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RESEARCH ARTICLE

Factors Affecting Bone Mineral Density in Hemodialysis Patients

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Abstract

Objective: Disorders of mineral metabolism and bone density are common complications in chronic kidney disease and are an important cause of morbidity. Recently used definition is chronic kidney disease-mineral and bone disorder (CKD-MBD). The aim of our study was to evaluate the correlation between bone mineral density and influencing factors in patients with end-stage renal failure undergoing hemodialysis.

Material and Methods: In our study, cases were evaluated by being divided into 3 groups depending on bone mineral density (BMD). Our study included 124 cases and was designed as a cross-sectional observational study. The demographic data of the cases were recorded separately for each case. Routine biochemical analyses were studied.

Results: The median vit D value of the patients with osteoporosis participated in the study was 14.44 mg/dl in the osteopenic group and the median value of the patients without osteoporosis was 20.14 mg/dl. The lowest and highest vit D values of the patients with osteoporosis were 3 mg/dl and 34.77 mg/dl, respectively. There was a statistically significant difference between all 3 groups for the age variable (p=0.002). There was a statistically significant difference between all 3 groups for the BMI variable (p=0.011). For 3 groups divided according to BMD measurements, statistically significant results were found in the PTH, Ferritin, Hgb, CRP, ALP, Albumin, e-GFR, hip and lumbar BMD values, respectively (p<0.001, p=0.001, p=0.004, p=0.001, p=0.003,p=0.005, p=0.001, p<0.001, p<0.001).

Conclusion: In conclusion, our study revealed that the most important risk factor associated with osteoporosis in patients undergoing hemodialysis was PTH elevation and low vitamin D levels. For this purpose, BMD measurements and biochemical parameters of CKD patients undergoing hemodialysis should be studied in appropriate periods by adhering to the guidelines. Vit D replacement should not be neglected in order to avoid osteoporosis and to treat the detected cases.

Key words: Chronic kidney injury, hemodialysis, bone mineral density, vitamin D

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Introduction

Disorders of mineral metabolism and bone density are common complications in chronic kidney disease and are an important condition worsening the quality of life and morbidity. There is evidence that these disorders in mineral and bone metabolism are associated with increased risk for cardiovascular calcification, morbidity and mortality (Block and Cunningham 2006). The term used to define abnormalities in bone morphology developing in CKD is renal osteodystrophy (Freemont and Malluche, 2005). Recently used definition of chronic kidney disease-mineral and bone disorder (CKD-

MBD) is evaluated as a systemic disease characterized by biochemical abnormalities (calcium, phosphate, parathyroid hormone (PTH) and vitamin D), abnormalities in bone turnover and extraskeletal calcification. Secondary hyperparathyroidism is an important condition predicating biochemical abnormalities for CKD-MBD (Quarles and Berkoben, 2018). Routine measurement of serum levels of calcium, phosphate and PTH is the most practical way to monitor secondary hyperparathyroidism (Ketteler et al., 2017).

Dual-energy x-ray absorptiometry (DXA) of the spine, hip and forearm is the only technique for the diagnosis of osteoporosis in the absence of a fragility fracture and is the best technique to monitor changes in BMD over time for a number of reasons (Cosman et al.,2014). The World Health Organization (WHO) classification is still widely used to determine bone density. The WHO has defined the diagnostic thresholds for low bone mass and osteoporosis according to the T-score of BMD measurements compared to the young adult reference population (Report of WHO study Group,1994).

Since osteoporosis is an important cause of mortality and morbidity in CKD, it is important to determine the risk factors. Appropriate renal replacement therapy should be determined and osteoporosis should be avoided in patients who are at risk in this respect. These patients should also be examined and treated properly for osteoporosis. Protecting these patients from osteoporosis is very important.

The aim of our study was to evaluate the correlation between bone mineral density and influencing factors in patients with end-stage renal failure undergoing hemodialysis. In addition, it was aimed to investigate the prevalence of osteoporosis in CKD patients in our region.

Methods

Ethical approval for the study was obtained from the Clinical Research Ethics Committee of the Ordu University, Faculty of Medicine (Date:29.11.2018 Decision Number: 2018/238). Volunteer consent was obtained from all patients participated in our study.

Our study included 124 cases and was designed as a cross-sectional observational study. The demographic data of the cases (age, BMI, gender) were recorded separately for each case. Hemogram was studied with a Cell-dyn ruby device. Routine biochemical analyses (serum BUN, creatinine, albumin, potassium, calcium, CRP, iron, uric acid) were studied with a Cobas c501 module, hormones (folate, vitamin B12, vitamin D, ferritin, PTH) with a Roche-cobas e 601 device. Bone densitometry was measured with a hologic SQ-15882 device using the dual-energy x-ray absorptiometry (DXA) technique.

Body mass indexes (BMI) of all cases were calculated with the formula of BMI=weight (kg)/height $(m)^2$. The cases were divided into 3 groups according to the BMD criteria of the world health organization. T score above -1 was considered as normal, T score of (-1) to (2.5) was considered as osteopenia and T score below -2.5 was considered as osteoporosis. The healthy participants did not have any known disease and were admitted to our outpatient clinic for a check-up. There were no biochemical abnormalities in their laboratory tests and no hematuria and proteinuria in their urinalyses. The estimated glomerular rate (e-GFR) of healthy subjects was calculated using the MDRD equation. All of them had an e-GFR of >60ml/min/1.73m2. The patients receiving hemodialysis treatment were undergoing hemodialysis 3 days a week for at least 3 months.

Our exclusion criteria were as follows: patients with active infection/inflammation, patients with malignancy, peritoneal dialysis patients, pregnant women and patients who did not want to participate in the study.

Statistical Analysis:

The data were analyzed using the IBM SPSS v.23. The normality assessment of the data was analyzed by the Shapiro Wilk test. The Kruskal-Wallis test was used for the comparison of non-normally distributed data between 3 groups. Values showing normal distribution were analyzed by the one-way analysis of variance (ANOVA). The analysis results were presented as mean ± standard deviation for data showing quantitative and normal distribution, and as median (min-max) for data not showing normal distribution. The significance level was accepted as $p<0.05$.

Results

One-hundred and twenty-four patients were included in our study, 70 (56.5%) were female and 54 (43.5%) were male. Of the cases, 35 (28.22%) were normal, 51 (41.12%) were osteopenic and 38 (30.64%) were osteoporotic according to the BMD measurement results. Of the patients undergoing hemodialysis, 26 (45.6%) had osteoporosis, 21 (36.8%) had osteopenia and 10 (17.5%) had normal

BMD. The mean age of the patients was 58.84 and there was no statistically significant difference between the mean ages of the groups. For each of the 3 groups, statistically significant results were found in the PTH, Ferritin, Hgb, CRP, ALP, Albumin, e-GFR, hip and lumbar BMD values. No statistically significant results were found in the Ca, P, uric acid, folic acid and B12 values for each of the 3 groups. The descriptive statistical values of the cases are presented in Table 1.

Table 2 shows the gender distribution of all cases (HD and healthy volunteer patients).

There was no significant difference between the healthy participants and HD group in terms of gender (p=0.06)

The descriptive statistical values of the 3 groups according to the T score (normal, osteopenic and osteoporotic) are presented in Table 3.

The median vit D value of the patients with osteoporosis participated in the study was 14.44 mg/dl in the osteopenic group and the median value of the patients without osteoporosis was 20.14 mg/dl. The lowest and highest 25 OH vit D values of the patients with osteoporosis were 3 mg/dl and 34.77 mg/dl, respectively. There was a statistically significant difference between all 3 groups for the age variable (p=0.002). There was a statistically significant difference between all 3 groups for the BMI variable (p=0.011). There was a statistically significant difference between all 3 groups for the total hip BMD variable (p<0.001). Likewise, there was a statistically significant difference between all 3 groups for the total lumbar BMD variable (p<0.001). Again, there was a statistically significant difference between all 3 groups for the creatine, e-GFR, albumin, ALP variables (p values: p = 0.006, p = 0.001, p = 0.005, p = 0.003, respectively). Likewise, there was a statistically significant difference between all 3 groups for the PTH and ferritin variables (p values: p<0.001, p=0.001, respectively). Again similarly, there was a statistically significant difference between all 3 groups for the CRP, Hgb variables (p values: p=0.001, p=0.004, respectively). There was no statistically significant difference for the Ca, P and uric acid variables (p values: p=0.322,p=0.332,p=0.274, respectively).

The correlation between the BMD measurements and variables according to the Spearman's rank correlation analysis is presented in Table 4.

Table 1: The descriptive statistical values of all cases

	Mean ± std	**Min-Max**	**P value**
Total Hip BMD	0.865±0.186	0.446-1.354	p<0.001*
Total Lumbar BMD	0.975±0.175	0.383-1.406	p<0.001*
e-GFR (ml/min/1.73 $m^{2)}$	48.95±41.223	4-146	p=0.001*
Albumin (g/dl)	4.272±0.465	2.7-5.3	p=0.005*
ALP	98.78±63.11	31-442	p=0.003*
Ca	9.534±0.72	7.9-11.5	p=0.234* ^{NS}
P	3.915±1.252	0.6-10.5	p=0.332* ^{NS}
CRP	1.248±2.872	0-24.05	p=0.001*
Uric acid	5.541±1.478	1.7-10.2	p=0.274* ^{NS}
Hgb (g/dl)	12.224±1.858	7.6-19.4	p=0.004*
Folic acid	7.39±5.04	0.6-20	p=0.619* ^{NS}
B12	4.36±357.228	96.57-2000	p=0.389*^{NS}
Ferritin	5.623±602.882	6.4-2000	p=0.001*
PTH	1.489±188.83	2.85-1045	p<0.001*
Vit D	17.086±8.851	3-41.35	p=0.002*
Age	58.84±13.318	22-84	p=0.402*^{NS}
BMI	29.972±6.495	17.08-52.21	p=0.001*

(*): Kruskal-Wallis test NS: Non-Significance

Table 2: The gender distribution of the cases

Gender	**Healthy Participant**	**Hemodialysis**	**Total**
Female	43 (61.4%)	27 (38.6%)	70
Male	24 (44.4%)	30 (555.6%)	54
Total	67 (54%)	57 (46%)	124

Table 3: The descriptive statistical values of the 3 groups according to the T score

	Mean ± std	Min-Max	P value
Total Hip BMD			
Normal	1.050±0.110	0.81-1.246	p<0.001$^{\mu}$
Osteopenia	0.858±0.108	0.643-1.119	
Osteoporosis	0.699±0.138	0.446-0.999	
Total Lumbar BMD			
Normal	1.115±0.966	0.933-1.307	p<0.001 $^{\mu}$
Osteopenia	0.953±0.94	0.787-1.139	
Osteoporosis	0.811±0.158	0.383-1.134	
Ferritin			
Normal	386.307±508.398	6.4-1433	p=0.001 $^{\mu}$
Osteopenia	552.423±606.130	8.18-2000	
Osteoporosis	890.621±641.525	7.08-2000	
PTH			
Normal	99±103.747	27.28-475.4	p<0.001 $^{\mu}$
Osteopenia	143.393±195.957	2.85-961	
Osteoporosis	212.583±217.785	26.38-1045	
Vit D			
Normal	19.491±7.75	4.68-34.84	p=0.002 $^{\mu}$
Osteopenia	17.556±10.083	3-41.35	
Osteoporosis	14.316±7.278	3-34.77	
BMI			
Normal	31.023±6.410	20.35-52.21	p=0.011 $^{\mu}$
Osteopenia	30.517±6.417	20.70-45.52	
Osteoporosis	27.513±6.685	17.08-42.5	

Table 4: The correlation between the BMD measurements and variables according to the Spearman's rank correlation analysis

	r	p
Age	0.25	P=0.005*
BMI	-0.254	P=0.005*
Creatinine	0.274	P=0.002*
e-GFR	-0.33	P<0.001***
Albumin	-0.287	P=0.001**
ALP	0.295	P=0.001**
Ca	-0.134	P=0.144^{NS}
P	0.037	P=0.688^{NS}
CRP	0.318	P<0.001***
Uric acid	-0.147	P=0.108^{NS}
Hgb	-0.284	P=0.002*
Folate	-0.81	P=0.387^{NS}
B12	-0.093	P=0.318^{NS}
Ferritin	0.319	P<0.001***
PTH	0.331	P<0.001***
Vit D	-0.326	P<0.001***

(*): According to the Sperman's rank correlation analysis p<0.05
(**): According to the Sperman's rank correlation analysis p=0.001
(***): According to the Sperman's rank correlation analysis p<0.001
NS: Non-significance

When the correlation between the variables were analyzed according to the Sperman's rank correlation analysis and BMD measurement results, there were significant correlations between many parameters. There was a positive statistically significant correlation between the age and BMD results. In other words, as age increased, the risk of osteoporosis increased (r=0.25, p=0.005). As creatinine clearance decreased, the risk of osteoporosis increased (r=-0.33, p<0.001). Likewise, as the albumin value decreased, the risk of osteoporosis increased (r=-0.287, p=0.001). As the level of alkaline phosphatase increased, the rate of osteoporosis increased (r=0.295, p=0.001). There was a positive correlation between the CRP and ferritin levels and osteoporosis risk (r=0.318, p<0.001, r=0.319, p<0.001). In terms of the risk of developing osteoporosis, we found a positive correlation with PTH and a negative moderately significant correlation with vit D level (r=0.331, p<0.001, r=-0.326, p<0.001). It can be said that the strongest risk factor for the development of renal osteodystrophy was PTH elevation and decreased vit D level in our study.

Discussion

Basically, the bone cells have a less vitality in CKD patients than in normal individuals due to increased uremic toxins and insulin resistance. Uremic osteoporosis describes qualitative bone loss in normal bone structure due to uremic toxins. As renal failure progresses, metabolic acidosis and hyponatremia also cause bone loss (Posa et al., 2016). Disorders of the mineral metabolism in regard to Ca, P, Mg, PTH and vit D metabolism are common in chronic kidney disease. These abnormalities also affect the skeleton as much as other factors related to the uremic condition. Traditionally, the diseases associated with these are considered as bone lesions and the bone-related findings are defined as renal osteodystrophy. However, recent evidence suggests that mineral disorders also play an important role in the pathogenesis of non-skeletal calcifications and result in vascular calcification and cardiovascular complications and mortality. It is defined as mineral and bone disorders in chronic kidney disease (CKD-MBD: chronic kidney disease-mineral and bone disorder) to describe this broad pathological spectrum including both bone and other findings. CKD-MBD is associated with extensive biochemical and clinical disorders (Tominaga et al., 2007; Defechereux and Meurisse, 2009). Vascular calcification, bone abnormalities develop due to the effect of these. This extensive clinical syndrome leads to cardiovascular disease, fracture, decrease in quality of life and mortality, as a result of these underlying pathological developments (Aksu et al., 2005).

CKD-related bone mineral disorders are a major health problem. The prevalence of osteoporosis varies depending on CKD stages. Fractures in early-stage CKD patients (stage 1 - 3a CKD) are more similar to traditional osteoporosis. However, most patients with stage 4 or 5 CKD have a certain degree of low bone mineral density (BMD) and/or a certain level of CKD-MBD. Osteoporosis, which is one of the causes of CKD-MBD, has been found in 53% of patients with CKD (Festuccia et al., 2017). In our study, osteoporosis was found in 26 (45.6%) of the patients under hemodialysis, similar to the rates in the literature.

In the study by Onat SS et al., (2013) there was a statistically significant difference between the age groups and femur and lumbar T score, and as the age progressed, the T score worsened. In the study by Aslan A et al., (2013) a negative correlation was found between age and BMD. In the study of global osteoporotic fracture burden by Johnel and Kanis et al., (2006) it was shown that hip fracture peaked between the ages of 75 and 79 in males and females, but the highest age range was 50-59 years for all fractures, and that the rate of hip fracture decreased after the age of 80. In our study, there was a positive significant correlation between age and BMD results. As age increased, bone mineral density decreased; in other words, as age increased, the risk of osteoporosis increased. Our study is consistent with the study by Onat S and Aslan A et al. from this aspect. Our study is not consistent with the study by Johnel and Kanis et al., (2006) in terms of the risk of hip fracture due to osteoporosis after the age of 80, and we are of the opinion that this is due to the fact that only BMD measurement was made in our study, whereas the study by Johnel O et al. was at the same time about the determination of fractures.

Vitamin D is a hormone required for normal bone formation and mineralization, and plays a critical role in bone biology (Posa et al ., 2016). In secondary hyperparathyroidism, vit D also plays an important role with other changes in mineral metabolism. Vit D deficiency is common at advanced stages of CKD, and BMD is positively correlated with serum 25 (OH) D concentration (Elder et al., 2006). When Heike A et al. investigated the correlation between vitamin D and BMD in various races and age groups, they found a positive correlation between vit D and BMD in all races and age groups, especially in the white race (Bischoff-Ferrari et al., 2004). Collins et al. (1998) found a similar positive correlation between hip BMD and vit D, Fradinger and Zanchetta (2001) between femur BMD and vit D. In numerous studies, there was a positive correlation between vitamin D and BMD. In our study, we also found a significant decrease in the bone densitometers of the patients with low vitamin D levels.

In terms of impaired calcium and phosphate balance in CKD, hypersecretion of parathyroid hormone is initially beneficial for the body, but as the process progresses, elevated PTH levels lead to increased osteoclastic activity and bone resorption. Mandiroglu S et al. found a negative correlation between intact PTH (iPTH) and BMD in hemodialysis patients (Mandiroglu et al., 2013). Likewise, Hutchison et al. found that iPTH values were significantly higher in hemodialysis patients with severe osteitis fibrosa (Hutchison et al., 1993). In our study, we also found that PTH levels were

significantly higher in osteopenia and osteoporosis groups compared to the patients with normal BMD measurements. Compared with other studies, we found that PTH was high in both osteoporosis and osteoporosis group in our study. The most important factor in terms of the risk of developing osteoporosis was found to be PTH elevation and low vitamin D levels in our study. This is due to the fact that our Black Sea region is less sunny and very cloudy and rainy throughout the year.

In the study by Oh et al., (2017) it was shown that low Hb levels or anemia findings did not imply BMD loss, but patients with anemia as a phenotype of various diseases other than typical iron deficiency anemia were more likely to have BMD loss. Therefore, BMD assessment may be significant in patients with underlying disease and anemia findings. In a study by Huang et al., (2009) the factors affecting osteoporosis in patients undergoing hemodialysis were investigated. According to the results of this study, body weight, body mass index, gender and postmenopausal or amenorrheic status were found to be important for osteoporosis. However, it was found that the hemoglobin level and age were not very effective. In our study, there was a negative correlation between hemoglobin and BMD in hemodialysis patients without iron deficiency anemia but with chronic disease anemia due to CKD. Our study was consistent with the literature. Unlike the study by Huang et al. (2009) Hgb level and age were also found to be significant risk factors for osteoporosis in our study.

In the study by Edwards et al. (2008) there was a significant correlation between low albumin levels and the risk of developing osteoporosis in CKD with hip fracture developed secondary to osteoporosis. Likewise, in our study, we found a significant correlation between low albumin levels and the risk of developing osteoporosis. We are of the opinion that the nutritional limitations of hemodialysis patients lead to decreased albumin levels. Our results are consistent with the literature findings.

In a study by Huang et al. (2015) investigating the correlation between Mg level and osteoporosis in CKD patients, there was a correlation between decreased Mg levels and osteoporosis. The authors also analyzed ALP levels. They found a correlation between elevated ALP level and osteoporosis development. In our study, we also found a significant correlation between ALP elevation and osteoporosis development. In this respect, our results are similar to the study results of Huang et al (2015).

Conclusion

In conclusion, we found that in our study, low vit D levels, as well as elevated PTH levels most important risk factor contributing to osteoporosis in patients with end-stage renal failure undergoing hemodialysis. It is important to determine the risk factors since osteoporosis is an important cause of mortality and morbidity in patients with end-stage renal disease. For this purpose, BMD measurements and biochemical parameters of CKD patients undergoing hemodialysis should be studied in appropriate periods by adhering to the guidelines. Vit D replacement should not be neglected in order to avoid osteoporosis and to treat the detected cases.

Patient Approval: Ethics committee approval was received for this study from Clinical Research Ethics Committee of Ordu University Medical Faculty. (Date: 29.11.2018 Decision Number: 2018/238).

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