Changes in Bone Mineral Density and Related Influencing Factors Assessed by Quantitative Computed Tomography in Maintenance Dialysis Patients

Hao Zhan[1,2], Qi-Chun Chen[1,2], Han-Qiu Wu[1,2], Tian-Tian Liu[1,2], Li-Wei Zou[1,2] and Long-Sheng Wang[1,2]

[1]*Department of Radiology, The Second Affiliated Hospital of Anhui Medical University, Hefei, China*
[2]*Medical Imaging Research Centre, Anhui Medical University, Hefei, China*

ABSTRACT

Objective: To investigate the changes in volumetric bone mineral density (vBMD) assessed by quantitative computed tomography (QCT) in chronic kidney disease (CKD) patients on maintenance dialysis.

Study Design: Descriptive study.

Place and Duration of the Study: Department of Radiology, The Second Affiliated Hospital of Anhui Medical University, Hefei, China, from March to July 2022.

Methodology: Maintenance dialysis patients were selected for this study, and parameters related to renal function and bone metabolism markers were recorded. Patients undergoing routine physical examination were age-matched with maintenance dialysis patients to serve as the control group. vBMD scans of the lumbar spine (L1-3) were obtained by QCT for all participants.

Results: Among the 141 maintenance dialysis patients, there were 67 patients with secondary hyperparathyroidism (SHPT) and 74 patients with non-secondary hyperparathyroidism (non-SHPT) with mean vBMDs of 145.99±55.13 mg/cm^3 and 129.10±44.20 mg/cm^3, respectively. The 159 individuals in the control group had mean age of 52.77±11.66 years and mean vBMD of 129.62±36.36 mg/cm^3. The vBMD of the SHPT group was greater than that of both the non-SHPT group and the control group (all $p<0.05$). For dialysis patients, vBMD was positively correlated with calcium-phosphorus product and intact parathyroid hormone (iPTH) levels ($r = 0.181$, 0.214, respectively, $p<0.05$); vBMD was inversely correlated with age ($r = -0.555$, $p<0.05$). After adjusting for the covariates, vBMD remained positively correlated with iPTH ($r = 0.184$, $p<0.05$).

Conclusion: Increased lumbar vertebral vBMD in maintenance dialysis patients may be associated with high iPTH, providing clinicians with a new understanding of the changes in bone mineral density in maintenance dialysis patients.

Key Words: *Bone mineral density, Quantitative computed tomography, Chronic kidney disease, Maintenance dialysis.*

How to cite this article: Zhan H, Chen QC, Wu HQ, Liu TT, Zou LW, Wang LS. Changes in Bone Mineral Density and Related Influencing Factors Assessed by Quantitative Computed Tomography in Maintenance Dialysis Patients. *J Coll Physicians Surg Pak* 2023; **33(10)**:1113-1117.

INTRODUCTION

Chronic kidney disease (CKD) is a global health problem with significant morbidity and mortality.[1] Based on statistics, the global prevalence of the 5 stages of CKD was estimated to be between 11.7-15.1%.[2] In 2006, the Kidney Disease Improving Global Outcomes' (KDIGO) Work Group referred to the systemic clinical manifestations of changes in the metabolism of intact parathyroid hormone (iPTH), calcium and phosphorus in patients with end-stage renal disease (ESRD) as chronic kidney disease-mineral and bone disorder (CKD-MBD).[3]

Correspondence to: Dr. Long-Sheng Wang, Department of Radiology, The Second Affiliated Hospital of Anhui Medical University, Hefei, China
E-mail: wangls1125@sina.com

Received: January 31, 2023; Revised: September 02, 2023; Accepted: September 04, 2023
DOI: https://doi.org/10.29271/jcpsp.2023.10.1113

A recent meta-analysis presented that low bone mineral density (BMD) is associated with increased mortality in CKD,[4] which accounts for CKD-MBD that accelerates not only bone diseases (such as osteoporosis and renal osteodystrophy) but also vascular calcification and cardiovascular diseases. In addition, the increasing evidence suggests that bone changes in patients with ESRD, no matter whether maintained hemodialysis or peritoneal dialysis, are strongly associated with osteoporosis and metastatic vascular or other soft tissue calcification,[5,6] highlighting the importance of BMD measurements.

It was hypothesised that because parathyroid hormone (PTH) had a major influence on bone conversion, different PTH levels may lead to different degrees of bone density changes. Therefore, this study was performed to explore changes in lumbar spine cancellous vBMD and associated influences in maintenance dialysis patients by QCT examinations, compared to controls.

METHODOLOGY

A total of 195 patients with ESRD (Stage 5) on dialysis were enrolled at the Department of Radiology, The Second Affiliated

Hospital of Anhui Medical University, Hefei, China, between March and July 2022 as the research group. The inclusion criteria was complete laboratory indicators, clinical and CT examination data, and age ≥18 years. The exclusion criteria was dialysis duration <3 months, diagnosis of malignant disease, liver function impairment, coexistent infectious or autoimmune diseases, and parathyroidectomy.

The research group was divided into those with secondary hyperparathyroidism (SHPT) and non-secondary hyperparathyroidism (non-SHPT) according to the clinical diagnosis. Another 160 individuals undergoing physical examination in the hospital were selected as the control group. The age of the individuals in the control group matched those of the patients on maintenance dialysis. In the control group, an outlier was rejected according to the criteria that the vBMD value is beyond the limit of $\bar{x} \pm 3s$. Figure 1 presents a flow chart for selection of maintenance dialysis patients for analysis.

Data on patient demographic parameters, laboratory results, comorbidities, type of dialysis and dialysis vintage were obtained from the patients' medical records. Laboratory data included serum creatinine (Scr), blood urea nitrogen (BUN), uric acid (UA), phosphorus, serum calcium, calcium-phosphorus product (Ca×P), iPTH, and alkaline phosphatase (ALP).

The original CT image of the lumbar spine was acquired by using the Siemens 64-slice CT scanner. The scanner was calibrated using a body membrane calibration model. The original lumbar spine volume data were delivered to the QCT Pro6.1 software (Mindways, USA) to assess vBMD. Measurement of the lumbar vBMD: the region of interest (ROI) was automatically outlined in the mid-plane of the L1, L2, and L3 vertebrae respectively, with appropriate manual adjustments made by a trained radiologist to avoid cortical bone surrounding the vertebral body and osteosclerotic areas. The vBMD values of the L1, L2, and L3 vertebral bodies were obtained, averaged and repeated twice, and ultimately averaged as final vBMD value. Criteria recommended by the latest Chinese expert consensus were used to classify vBMD.[7] For vBMD in spinal trabeculae, the values were thresholded at >120 mg/cm^3 as normal, 80 mg/cm^3 ≤vBMD ≤120 mg/cm^3 as osteoporotic and <80 mg/cm^3 as osteopenia.

SPSS 25.0 statistical software was used for the data analysis. Continuous variables were expressed as mean ± standard deviation (SD) and discrete variables were expressed as number (percentage). Normality between continuous variables was analysed using the Kolmogorov-Smirnov test. Independent two-sample t-test was used to compare the differences between the SHPT group and non-SHPT group in terms of clinical, demographic, and biochemical parameters. Differences in categorical information between multiple groups were assessed by Pearson's Chi-square test. One-way analysis of variance (ANOVA) was used to compare the quantitative data between the three groups if the normal distribution was met, and LSD was used for post-testing. The Kruskal–Wallis H test was used to test for differences in vBMD between the multiple groups. Spearman correlation analysis was used to evaluate the relationships between lumbar spine vBMD and other variables. The value of $p<0.05$ was considered statistically significant.

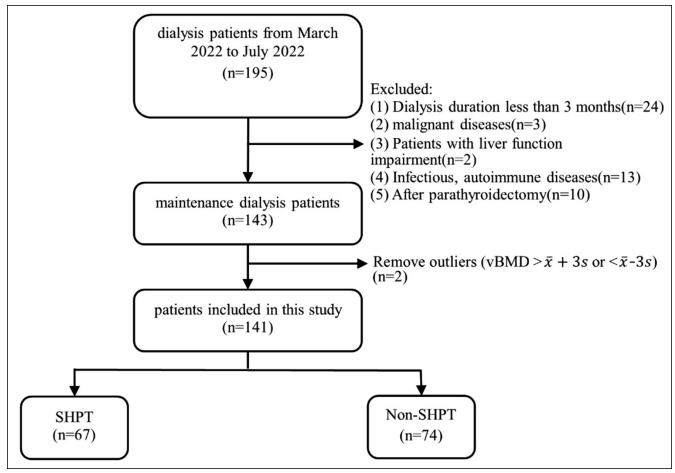

Figure 1: Flow diagram of participants throughout the study.

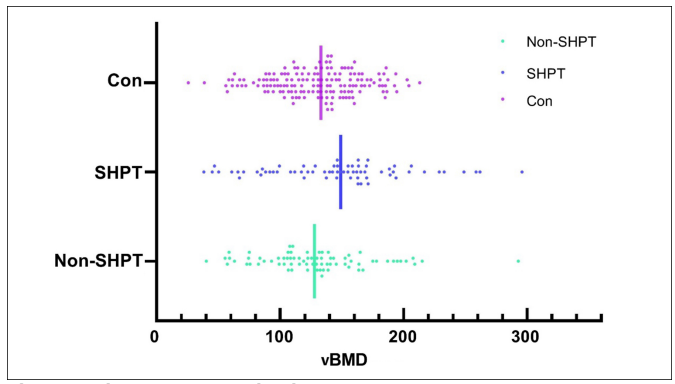

Figure 2: The BMD among the three groups.

RESULTS

There were 141 patients on maintenance dialysis in the study, including 68 males and 73 females with a mean age of 54.56 ±12.62 years. The mean dialysis vintage was 6.40±4.16 years, and chronic glomerulonephritis was the most common primary cause of maintenance dialysis (27.66%). There were 122 maintenance dialysis patients with varying degrees of abdominal aortic calcification (86.52%). The vBMD ranged from 38.3 mg/cm^3~295.9 mg/cm^3, and the mean was 137.13 (SD = 50.23) mg/cm^3. In total, the 159 patients in the control group had normal renal function (estimated glomerular filtration rate (eGFR) ≥60 mL/min^{-1} 1.73 m^{-2}), including 71 males and 88 females, with a mean age of 52.77±11.66 years and vBMD of 129.62±36.36 mg/cm^3.

According to the clinical diagnostic criteria, the patients of maintenance dialysis were classified into two groups, namely, the SHPT group (n = 67) and the non-SHPT group (n = 74). There was no statistically significant difference in the gender ratio between the two groups (p>0.05). Patients in the non-SHPT group were older than those in the SHPT group (p = 0.004).

Table I: Comparison of demographic and biochemical parameters between SHPT and non-SHPT patients.

Characteristics	All (reference value)	SHPT	Non-SHPT	p-value
No. of patients	141	67	74	
Gender (M/F)	68/73	32/35	36/38	0.916 [a]
Age (years)	54.56±12.62	51.37±11.59	57.45±12.97	0.004 [b**]
Cause of CKD				
Glomerulonephritis (%)	39(27.66)	23(34.33)	16(21.62)	0.304 [a]
Diabetes (%)	23(16.31)	9(13.43)	14(18.92)	
Hypertension (%)	24(17.02)	12(17.91)	12(16.22)	
Other (%)	19(13.48)	10(14.93)	9(12.16)	
Unknown (%)	36(25.53)	13(19.40)	23(31.08)	
Type of dialysis (HD/PD)	116/25	53/14	63/11	0.349[a]
Dialysis vintage (years)	6.40±4.16	7.40±4.34	5.50±3.79	0.006 [b**]
Hypertension [n(%)]	115(81.6)	55 (82.1%)	60(81.1%)	0.877 [a]
BUN (mmol/L)	21.50±7.05 (3.1-8.8)	21.24±7.28	21.73±6.86	0.680 [b]
Scr (μmol/L)	877.41±242.96 (41-81)	870.21±270.81	884.01±215.96	0.741 [b]
UA (μmol/L)	409.83±108.51 (155-357)	396.83±115.98	421.59±100.81	0.180 [b]
Calcium (mmol/L)	2.24±0.21 (2.11-2.52)	2.26±0.18	2.23±0.23	0.507 [b]
Phosphate (mmol/L)	1.79±0.56 (0.85-1.51)	1.82±0.61	1.75±0.51	0.472 [b]
Ca×P ($mmol^2/L^2$)	4.00±1.31	4.11±1.45	3.90±1.18	0.342 [b]
iPTH (pg/ml)	609.01±613.24 (10-69)	950.26±718.22	300.04±226.25	<0.001 [b**]
ALP (U/L)	185.73±253.11 (35-135)	278.97±343.08	101.44±36.79	<0.001 [b**]

*HD = Hemodialysis; PD = Peritoneal dialysis; BUN = Blood urea nitrogen; Scr = Serum creatinine; UA = Uric acid; Ca x P = Calcium-phosphorus product; iPTH = Intact parathyroid hormone; ALP = Alkaline phosphatase. [a]Pearson's Chi-square, [b]Independent two-sample t-test; *p <0.05, **p <0.01.*

Table II: Comparison of age, gender, and lumbar spine vBMD between SHPT and non-SHPT patients in the control group.

	SHPT (n=67)	Non-SHPT (n=74)	Control (n=159)	χ^2 / F / H	p
Gender (M/F)	32/35	36/38	71/88	0.395 [b]	0.821[*]
Age (years)	51.37±11.59	57.45±12.97 [e]	52.77±11.66	5.351 [a]	0.005
vBMD (mg/cm^3)	145.99±55.13 [d]	129.10±44.20	129.62±36.36	6.861 [c]	0.032[*]
vBMD stratification					
Normal (%)	46(68.66)	43(58.11)	94(59.12)	12.168 [c]	0.002[**]
Osteopenia (%)	13(19.40)	21(28.38)	51(32.08)	0.886 [c]	0.642
Osteoporosis (%)	8(11.94)	10(13.51)	14(8.80)	1.731 [c]	0.421

*[a]ANOVA, [b]Pearson's Chi-square, [c]Kruskal-Wallis H test; [d]p <0.05, compared with the non-SHPT group and the control group; [e]p <0.05, compared with the other two groups respectively; *p <0.05, **p <0.01.*

Table III: Correlation of lumber spine vBMD with demographic and biochemical parameters.

	Lumber spine vBMD	
	r	p-value
Age (years)	-0.555	<0.001[**]
Gender (M/F)	0.118	0.165
Type of dialysis (PD/HD)	-0.026	0.764
Dialysis vintage (years)	0.055	0.520
Scr (μmol/L)	0.133	0.116
Calcium (mmol/L)	0.111	0.196
Phosphate (mmol/L)	0.134	0.118
Ca × P ($mmol^2/L^2$)	0.181	0.035[*]
iPTH (pg/ml)	0.214	0.011[*]
ALP (U/L)	0.111	0.195

*PD = Peritoneal dialysis; HD = Hemodialysis; Scr = Serum creatinine; Ca x P = Calcium-phosphorus product, iPTH = Intact parathyroid hormone; ALP = Alkaline phosphatase. *p <0.05, **p <0.01.*

There was no significant statistical difference in the type of dialysis between the two groups, but the dialysis duration of the SHPT group was longer than that of the non-SHPT group, and the differential between the two groups was statistically significant (p = 0.006). Significantly increased ALP and iPTH levels were noted in the SHPT group as compared to the non-SHPT group (p<0.001, Table I).

The mean vBMDs of the three groups (SHPT, non-SHPT, and control group) were 146.0 mg/cm^3, 129.1 mg/cm^3 and 129.6 mg/cm^3, respectively. Figure 2 represents the median value and distribution of vBMD among the three groups. Differences in bone density were noted among the three groups. Specifically, patients in the SHPT group had greater vBMD than those in the control and non-SHPT groups, and the vBMD differences were statistically significant (p <0.05). The proportion of BMD >120 mg/cm^3 was significantly higher in the SHPT group than in the non-SHPT and control groups (Table II). vBMD was weakly and positively associated with Ca x P (r = 0.181, p = 0.035) and iPTH (r = 0.214, p = 0.011) and moderately negatively correlated with age (r = -0.555, p <0.001). The bone mass did not correlate with dialysis type, duration of dialysis, or other biochemical markers, such as Scr, calcium and ALP levels (Table III). After adjusting for the three covariates of age and calcium-phosphorus product, vBMD remained positively correlated with iPTH (r = 0.184, p = 0.034).

DISCUSSION

In this study, the vBMD of vertebral trabecular bone was quantified by QCT. It was assessed the factors that influenced

vBMD in maintenance dialysis patients. Maintenance dialysis patients had higher vBMD, especially in the SHPT group, compared with the healthy controls. According to correlation analysis, vBMD was positively correlated with iPTH, and this relationship remained stable even after an adjustment for multiple covariates. It was demonstrated that increased vBMD in maintenance dialysis patients may be associated with high iPTH levels. This result suggested that maintenance dialysis patients, especially those with hyperparathyroidism, may have their bone abnormalities incorrectly deemed normal due to a lack of upper limit of bone mass measured by vBMD.

In this study, vBMD was higher in dialysis patients with SHPT compared to the healthy controls. However, the previous studies have generally reported a high prevalence of decreased BMD and a high risk of fracture in patients with advanced CKD. Most studies have shown that abnormal bone conversion in end-stage renal disease leads to osteoporosis and osteopenia[8,9] and that lower BMD values are related to an increased risk of death in CKD patients.[4] In a study of 200 hemodialysis patients, it was found that BMD decreased with increasing age and disease duration.[10] In patients with ESRD, bone loss is accelerated. Both hip and spine bone density were lower in ESRD patients in the study.[11] Similar to this study, previous studies have suggested that patients with CKD who developed renal osteodystrophy may exhibit high BMD. Gregson *et al*. summarised the causes of high bone density measured by DXA and proposed that renal osteodystrophy may be relevant to the over-mineralisation of bone tissue areas measured in the rib, pelvic, and spinal.[12] It has been reported that patients with CKD can exhibit osteosclerosis on imaging, such as the Rugger-jersey spine, which can show high bone density measured on QCT due to its inhomogeneous bone distribution.[13] Malluche *et al*. studied bone biopsies from 630 patients with hemodialysis, of which, 3% had mineralisation defects and potentially exhibited increased cancellous bone mass.[14]

A correlation study of lumbar spine BMD, revealed that lumbar spine BMD was positively correlated with PTH, suggesting that increased BMD in maintenance dialysis patients may be associated with SHPT. SHPT is a common complication in patients with CKD. Changes in calcium, phosphorus and PTH metabolism in individuals with end-stage renal disease can cause a range of comprehensive clinical symptoms of CKD-MBD. PTH is a major initiator of bone remodelling. PTH is anabolic in bone trabeculae and catabolic in cortical bone, producing a complex bone profile. High PTH levels in dialysis patients have more complex cancellous bone surfaces. In addition, patients with SHPT can exhibit a high bone conversion rate. Specifically, both osteoblasts and osteoclasts are reactive, and bone-like hyperplasia is noted when osteoblasts are overproduced, which can appear as osteosclerosis on imaging.[15] The SHPT model of chronic renal failure was constructed using adenine-fed rats, and pathological and histological analysis of rat bones revealed increased bone-like tissues in the bone cortex and increased bone resorption cavities with osteoclasts, osteoblasts and fibrosis. Increased bone-like trabeculae were observed in the distal femoral epiphysis. In addition, osteogenic changes were observed in haematoxylin-eosin staining of decalcified sections of bone trabeculae.[16] The mechanism by which parathyroid hormone induces bone formation is partly due to its capacity to downregulate SOST/sclerostin expression in osteoblasts and activate the anabolic Wnt signalling pathway.[17] In addition, reduced renal 1a-hydroxylase and reduced 1,25(OH)2D3 may lead to reduced trabecular bone resorption, increased bone volume, massive increase in bone-like tissue, and increased fibrosis.[18,19] Researchers have found that parathyroid function does affect the morphological properties of cancellous bone and that high parathyroid hormone levels appear to be associated with more cancellous bone branching. However, the effects of parathyroid hormone are not sufficient to alter cancellous bone junctions and bone mechanical strength does not increase.[20]

However, there are certain limitations to this study. The main limitation is the single-centre, cross-sectional design. In addition, this study measured BMD at only one site, that is, the lumbar spine, and the measurements obtained at this site are not representative of changes in whole-body BMD. Because these patients were not followed up, it is unknown whether secondary hyperparathyroidism patients with increased bone mineral density will subsequently become osteoporotic at one stage or not.

CONCLUSION

The bone mineral metabolism is altered in maintenance dialysis sufferers with end-stage renal disease. Increased BMD is closely linked to SHPT. Clinicians need to pay particular attention to CKD patients with SHPT, as normal bone density measured by QCT may mask underlying bone lesions. Thus, regular BMD measurements are necessary to monitor bone changes to improve the quality of life and survival of dialysis patients.

ETHICAL APPROVAL:

This study was approved by the ethics committee of the Second Affiliated Hospital of Anhui Medical University (Ethical Approval No.YX2022-172).

PATIENTS' CONSENT:

The requirement for patients' informed consent was waived owing to the retrospective nature of the study. All data were anonymised before analysis.

COMPETING INTEREST:

The authors declared no potential conflict of interest with respect to the research, authorship, or publication of this article.

AUTHORS' CONTRIBUTION:

HZ: Methodology, conceptualisation, data curation, formal analysis, writing of original draft.
QC: Supervision and development of resources.
HW: Supervision, investigation, data curation and conceptualisation.
TL: Data curation and formal analysis.
LZ, LW: Critically revised the manuscript.
All authors approved the final version of the manuscript to be published.

REFERENCES

1. Webster AC, Nagler EV, Morton RL, Masson P. Chronic kidney disease. *Lancet* 2017; **389(10075)**:1238-52. doi: 10.1016/S0140-6736(16)32064-5.
2. Hill NR, Fatoba ST, Oke JL, Hirst JA, O Callaghan CA, Lasserson DS, *et al*. Global prevalence of chronic kidney disease – A systematic review and meta-analysis. *PLoS One* 2016; **11(7)**:e158765. doi: 10.1371/journal.pone.0158765.
3. Moe S, Drueke T, Cunningham J, Goodman W, Martin K, Olgaard K, *et al*. Definition, evaluation, and classification of renal osteodystrophy: A position statement from kidney disease: Improving global outcomes (KDIGO). *Kidney Int* 2006; **69(11)**:1945-53. doi: 10.1038/sj.ki.5000414.
4. Jiang C, Yan C, Duan J. Bone mineral density is inversely associated with mortality in chronic kidney disease patients: A meta-analysis. *J Bone Mineral Res* 2022; **37 (11)**:2094-102. doi: 10.1002/jbmr.4681.
5. Chen TY, Yang J, Zuo L, Wang L, Wang LF. Relationship of abdominal aortic calcification with lumbar vertebral volumetric bone mineral density assessed by quantitative computed tomography in maintenance hemodialysis patients. *Arch Osteoporos* 2022; **17(1)**: 24. doi: 10.1007/s11657-022-01059-z.
6. Salam S, Gallagher O, Gossiel F, Paggiosi M, Eastell R, Khwaja A. Vascular calcification relationship to vascular biomarkers and bone metabolism in advanced chronic kidney disease. *Bone* 2021; **143**: 115699. doi: 10.1016/j.bone.2020.115699.
7. Cheng X, Yuan H, Cheng J, Weng X, Xu H, Gao J, *et al*. Chinese expert consensus on the diagnosis of osteoporosis by imaging and bone mineral density. *Quant Imag Med Surg* 2020; **10(10)**: 2066-77. doi: 10.21037/qims-2020-16.
8. Huang GS, Chu TS, Lou MF, Hwang SL, Yang RS. Factors associated with low bone mass in the hemodialysis patients: A cross-sectional correlation study. *BMC Musculoskelet Disord* 2009; **10**: 60. doi: 10.1186/1471-2474-10-60.
9. Kocak SY, Ozdemir A. Comparison of bone mineral density and biochemical factors in hemodialysis and peritoneal dialysis patients. *Clin Nephrol* 2022; **98(3)**: 115-22. doi: 10.5414/CN110729.
10. Amirkhanlou S, Roshandel G, Aghaei M, Mohebi H, Tabatabei SS, Momen S, *et al*. Assessment of bone mineral density in patients undergoing hemodialysis; An iranian population-based study. *Arch Iran Med* 2021; **24(8)**: 599-606. doi: 10.34172/aim.2021.85.
11. Nazzal Z, Khader S, Zawyani H, Abdallah M, Sawalmeh O, Hamdan Z. Bone mineral density in Palestinian patients with end-stage renal disease and the related clinical and biochemical factors: Cross-sectional study. *PLoS One* 2020; **15(11)**:e241201. doi: 10.1371/journal.pone.0241201.
12. Gregson CL, Hardcastle SA, Cooper C, Tobias JH. Friend or foe: High bone mineral density on routine bone density scanning, a review of causes and management. *Rheumatol* 2013; **52(6)**: 968-85. doi: 10.1093/rheumatology/ket007.
13. Ito M, Hayashi K, Ito M. Vertebral density distribution pattern: CT classification of patients undergoing maintenance hemodialysis. *Radiol* 1991; **180(1)**:253-7. doi: 10.1148/radiology.180.1.2052705.
14. Malluche HH, Mawad HW, Monier-Faugere MC. Renal osteodystrophy in the first decade of the new millennium: analysis of 630 bone biopsies in black and white patients. *J Bone Miner Res* 2011; **26(6)**: 1368-76. doi: 10.1002/jbmr.309.
15. Jevtic V. Imaging of renal osteodystrophy. *European J Radiol* 2003; **46(2)**:85-95. doi: 10.1016/S0720-048X(03)00072-X.
16. Tamagaki K, Yuan Q, Ohkawa H, Imazeki I, Moriguchi Y, Imai N, *et al*. Severe hyperparathyroidism with bone abnormalities and metastatic calcification in rats with adenine-induced uraemia. *Nephrology Dialysis Transplantation* 2006; **21(3)**: 651-9. doi: 10.1093/ndt/gfi273.
17. Silva BC, Bilezikian JP. Parathyroid hormone: Anabolic and catabolic actions on the skeleton. *Curr Opin Pharmacol* 2015; **22**:41-50. doi: 10.1016/j.coph.2015.03.005.
18. Fukushima M, Niki R, Ohkawa H, Shimizu T, Matsunaga I, Nakano H, *et al*. Comparative therapeutic effects of vitamin D3 and its derivatives on experimental renal osteodystrophy. *Endocrinol* 1980; **107(1)**:328-33. doi: 10.1210/endo-107-1-328.
19. Miller WL, Portale AA. Vitamin D 1 alpha-hydroxylase. *Trends Endocrinol Metab* 2000; **11(8)**:315-9. doi: 10.1016/s1043-2760(00)00287-3.
20. Kazama JJ, Wakasugi M. Parathyroid hormone and bone in dialysis patients. *Therapeutic Apheresis Dialysis* 2018; **22(3)**:229-35. doi: 10.1111/1744-9987.12678.