bone microarchitecture to estimate the risk of fracture in the early stages of CKD in clinical settings. However, the results need further evaluation in prospective controlled studies.

Authors' contributions

Conceptualization: Zuzana Kužmová, Martin Kužma and Juraj Payer; Methodology: Zuzana Kužmová, Martin Kužma, Andrea Gažová, Ján Kyselovič; Validation: Peter Jackuliak, Zdenko Killinger; Formal Analysis, Zuzana Kužmová, Martin Kužma; Investigation, Zuzana Kužmová, Magdaléna Kovářová; Resources, Zuzana Kužmová, Martin Kužma, Peter Jackuliak; Data Curation, Zuzana Kužmová, Magdaléna Kovářová, Andrea Gažová Writing – Original Draft Preparation, Zuzana Kužmová, Martin Kužma, Juraj Payer; Writing – Review & Editing, Martin Kužma, Zuzana Kužmová, Zdenko Killinger, Juraj Payer; Supervision, Juraj Payer, Martin Kužma, Jan Kyselovič;

Institutional Review Board Statement: The study was carried out according to the Declaration of Helsinki guidelines and was approved by the local Ethics Committee of the University Hospital of Bratislava, number of statements: 146/2019, date of approval: 12- JUL-2019

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data availability statement: on request from Martin Kuma, martin.kuzma@fmed.uniba.sk.

Conflict of Interest

There is no conflict of interest.

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References

KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Kidney Int Suppl: S1-130. 2009.

ALEKSOVA J, KURNIAWAN S, ELDER GJ: 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: 1447-1455, 2018. https://doi.org/10.1007/s00198-018-4468-y

ALEM AM, SHERRARD DJ, GILLEN DL, WEISS NS, BERESFORD SA, HECKBERT SR, WONG C, STEHMAN-BREEN C: Increased risk of hip fracture among patients with end-stage renal disease. Kidney Int 58: 396-399, 2000. https://doi.org/10.1046/j.1523-1755.2000.00178.x

AVIN KG, MOORTHI RN: Bone is not alone: the effects of skeletal muscle dysfunction in chronic kidney disease. Curr Osteoporos Rep 13: 173-179, 2015. https://doi.org/10.1007/s11914-015-0261-4

BEZERRA DE CARVALHO KS, VASCO RFV, CUSTODIO MR, JORGETTI V, MOYSÉS RMA, ELIAS RM: Chronic kidney disease is associated with low BMD at the hip but not at the spine. Osteoporos Int 30: 1015-1023, 2019.

BRUNEROVA L, RONOVA P, VERESOVA J, BERANOVA P, POTOEKOVA J, KASALICKY P, RYCHLIK I: Osteoporosis and impaired trabecular bone score in hemodialysis patients. Kidney Blood Press Res 41: 345-354, 2016. https://doi.org/10.1159/000443439

CARNEY EF: The impact of chronic kidney disease on global health. Nature Reviews Nephrology 16: 251-251. 2020. https://doi.org/10.1038/s41581-020-0268-7

IIMORI S, MORI Y, AKITA W, KUYAMA T, TAKADA S, ASAI T, KUWAHARA M, SASAKI S, TSUKAMOTO Y: Diagnostic usefulness of bone mineral density and biochemical markers of bone turnover in predicting fracture in CKD stage 5D patients--a single-center cohort study. Nephrol Dial Transplant 27: 345-351. 2012. https://doi.org/10.1093/ndt/gfr317

ISAKOVA T, NICKOLAS TL, DENBURG M, YARLAGADDA S, WEINER DE, GUTIÉRREZ OM, BANSAL V, ROSAS SE, NIGWEKAR S, YEE J, KRAMER H: KDOQI US Commentary on the 2017 KDIGO Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Am J Kidney Dis 70: 737-751. 2017. https://doi.org/10.1053/j.ajkd.2017.07.019

JACKULIAK P, KUŽMA M, KILLINGER Z, PAYER J: Good long-term glycemic compensation is associated with better trabecular bone score in postmenopausal women with type 2 diabetes. Physiol Res 68: S149-S156, 2019. https://doi.org/10.33549/physiolres.934304

KLAWANSKY S, KOMAROFF E, CAVANAUGH JR PF, MITCHELL DY, GORDON MJ, CONNELLY JE, ROSS SD: Relationship between age, renal function and bone mineral density in the US population. Osteoporosis International 14: 570-576, 2003. https://doi.org/10.1007/s00198-003-1435-y

KOMABA H: [CKD-MBD (Chronic Kidney Disease-Mineral and Bone Disorder). Role of FGF23-Klotho axis in CKD-MBD]. (Article in Japanese) Clin Calcium 20: 1028-1036, 2010.

KURO-O M: The FGF23 and Klotho system beyond mineral metabolism. Clin Exp Nephrol 21: 64-69, 2017. https://doi.org/10.1007/s10157-016-1357-6

KUŽMA M, VAŇUGA P, SÁGOVÁ I, PÁVAI D, JACKULIAK P, KILLINGER Z, BINKLEY NC, WINZENRIETH R, GENANT HK, PAYER J: Non-invasive DXA-derived bone structure assessment of acromegaly patients: a cross-sectional study. Eur J Endocrinol 180: 201-211. 2019. https://doi.org/10.1530/EJE-18-0881

McCLOSKEY EV, ODÉN A, HARVEY NC, LESLIE WD, HANS D, JOHANSSON H, BARKMANN R, BOUTROY S, BROWN J, CHAPURLAT R, ELDERS PJ, FUJITA Y, GLÜER C-C, GOLTZMAN D, IKI M, KARLSSON M, KINDMARK A, KOTOWICZ M, KURUMATANI N, KWOK T, LAMY O, LEUNG J, LIPPUNER K, LJUNGGREN Ö, LORENTZON M, MELLSTRÖM D, MERLIJN T, OEI L, OHLSSON C, PASCO JA, RIVADENEIRA F, ROSENGREN B, SORNAY-RENDU E, SZULC P, TAMAKI J, KANIS JA: A meta-analysis of trabecular bone score in fracture risk prediction and its relationship to FRAX. J Bone Mineral Res 31: 940-948, 2016. https://doi.org/10.1002/jbmr.2734

MUÑOZ-CASTAÑEDA JR, RODELO-HAAD C: Klotho/FGF23 and Wnt signaling as important players in the comorbidities associated with chronic kidney disease. Toxins 12: 185, 2020. https://doi.org/10.3390/toxins12030185

MUÑOZ-TORRES M, MANZANARES CÓRDOVA R, GARCÍA-MARTÍN A, AVILÉS-PÉREZ MD, NIETO SERRANO R, ANDÚJAR-VERA F, GARCÍA-FONTANA B: Usefulness of trabecular bone score (TBS) to identify bone fragility in patients with primary hyperparathyroidism. J Clin Densitom 22: 162-170. 2019. https://doi.org/10.1016/j.jocd.2018.06.005

NAYLOR KL, McARTHUR E, LESLIE WD, FRASER LA, JAMAL SA, CADARETTE SM, POUGET JG, LOK CE, HODSMAN AB, ADACHI JD, GARG AX: The three-year incidence of fracture in chronic kidney disease. Kidney Int 86: 810-818, 2014. https://doi.org/10.1038/ki.2013.547

NAYLOR KL, PRIOR J, GARG AX, BERGER C, LANGSETMO L, ADACHI JD, GOLTZMAN D, KOVACS CS, JOSSE RG, LESLIE WD: Trabecular bone score and incident fragility fracture risk in adults with reduced kidney function. Clin J Am Soc Nephrol 11: 2032-2040. 2016. https://doi.org/10.2215/CJN.00720116

NICKOLAS TL, McMAHON DJ, SHANE E: Relationship between moderate to severe kidney disease and hip fracture in the United States. J Am Soc Nephrol 17: 3223-3232, 2006. https://doi.org/10.1681/ASN.2005111194

PIMENTEL A, URENA-TORRES P, ZILLIKENS MC, BOVER J, COHEN-SOLAL M: Fractures in patients with CKD-diagnosis, treatment, and prevention: a review by members of the European Calcified Tissue Society and the European Renal Association of Nephrology Dialysis and Transplantation. Kidney Int 92: 1343-1355, 2017. https://doi.org/10.1016/j.kint.2017.07.021

RAMPERSAD C, WHITLOCK RH, LESLIE WD, RIGATTO C, KOMENDA P, BOHM C, HANS D, TANGRI N: Trabecular bone score in patients with chronic kidney disease. Osteoporos Int 31: 1905-1912, 2020. https://doi.org/10.1007/s00198-020-05458-1

RODELO-HAAD C, SANTAMARIA R, MUNOZ-CASTANEDA JR, PENDON-RUIZ DE MIER MV, MARTIN-MALO A, RODRIGUEZ M: FGF23, Biomarker or target? Toxins (Basel) 11: 2019. https://doi.org/10.3390/toxins11030175

RUPP T, BUTSCHEIDT S, VETTORAZZI E, OHEIM R, BARVENCIK F, AMLING M, ROLVIEN T: High FGF23 levels are associated with impaired trabecular bone microarchitecture in patients with osteoporosis. Osteoporos Int 30: 1655-1662, 2019. https://doi.org/10.1007/s00198-019-04996-7

SANDRU F, CARSOTE M, DUMITRASCU MC, ALBU SE, VALEA A: Glucocorticoids and trabecular bone score. J Med Life 13: 449-453, 2020.

WEISINGER JR, BELLORIN-FONT E: Outcomes associated with hypogonadism in women with chronic kidney disease. Adv Chronic Kidney Dis 11: 361-370. 2004. https://doi.org/10.1053/j.ackd.2004.07.009

WEST SL, LOK CE, LANGSETMO L, CHEUNG AM, SZABO E, PEARCE D, FUSARO M, WALD R, WEINSTEIN J, JAMAL SA: Bone mineral density predicts fractures in chronic kidney disease. J Bone Miner Res 30: 913-919, 2015. https://doi.org/10.1002/jbmr.2406

YAVROPOULOU MP, VAIOS V, PIKILIDOU M, CHRYSSOGONIDIS I, SACHINIDOU M, TOURNIS S, MAKRIS K, KOTSA K, DANIILIDIS M, HARITANTI A, LIAKOPOULOS V: Bone quality assessment as measured by trabecular bone score in patients with end-stage renal disease on dialysis. J Clin Densitom 20: 490-497, 2017. https://doi.org/10.1016/j.jocd.2016.11.002

YENCHEK RH, IX JH, SHLIPAK MG, BAUER DC, RIANON NJ, KRITCHEVSKY SB, HARRIS TB, NEWMAN AB, CAULEY JA, FRIED LF: Bone mineral density and fracture risk in older individuals with CKD. Clin J Am Soc Nephrol 7: 1130-1136, 2012. https://doi.org/10.2215/CJN.12871211

YOON HE, KIM Y, SHIN SJ, HONG YS, KANG KY: Factors associated with low trabecular bone scores in patients with end-stage kidney disease. J Bone Miner Metab 37: 475-483, 2019. https://doi.org/10.1007/s00774-018-0938-8

ZOU D, WU W, HE Y, MA S, GAO J: The role of klotho in chronic kidney disease. BMC Nephrol 19: 285, 2018. https://doi.org/10.1186/s12882-018-1094-z