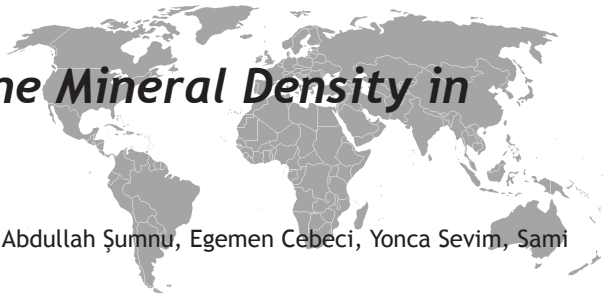
The Factors Effective on Bone Mineral Density in Peritoneal Dialysis Patients



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ABSTRACT

Bone mineral metabolism deteriorates gradually beginning from the early stages of chronic kidney disease (CKD). But, the KDIGO-2009 guideline could not provide high quality data regarding the biochemical tests related with bone mineral disorder in CKD. The aim of our study was to analyse the relationship between bone mineral densitometry and clinical and biochemical parameters in chronic peritoneal dialysis (PD) patients. Besides the demographic parameters, routine hematological and biochemical analysis results of PD patients followed up in our clinic were recorded. Bone mineral density (BMD) was measured at lumbar vertebrae and femur neck using DEXA machine. The mean lumbar T- and femur T-score were -1.03±1.20 (minimum:-3.73; maximum:+1.75) and -2.49±1.20 (minimum:-4.63; maximum:-0.51), respectively. Lumbar T score was significantly higher than femur T score (p<0.0001). Eight patients had BMD within normal limits; there was osteopenia in 16 and osteoporosis in 29 patients. While there was a negative correlation between femur T-score and age (r=-0.36, p=0.026), no correlation was detected between lumbar T-score and age (r=-0.17, p=0.21). With multivariate analysis of the factors related with femur T-score; age and body mass index (BMI) were the independent determinants while gender, parathyroid hormone levels and use of active vitamin D were not effective. Age was related negatively while BMI was related positively with BMD: BMD measurement at femur is more accurate than that at lumbar vertebrae in PD patients. BMD is low in most of the PD patients; and age and BMI are the major determinative factors.

Key words: *Bone mineral density, peritoneal dialysis, osteoporosis*

Periton Diyaliz Hastalarında Kemik Dansitesini Etkiliyen Faktörler

ÖZET

Kronik böbrek yetersizliği (KBY)'nin erken evrelerinden başlayarak kemik-mineral metabolizması giderek bozulur. Ancak KDIGO-2009 kılavuzunda KBY'de kemik mineral bozukluğu ile ilişkili verilerin çoğunluğunun kanıt düzeyi düşük olduğu ifade edilmiştir. Bu çalışmada, kronik periton diyalizi (PD) hastalarımızın kemik mineral dansitesi (KMD) ölçümleri ile klinik ve biyokimyasal parametreleri arasındaki ilişkiyi araştırdık. Hastanemizin PD ünitesinden takipli 53 hastanın demografik verileri yanında rutin hematolojik ve biyokimyasal tetkikleri kaydedildi. Hastalarda lomber vertebra ve femur boynundan DEXA cihazıyla kemik mineral dansitesi (KMD) ölçümü yapıldı. Hastaların lomber-T skoru -1.03±1.20[(-3.73)-(+1.75)] bulunur iken femur-T skoru -2.49±1.20[(-4.63)-(0.51)] olarak saptandı. Lomber T skoru, femur T skorundan anlamlı olarak daha yüksekti (p<0.0001). Sekiz hastanın KMD değeri normalken 16'sında osteopenia, 29'unda osteoporoz saptandı. Femur-T skor ile yaş arasında negatif korelasyon saptanırken(r=-0.36, p=0.026), lomber-T skoruyla yaş arasında korelasyon saptanmadı(r=-0.17, p=0.21). Femur-T skoruyla ilişkili parametrelerin çok değişkenli analizi yapıldığında; yaş ve VKİ, femur-T skorunun bağımsız belirleyicileri olduğu, cinsiyet, PTH düzeyi ve aktif D vitamin kullanımının anlamlı olarak etkilemediği saptandı. Yaş negatif, VKİ ise pozitif yönde etkiliydi. PD hastalarında femur boynundan yapılan KMD ölçümleri lomber vertebradan yapılan ölçümlere göre daha anlamlıdır. PD hastalarının çoğunda KMD düşüklüğü mevcuttur ve özellikle yaş ve VKİ majör etkili faktörlerdir.

Anahtar kelimeler: *Kemik mineral yoğunluğu, periton diyalizi, osteoporoz*

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INTRODUCTION

Chronic kidney disease (CKD) is an important health problem for both the patients and the general population due to its high morbidity and mortality. The early and proper diagnosis of pathologies is important in those patients. These pathologies increase significantly when dialysis initiated. As it is well known; defects in bone structure and mineral metabolism occur in CKD beginning from the early stages. Measurement of bone mineral density (BMD) is a reliable predictor of future fracture in postmenopausal and senile osteoporosis in the general population. The decrease in bone mass results in increased friability. It is not possible to consider patients with stage 5 CKD similar to the general population. Since osteoporosis is only a part of a very complex metabolic bone disorders including secondary hyperparathyroidism, osteomalacia and adynamic bone disease.

According to KDIGO 2009 guidelines; routine measurement of BMD in patients with stage 3-5 CKD is not recommended; because it is not useful in determining fracture risk and identifying the type of bone mineral disorder. But the grade and quality of the recommendations are not strong enough (1). All of the studies leading to this comment are cross sectional with varying and indefinite results. Similarly, the biochemical tests for diagnosis of CKD related bone mineral disease are also not strong. Our aim was to study the relationship of BMD findings with clinical and biochemical parameters among peritoneal dialysis (PD) patients followed up in our unit.

MATERIAL AND METHODS

Chronic PD patients who gave informed consent and who did not have exclusion criteria among 69 patients followed up in our PD unit were included into this cross sectional study. Patients aged less than 18 and more than 80 years, those with dialysis duration less than three months and patients with malignancy were excluded. The demographic data including age, gender, weight, height, body mass index (BMI) were recorded as well as primary kidney disease, duration of CKD and dialysis, the modality of PD treatment, the drugs used (angiotensin converting enzyme inhibitors-ACEi-, angiotensin receptor blockers-ARB-, other antihypertensive drugs, statins, active vitamin D) were recorded.

Comorbidities

Hypertension, hyperlipidemia, diabetes mellitus and ischemic heart disease were recorded as comorbidities. Hypertension was accepted to be present in the presence of history of hypertension; or measurement of blood pressure more than 140/90 mmHg at two separate times. Diabetes mellitus was diagnosed in in the presence of fasting blood glucose level above 126 mg/dl; or blood glucose level above 200 mg/dl at any time or at the second hour of oral glucose tolerance test; and was recorded if the patient had history of diabetes mellitus. The diagnosis of hyperlipidemia was put according to the criteria of National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) III; age and the other risk factors of the patients. Ischemic heart disease was diagnosed if the patient had history of acute coronary syndrome, coronary artery by-pass surgery or coronary interventions; typical symptoms of coronary artery disease (angina pectoris, angina equivalent), and positive findings on electrocardiography, echocardiography, stress tests or coronary angiography.

Laboratory

Serum glucose, urea, creatinin, uric acid, cholesterol, triglyceride, sodium, potassium, calcium, phosphorus, parathyroid hormone (PTH), total protein, albumin, aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), leukocyte count, hemoglobin, hematocrit, ferritin, high sensitive C-reactive protein (hsCRP) levels were studied with samples obtained after 12 hours of fasting. Serum glucose, urea, creatinin, uric acid, lipid parameters, sodium, potassium, calcium, phosphorus, total protein, albumin, AST, ALT and ALP levels were studied by appropriate methods using Siemens Advia 2400 auto analyzer. Hematological parameters were studied from samples kept in tubes with ethylene diamine tetra acetic acid (EDTA) using ABX Pentra DX120 machine. PTH and ferritin levels were studied by immunoassay method using Siemens Advia Centaur® XP machine. hsCRP levels were studied using Siemens Advia 2400® machine by turbidometric method.

Measurement of BMD

The measurement was performed at L2-L4 anteroposterior lumbar vertebrae and femoral neck using Norland Cooper Surgical Inc.-USA dual-energy X-ray absorptiometry (DEXA) machine. Results were expressed as T scores. Patients were divided into three groups de-

scribed by World Health Organization according to the T scores measured (2): Normal (Femur T score>-1); osteopenia (-2.5<T score<-1) and osteoporosis (T score<-2.5).

Statistical Analysis

The statistical analysis was carried out with Statistical Package for Social Sciences for Windows ver. 15.0. All numerical variables were given as mean ± standard deviation. Two groups were compared with paired Student's t-test or Mann Whitney U tests when necessary. Chi-square test with Yates correction and Fisher's exact test were used for 2X2 contingency tables when appropriate for non-numerical data. Correlations between T scores and other numerical parameters were analyzed with Spearman's rho correlation test. Groups were compared with Student's t-test. Comparisons in the BMD groups and PTH groups were made by Kruskal Wallis-H analysis of variance because the distribution was abnormal. P values less than 0.05 were accepted as significant. Multivariate analyses of the parameters related to femur T score was carried out with linear regression model with "enter" method.

***Table 1**. The demographic and clinical data of the patients.*

	Mean	*Std. Dev.*	*Minimum*	*Maximum*
Demographic data				
Age	*52.7*	*15.2*	*24.0*	*75.0*
Gender (female/male)	*30/23*			
Duration of CKD (years)	*7.2*	*4.6*	*1.0*	*26.0*
PD duration (months)	*41.7*	*24.8*	*4.0*	*96.0*
Weight (kg)	*71.2*	*16.4*	*42.2*	*107.5*
BMI (kg/m2)	*27.6*	*6.5*	*15.9*	*43.6*
Height (cm)	*161.0*	*11.3*	*142.0*	*190.0*
BSA (m2)	*1.74*	*0.21*	*1.28*	*2.24*
Systolic BP (mmHg)	*128*	*21*	*90*	*180*
Diastolic BP (mmHg)	*80*	*10*	*60*	*100*
Mean BP (mmHg)	*96*	*13*	*70*	*126*
PD modality n, (%)				
CAPD		*33 (62.3)*		
APD		*10 (18.9)*		
CCPD		*7 (13.2)*		
Hybrid regime		*3 (5.7)*		
Primary kidney disease n. %				
Hypertensive nephrosclerosis		*8 (15.1)*		
Diabetic nephropathy		*14 (26.4)*		
Glomerulonephritis			*6 (11.3)*	
ADPKD		*3 (5.7)*		
Chronic pyelonephritis		*5 (9.4)*		
VUR nephropathy		*3 (5.7)*		
Unknown		*14 (26.4)*		
Drugs n. %				
ACE inhibitors		*8 (15.1)*		
ARB		*6 (11.3)*		
Acetylsalicylic acid		*12 (22.6)*		
Statin		*13 (24)*		
Beta blockers		*20 (37.7)*		
Active vitamin D		*19 (35.8)*		
Erythropoiesis stimulating agents		*14 (26.4)*		
Comorbidities n. %				
No		*12 (22.6)*		
Hypertension		*41 (77)*		
Ischemic heart disease		*9 (17)*		
Diabetes mellitus		*15 (28.3)*		
Hyperlipidemia		*21 (39)*		
Heart failure		*4 (7.5)*		

CKD: Chronic kidney disease; PD: Peritoneal dialysis; BMI: Body mass index; BSA: Body surface area; BP: Blood pressure; CAPD: Continuous ambulatory peritoneal dialysis; APD: Automated peritoneal dialysis; CCPD: Chronic cyclic peritoneal dialysis; ADPKD: Autosomal dominant polycystic kidney disease; VUR: Vesicoureteral reflux; ACE: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker.

***Table 2**. Biochemical data and BMD values.*

	Mean	Std. Dev.	Minimum	Maximum
Biochemical data				
Glucose (mg/dl)	*136*	*81*	*72*	*479*
Urea (mg/dl)	*100*	*35*	*11*	*211*
Creatinine (mg/dl)	*8*	*2.8*	*4*	*16.3*
Uric acid (mg/dl)	*6.0*	*1.0*	*4.0*	*8.8*
Sodium (mEq/L)	*138.0*	*3.7*	*128.0*	*148.0*
Potassium (mEq/L)	*4.1*	*.6*	*3.0*	*6.0*
Calcium (mg/dl)	*9.0*	*.6*	*7.9*	*10.3*
Phosphorus (mg/dl)	*5.0*	*1.2*	*2.9*	*8.6*
CaxP (mg2/dl2)	*45.7*	*12.2*	*24.0*	*77.0*
PTH (pg/mL)	*560*	*429*	*80*	*1900*
AST (U/L)	*17*	*7*	*6*	*450*
ALT (U/L)	*17*	*10*	*5*	*68*
ALP (U/L)	*135*	*193*	*45*	*1428*
GGT (U/L)	*29*	*50*	*8*	*353*
LDH (U/L)	*197*	*52*	*95*	*367*
Total protein (g/dl)	*6.5*	*.7*	*5.0*	*8.5*
Albumin (g/dl)	*3.7*	*0.3*	*2.7*	*4.5*
hsCRP (mg/dl)	*2.06*	*4.28*	*.01*	*26.01*
Iron (µg/dl)	*66*	*22*	*16*	*158*
Total iron binding capacity (µg/dl)	*247*	*33*	*195*	*338*
Transferrin saturation (%)	*26.9*	*9.9*	*6.2*	*61.0*
Ferritin (ng/mL)	*387.6*	*321.8*	*24.9*	*1650.0*
Hematocrit (%)	*32.6*	*4.0*	*21.4*	*42.7*
Leukocyte (/µL)	*8339*	*2663*	*3500*	*16800*
Hemoglobin (g/dl)	*10.7*	*1.3*	*6.9*	*14.3*
Thrombocyte (x1000/ µL)	*275.4*	*99.1*	*40.0*	*567.0*
MCV (fl)	*91.9*	*4.8*	*82.1*	*107.0*
Total cholesterol (mg/dl)	*188*	*44*	*113*	*338*
HDL cholesterol (mg/dl)	*42*	*16*	*20*	*90*
LDL cholesterol (mg/dl)	*112*	*34*	*58*	*235*
VLDL cholesterol (mg/dl)	*33*	*16*	*12*	*79*
Triglyceride (mg/dl)	*172*	*94*	*35*	*475*
Residual urine volume (ml/day)	*819*	*790*	*0*	*2600*
BMD (T score)				
Lumbar vertebrae	*-1.03*	*1.20*	*-3.73*	*1.75*
Femoral neck	*-2.49*	*1.20*	*-4.63*	*0.51*

RESULTS

Fifty three patients (female/male: 30/23) were included in the study. The mean age in female and male patients was 50±15 years and 56±16 years, respectively. The demographic data and the basal laboratory findings are presented in Table-1 and Table-2. Lumbar and femur T scores were -1.03±1.20 (minimum:-3.73-maximum:+1.75) and -2.49±1.20 (minimum:-4.63-maximum:0.51), respectively. Lumbar T score was significantly higher than the femur T score ($p<0.0001$); and they were correlated with each other ($r=0.410$, $p=0.002$). Femur T score was negatively correlated significantly with age ($r= -0.36$, $p= 0.026$); while lumbar T score was not ($r= -0.17$, $p=0.21$) (Figure 1). There was no correlation of either lumbar or femur T scores with duration of CKD and PD treatment, weight, BMI, serum albumin, calcium, phosphorus, PTH, ALP and hemoglobin levels.

Eight patients had normal BMD values; while 16 had osteopenia and 29 had osteoporosis. The age, PD duration, treatment modality, peritoneal Kt/V, creatinine clear-

***Table 4**. The relationship between gender and BMD.*

		Mean	Std. deviation	p
Femur Neck	*Male*	*-2.97*	*0.91*	*0.01*
	Female	*-2.12*	*1.27*	
Lumbar vertebrae	*Male*	*-1.00*	*1.19*	*0.88*
	Female	*-1.05*	*1.23*	

Table 3. *The relationship between gender and BMD.*

	Female	Male	Total
	n, %	n, %	n, %
Normal	8 (27)	0(0)	8(15)
Osteopenia	10(33)	6(26)	16(30)
Osteoporosis	12(40)	17(74)	29(55)
Total	30	23	53

Table 5. *Multivariate analysis results of factors affecting on T cores measure at femoral neck.*

	B	Std. Error	Beta	P
Constant	-2.654	0.946	0.007	
Gender	-0.535	0.329	-0.223	0.110
Age	-0.026	0.011	-0.329	0.019
BMI	0.062	0.027	0.335	0.027
PTH	0.000	0.000	0.068	0.642
Active vitamin D	-0.135	0.329	-0.054	0.684

ance, calcium, phosphorus, ALP and PTH levels were similar in patients with normal BMD, osteopenia and osteoporosis. Patients with normal BMD were all female (p=0.011); and the groups with osteopenia and osteoporosis were similar regarding gender (p= 0.17) (Table 3). Femoral T scores were significantly higher in women (Table 4, Figure 2).

There was no correlation of BMD with the presence of DM, hypertension, hyperlipidemia and ischemic heart disease. Patients grouped according to their PTH levels as low (<150pg/ml, n: 6), normal (150-300pg/ml, n: 6) and high (>300pg/ml, n: 41) had similar lumbar (p=0.18) and femur (p=0.37) T scores. With multivariate analysis conducted with parameters related with femur T score; age and BMI were found to be the independent variables determining femur T score, while gender, PTH level and active vitamin D treatment did not affect T score (Table 5). BMD was negatively correlated with age and positively with BMI.

DISCUSSION

We detected in our study a statistically significant difference between lumbar and femur T scores in our patients (p<0.001). BMD measured by DEXA at lumbar vertebrae may be overestimating in both uremic and nonuremic population. This is thought to be due to the presence of osteophytes, aortic calcification and scoliosis (3,4). T scores at the femoral neck have been measured as lower than in the lumbar vertebrae in other studies also (5-9). Arici et al (10) and Pongchaiyakul et al (11) found difference between T scores measured at hip in uremic patients compared with the control group; while corresponding measurements at spine were similar.

When T score at femur was considered; eight of the patients (15%) had normal T scores while 16 cases (30%) had osteopenia and the remainder 29 patients (55%) had osteoporosis. Patients with normal BMD, osteopenia and osteoporosis had similar age, PD duration, treatment modality, peritoneal Kt/V, creatinin clearance, calcium,

Figure 1. *The relationship between femur T score and age*

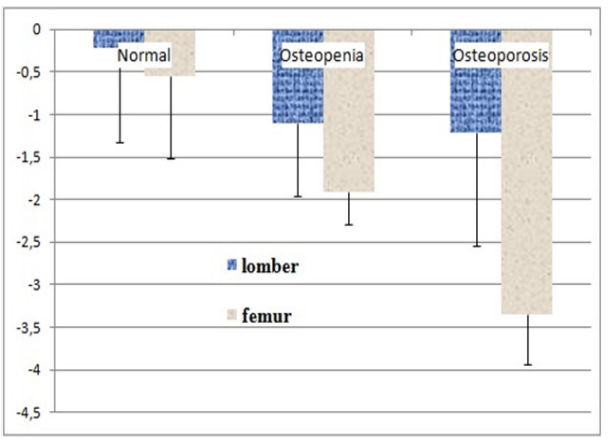

Figure 2. *The femur and lumbar T scores according to the BMD groups*

Table 6. *Osteopenia and osteoporosis prevalances in dialysis patients*

	Dialysis type	Patient number	Age	Dialysis duration (month)	Osteopenia (%)	Osteoporosis (%)	BMI (kg/m2)	PTH (pg/ml)
Ersoy et al.(9)	PD	292	56±16	37.2±25.2	30	26	25.2±4.6	255.6±348.2
Negri et al. (5)	PD	65	E: 53.2±13.1 K: 48.3±13.1	40.3±23.2	56.9	21.5	NA	NA
Baszko-Blaszyk et al. (12)	PD	37	E: 51.7±15.8 K: 41.8±14.1	<12	40.5	21.6	NA	214.4±306.6
Taal et al.(7)	HD	88	58.2±17.3	41.5	48.9	19.3	23.9±4.4	238.8±222.1
Urena et al.(13)	HD	70	60.5±14.3	76.8±81.6	43	47	23.0±4.4	298.0±301.0
Our study	PD	53	52.7±15.2	41.7±24.8	30	55	27.6±6.5	560.0±429.0

NA: Not available

phosphorus, ALP and PTH levels. Different osteopenia and osteoporosis prevalence rates have been reported in dialysis patients in the literature (Table 6). The higher osteoporosis prevalence detected in our study could not be explained by the mean age, dialysis duration or BMI; but the most striking difference was about PTH levels which was higher than the above mentioned studies (560±429 pg/ml vs. 214.4±306.6 and 298±301 pg/ml). Although PTH levels were relatively high, there was no correlation between PTH levels and T scores. Subgroups with low, normal and high PTH levels had similar T scores at femur and lumbar vertebrae. Grzegorzewska et al (14) reported that elevated PTH level is important in prediction of BMD with the lowest values seen in patients with the highest PTH levels. But there are studies showing no relation (9,19,20) or negative correlation also (7,15-18). Beyond the speculations related to the geographical or racial differances, these variations may be associated to PTH level. Because it is well known that the effects of PTH on bone structure and turnover are long term effects. So it is difficult to make connection between PTH level and BMD in a cross sectional study. Moreover, PTH levels change continuously due to many factors including dialysis dose, medications, measurement methods, etc. Supporting this idea, PTH levels reported in the above mentioned studies have high level of standard deviation.

The strong correlation between age and BMD seen in the general population may be weakened in the dialysis population due to many factors affecting on BMD other than age. We detected a statistically significant negative correlation between age and T score measured at femur (r= -0.36, p= 0.026), while age was not correlated with the corresponding measurement at lumbar vertebrae. Ersoy et al (9) reported a strong negative correlation with age; while Taal et al (7) found this relation only in females and Grzegorzewska et al (8) only with measurement at femur, similar to our study. The prevalence of osteopenia and osteoporosis were similar in male and female patients (p= 0.17); while patients with normal BMD value were all female (p=0.011). Female patients were found to have higher T scores at femur compared with male patients. But with multivariate analysis, the relation with gender disappeared, leaving age and BMI as the major determinants of T score measures at femur. This may be explained by lower mean age higher mean BMI detected in females. Ersoy et al (9) reported no correlation between gender and BMD, while Taal et al (7) detected negative correlation between female gender and BMD at hip in hemodialysis (HD) patients. Orlic et al (14) found BMD values at both femur and lumbar vertebrae lower in female HD patients. Negri et al (5) reported that the mean femur and lumbar T scores were similar in both gender in PD patients; but total bone mineral content was significantly lower in female patients. In a recent study conducted in HD patients, it was reported that the decrease in bone volumetric density detected by high resolution peripheric quantitative computerized tomography was less in males compared with females (21). Grzegorzewska et al (8) found no relation between BMD (both femur and lumbar vertebrae) and gender in patients with dialysis duration more than 20 months. We detected no correlation between BMD and weight, BMI, serum albumin levels. But with multivariate analysis; BMI together with age were the major independent variable for T core measured at femur. This finding is consistent with the literature showing positive correlation between BMD and BMI (7,9,22,23).

In conclusion, BMD measurements performed at femur are more reliable compared with measurements at lumbar vertebrae in PD patients. The majority of PD patients have low T scores; with age and BMI being the major determinants.

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