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Assessment of Bone Mineral Density in Patients Undergoing Hemodialysis; An Iranian Population-Based Study

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Abstract

Background: End-stage renal disease (ESRD) is a condition in which bone turnover and metabolism is impaired; thus, osteoporosis and low bone density are subsequently inevitable. We aimed to determine bone mineral density (BMD) and biochemical markers, and associated factors in hemodialysis (HD) patients.

Methods: Patients aged 30-70 years undergoing HD between 2015 to 2019 were enrolled in this cross-sectional study. BMD measured by dual energy x-ray absorptiometry (DEXA) and biochemical laboratory tests were assessed in 200 patients undergoing HD. Statistical analysis was based on t test, Pearson, regression and Mann-Whitney tests using SPSS 16.

Results: Two hundred patients were investigated. Sixty percent of the patients were female. Mean ± SD of participants' age was 58.6 (±11.63) years and mean ± SD for duration of HD was 45.69 (± 43.76) months. Osteoporosis was found in 48% (n = 96) and low bone density in 36% (n = 76) of our patients. General osteoporosis was more frequent in those undergoing HD for more than 3 years, although not significantly ($P = 0.093$, odds ratio [OR] = 0.37). However, regional osteoporosis in hip and femoral neck, but not spine vertebrae, were significantly higher after three years of HD ($P = 0.036$, OR = 0.27; $P = 0.042$, OR = 0.27; and $P = 0.344$, OR = 0.56, respectively). Increased body mass index (BMI) correlated negatively with osteoporosis ($P = 0.050$).

Conclusion: With increasing age and duration of HD, BMD decreases. Higher BMI was associated with higher bone mass density. Bone density assessment seems to be necessary in patients undergoing HD.

Keywords: Biomarkers, Bone mineral density, Osteoporosis, Renal dialysis, Risk factors

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Introduction

The prevalence of chronic kidney disease (CKD) was estimated at 13% to 16%, during the period from 1999 to 2016, while it is going to face an 11%–18% increasing rate from 2015 to 2030.[1,2]

The consequences of chronic kidney failure not only include progression toward end-stage renal disease (ESRD) but also lead to a decrease in the function of other organs of the body. ESRD patients require renal replacement therapy (RRT) such as dialysis or renal transplant. The total number of ESRD patients undergoing renal RRT was 32 686, which equals 435.8 per million population. Hemodialysis (HD) (1) serves as the most common renal replacement modality in ESRD cases in Iran (47.7%–51.2%).[3-8]

CKD patients with coexisting bone derangements and osteoporosis are becoming common.[9] Also, osteoporosis is becoming an increasing health priority in Iran; for women those aged 50 years and over, the prevalence of osteoporosis and osteopenia is 22% and 59.9%,

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respectively; for men, the rate is approximately 11% and 50.1%, respectively.[10-13]

Due to the abnormal trajectory of the bone metabolism in ESRD cases, they suffer from faster bone resorption, which leads to a high prevalence of bone disorders such as decreased bone mass and osteoporosis.[14-17]

CKD-mineral bone disorder develops in relation to secondary hyperparathyroidism owing to accumulating phosphorus (P) in the circulating plasma, resulting in a rise in bone fractures and risk of cardiovascular compromise.[9]

A broad range of pathophysiologic states could increase the fracture risk in CKD cases, including parathyroid hormone (PTH) dysregulation, adynamic bone, HD-associated amyloidosis, bone architecture changes, vitamin D deficiency, hypocalcemia, nutritional disturbance, and elevated oxidative stress.[18]

In addition, other important risk factors such as old age and senescence, menarche age, female sex, and previous history of a fracture affect bone mineral density (BMD). On the other hand, the protective factors of bone mass in this population include bone weight, hemoglobin status and history of parathyroidectomy.[19,20]

For the above-mentioned reasons, ESRD patients are prone to a higher fracture risk.[21-23] The general risk of hip fracture is 4.4 times higher in dialysis patients compared to the general population.[21] Therefore, regular periodic assessment is important in such patients. Today, the recommended method of BMD measurement is dual energy x-ray absorptiometry (DEXA) in which the scanning time is short and the amount of radiation is low. This technique is the most widely used method that can detect BMD changes and bone mineral content in different parts of the skeleton, especially in the femoral neck and lumbar spine.[21,22,24-27]

Because osteoporosis is one of the major bone health problems in chronic cases of kidney failure, the current study aimed to investigate BMD and associated factors of decreased bone mass among Iranian patients undergoing HD.

Patients and Methods

In this cross-sectional study, we recruited 230 patients aged 30–70 years who were receiving HD in 5-Azar and Sayad Shirazi academic hospitals of Golestan University of Medical sciences (Gorgan, northern Iran), from May 2015 to April 2019; 200 cases were finally included in the study. Patients suffering from rheumatoid arthritis, primary hyperparathyroidism, dementia, underlying liver disease, malignancies, kidney transplantation; history of corticosteroid use, aluminum-containing medications, anticonvulsants, aromatase inhibitors, heparin, alcohol and thyroxine were excluded from the study. Also, patients whose first-degree relatives mentioned a history of symptomatic hip, spine or distal radius fracture were excluded from our study.

All the patients were assessed for the mentioned criteria by a nephrologist. The serum level of bone-related biochemical laboratory tests including serum calcium, phosphorous, intact PTH (iPTH), and vitamin D3 levels were measured.

BMD of the femoral neck and lumbar vertebrae were evaluated using the DEXA method by Hologic© QDR 4500, and interpreted according to the guidelines presented by the World Health Organization (WHO) and International Osteoporosis Foundation (IOF).[28-30] Body mass index (BMI) was classified according to the WHO standards as normal (18.50–24.99), overweight (≥25), and obese (≥30 kg/m²).[31]

All statistical analyses were performed using SPSS 16 and reported with mean, median, and standard deviation and error (SD, SE). The Mann–Whitney U test was used to analyze quantitative variables. Chi-square, and Fisher's exact test were used to analyze differences in categorical variables between groups. Pearson correlation was used to detect factors related with bone mass loss. Equality of variance between groups was examined by Levene's test. Regression analysis was performed to evaluate the correlations between dependent and independent variables. Values had 95% confidence intervals and a P value of less than 0.05 in Pearson chi-square and independent t test was set as the threshold for statistical significance.

The patients' information was kept confidential; the study design followed the Helsinki Declaration, and approved by the local Golestan University of Medical Sciences Ethics committee.

Results

A total of 200 patients were studied. Eighty (40%) were male and 120 patients (60%) were female.

The mean (± SD) for age was 58.06 (± 11.63) years. The average time on HD was 45.69 (± 43.76) months (range 0.8 to 204). Patients older than 60 constituted 54% of the participants.

Characteristics of the patients are shown in Table 1.

Table 2 and 3 show the mean and standard deviation of serum levels of vitamin D and other biochemical parameters , and bone mass indices in the study subjects.

Table 4 shows the frequency of different bone mass states in the study participants.

Out of a total of 200 patients included in the study, 96 cases (48%) had osteoporosis and mass below the expected range for age, who were categorized in osteoporotic group. Seventy-two individuals (36%) had decreased bone mass and 32 cases (16%) had normal bone density (Table 4).

Table 5 shows the relationship between osteoporosis and age.

According to the table above, the frequency of osteoporosis was significantly higher in cases over 60 years of age (P = 0.42, under 60/over 60 OR = 0.30).

Table 5 also shows that the relationship between the risk of osteoporosis and BMI is significant (P = 0.050, normal/overweight OR = 5.55).

Table 5 shows that the frequency of osteoporosis was

significantly higher in patients under HD for more than 36 months compared to those who underwent HD for 36 months or less, but this relationship was not statistically significant ($P = 0.093$, ≤3 years />3 years OR = 0.37).

However, total hip and femoral neck osteoporosis were significantly higher in cases with more than 3 years on HD ($P = 0.036$, ≤3 years />3 years OR = 0.27 and $P = 0.042$, ≤3 years />3 years OR = 0.27, respectively). No significant association was found between osteoporosis of the vertebrae and the duration of dialysis ($P = 0.344$,

≤3 years />3 years OR = 0.56), with regional osteoporosis assessment with a 36 months cut-off.

Table 5 shows that there was no significant relationship between osteoporosis and hypertension ($P = 0.624$, hypertension/no hypertension OR = 0.73), gender ($P = 0.73$, male/ female OR = 0.82) or diabetes mellitus, ($P = 0.750$, DM/ no DM OR = 1.2).

Table 6 shows the relationship between bone mass status and vitamin D3, calcium, iPTH and phosphorous.

As shown in Table 6, the mean serum level of vitamin D3 in people with osteoporosis was significantly lower than in the non-osteoporotic individuals; however, no significant relationship was observed between serum calcium levels and bone mass status of patients although it was lower in the osteoporotic group. The table also shows no significant relationship between iPTH, and phosphorus and bone mass density.

Discussion

As shown in Table 4, out of the total 200 patients undergoing HD, 96 cases (48%) had osteoporosis and a mass index lower than the expected amount for age was defined as the osteoporotic group. Seventy-two individuals (36%) had decreased bone mass and the bone density of 32 participants (16%) was in the normal range.

A previous report by Omidvar et al[33] showed that 78.8% of participants had femoral neck osteoporosis, but 48% had general osteoporosis in our study. The reason for this difference might be due to the difference in the accuracy of the equipment.

Age and Changes in Bone Mass Status

The results, as expected, showed that the frequency of osteoporosis was significantly higher in those ≥ 60 years. Our results are in line with previous studies in which older

Table 1. Demographics of the Participants

	Number	Percentage
Gender		
Male	80	40
Female	120	60
Age (y)		
<60	88	44
≥60	112	54
Duration of dialysis*		
≤3 years	124	62
>3 years	76	38
Hypertension		
Yes	148	74
No	52	26
Diabetes mellitus		
Yes	112	56
No	88	44
BMI		
Normal	84	42
Overweight - Obese	116	58

*Follows abnormal distribution.

Table 2. Mean and Standard Deviation of Serum Levels of Vitamin D and Biochemical Parameters

	Mean ± SD	Reference Range (32)	Skewness (SE)	Quartiles (Q_1, Q_3)
Vitamin D3	16.58 ± 5.44	25–80 ng/mL	-0.10 ± 0.34	12.75, 20
Calcium	8.81 ± 0.70	9–10.5 mg/dL	-015 ± 0.34	8.30, 9.32
iPTH	470.6 ± 337.42	50–330 pg/mL	0.65 ± 0.35	1.96, 7.20
Phosphorus*	6.09 ± 5.77	2.5–4.5 mg/dL	6.49 ± 0.34	4.30, 6.02

*Non-normal distribution

Table 3. Mean and Standard Deviation of Bone Mass Indices of the Subjects

	Mean ± SD	Skewness (SE)	Quartiles (Q1, Q3)
Total hip BMD	0.72 ± 0.14	0.37 ± 0.34	0.57, 0.80
Hip T-Score	-1.98 ± 0.94	0.05 ± 0.34	-3, -1.2
Hip Z-Score	-1.20 ± 0.92	0.12 ± 0.34	-1.92, -0.40
Femoral neck T-score	-2.01 ± 0.96	0.50 ± 0.34	-2.60, -1.58
Femoral neck Z-score	-0.93 ± 0.85	0.00 ± 0.34	-1.43, -0.40
Total spines BMD	-0.85 ± 0.13	0.42 ± 0.34	0.75, 0.94
Spines T-score	-1.92 ± 1.11	0.44 ± 0.34	-2.73, -1.33
Spines Z-score	-0.90 ± 0.14	0.37 ± 0.34	-1.9, -0.20

Table 4. Bone mass density of the patients

	Number	Percent
Osteoporosis	88	44
Below the expected range for age	8	4
Low bone density	76	36
Within the expected range for age	32	16
Total	200	100

age has been shown to be a risk factor for bone mass loss, and older people have had a higher rate of bone mass loss.[34,35] It is reported that 50% of Americans older than 50 are estimated to have or be at risk of developing hip osteoporosis by 2020; even more will be at the hazard of osteoporosis at other sites of the skeleton.[36]

BMI and Bone Mass Status
In the current study, the relationship between osteoporosis and BMI was statistically significant; the higher the BMI, the lower the rate of osteoporosis. Similar results

are reported in the literature, and higher BMI positively affects bone mass density.[34,35,37] While interpreting the current study, it is also worth considering a possibility for sparse data bias[38] which can occur even in quite large datasets.

Despite much debate on the effects of increasing BMI and weight on bone mass status, no clear reason has been introduced yet.[35] The increase in bone mass, in other words, a decrease in the frequency of osteoporosis in people with high BMI and weight, could be due to the interference of adipose tissue and soft tissue with the DEXA in determining the bone mass which results in false reports. On the other hand, adipose tissue has a role in estrogen production and increasing the serum levels of other hormones including leptin, insulin, and amylin, that directly or indirectly affect the activity of osteoblasts and osteoclasts, which may lead to improved bone density.[39] It may also be due to more mechanical pressure owing to the individual's heavier weight on the body skeleton, which increases bone density.[40,41]

Table 5. Relationship Between Osteoporosis and Age

	Osteoporotic Group*		Non-Osteoporotic		P-Value	Odds Ratio Range (95% CI)
	Number	Percent	Number	Percent	By Pearson Chi-square (2-Sided)	
Age (y)						
<60	28	31.8	60	68.2	0.042	0.30 (0.093–0.98)
≥60	68	60.7	44	39.3		
BMI						
Normal	60	71.4	24	28.6	0.050	5.55(1.62–19.02)
Overweight – obese	36	31	80	69		
Dialysis duration*						
≤3 years	48	38.7	76	61.3	0.093	0.37 (0.11–1.12)
>3 years	48	63.8	46	36.8		
Hypertension						
Yes	68	45.9	80	54.1	0.624	0.73 (0.2 –2.60)
No	28	53.8	24	46.2		
Gender Male	36	45	44	55	0.730	0.82 (0.26–2.55)
Female	60	50	60	50		
Diabetes mellitus						
Yes	56	50	56	50	0.750	1.20 (0.39–3.70)
No	40	45.5	48	54.5		

*Including "Osteoporosis" and "Below the Expected range for Age."
*P value was calculated by Mann-Whitney.

Table 6. Relationship Between Bone Mass Status and Vitamin D3, Calcium, iPTH and Phosphorous

	Mean ± SD		P-Value	Mean Difference
	Osteoporotic	Non-Osteoporotic	By Independent T test (2-Tailed)	
Vitamin D3	13.29 ± 4.36	19.62 ± 4.54	<0.001	-6.32
Calcium	8.64 ± 0.50	9 ± 0.83	0.100	-0.32
iPTH	416.30 ± 244.30	522.70 ± 406	0.285	-106.42
Phosphorous*	5.49 ± 1.83	6.65 ± 7.85	0.950	-1.15

*P value was calculated by Mann-Whitney.

Duration of HD and Bone Mass Status Changes

The frequency of osteoporosis in people undergoing HD for more than 36 months (3 years) was significantly higher than those who underwent HD for 3 years of less than, but it was not statistically significant. Our results are similar to the results of previous studies, although one-year cut-offs were considered in the previous studies mentioned.[19,42,43] There are also reports indicating no correlation between HD duration and bone mass.[31] However, in regional assessment, total hip and femoral neck osteoporosis was significantly higher in people under HD for more than 3 years. No significant relationship was found between osteoporosis of the vertebrae and the duration of dialysis. On the other hand, in a study by Huang et al, the results were contrarily only significant for the vertebrae and not statistically significant for total hip and femoral neck although the relationship was noticable.[19] In the study by Omidvar et al, as in our study, the rate of osteoporosis in femoral neck was higher than that in the lumbar vertebrae.[33] However, in a study by Polymeris et al, no association was found between dialysis duration and femoral neck and lumbar vertebrae bone density.[42]

Therefore, given the contradictory results between the different studies and the significant statistical relationship observed in our results, there may be a relationship between the duration of HD and bone loss, which was not fully elucidated in our cross-sectional study, possibly due to the smaller sample size or small changes which could be traced back in the specific time periods. The results also suggest that other factors, such as the architectural pattern and turnover of bone mass in different areas of the skeleton may not be detected by BMD analyzers like DEXA.[19]

Another point to mention is that in some studies mentioned above, as well as our current study, the rate of osteoporosis in the lumbar vertebrae inpatients under HD was lower than total hip and femoral neck, which is not common in the general population in whom osteoporosis is higher in the lumbar spine.[23,44,45] This could be due to the type of bone tissue in the lumbar vertebrae which mostly consists of the trabecular type.[46] The lower density of vertebrae makes them more prone to bone loss and fractures. Osteosclerotic changes of the vertebrae and the development of Roger Jersey vertebrae in patients undergoing chronic HD could be other explanations[47]; other causes related to HD may also account for this observation. Thus, more investigations are required to clarify these differences in the general population.

Hypertension and Bone Mass Status

The results of our current study show that there was no significant relationship between osteoporosis and hypertension; osteoporosis was lower in hypertensive patients. However, there are other studies reporting that hypertension is closely related to osteoporosis and is a risk factor for it.[48]

In a previous study,[49] thiazide could improve bone mass in patients suffering from high blood pressure. Our limited sample size or the relatively low incidence of hypertensive cases in our study could account for this discrepancy. In our opinion, more attention should be paid to patients with hypertension and osteoporosis, and their antihypertensive drugs should be carefully selected. Given limited direct data on the association between hypertension and osteoporosis, in spite of the relationship between antihypertensive drugs and osteoporosis[48,50,51] further investigations need to assess hypertension and BMD changes.

Gender and Bone Mass Status

Unlike previous studies[19,48] in which osteoporosis was higher in female patients on HD, no significant relationship was detected between sex and bone mass density, possibly due to the small sample size or the proximity of the age of men and women and the menopause of the women in our study.

Diabetes Mellitus and Bone Mass Status

The results revealed no significant relationship between osteoporosis and diabetes mellitus. In a study by Lian et al,[48] the proportion of diabetes was higher in the osteoporotic cases. In another study, mean femoral and hip BMD were lower in diabetic patients on HD.[52] Previous review studies have reported that diabetes and its complications could affect bone health. Even thiazolidinediones, which are prescribed in diabetes, could reduce bone mass and raise the risk of fractures. On the other hand, some studies also reported normal or increased bone mass in patients with diabetes.[53-55]

An emerging term - diabetic paradox - has been coined; it has been shown that in those suffering from diabetes mellitus, the risk of fracture is high despite normal or even increased bone mass density. In these cases, bone remodeling biochemical markers are reduced. In non-diabetic cases, 25% of trabecular and 3% of cortical bones are annually remodeled; so, if these processes are disrupted, bone density would be normal or even high but with poor quality and higher risk of fracture.[55]

Vitamin D3 and Bone Mass Status

As expected, our results showed that the mean serum levels of vitamin D3 in people having osteoporosis were significantly lower than non-osteoporotic cases, which is in agreement with previous reports [42,56-58]

Calcium and Bone Mass Status

We found that in the osteoporotic group, serum calcium level was lower although the relationship was not statistically significant, like what Shakoor et al[58] reported. Similarly in the study by Polymeris et al,[42] a significantly decreased calcium level was detected in osteoporotic cases. Calcium supplementation could have a positive effect on improving low bone mass density. The limited sample size could probably explain why our results were

not statistically significant.

iPTH and Bone Mass Status

We did not detect a significant relationship between the level of iPTH and BMD; the genetic basis of the studied Iranian population might be an explanation. However, in previous studies,[33,42,52] an inverse relationship was detected. Other studies have also shown that the serum level of iPTH is inversely related to BMD in lumbar vertebrae and femoral neck.[19]

Phosphorus and Bone Mass Status

We found no significant relationship between serum phosphorus level and bone mass status of the patients under HD; genetic reasons might explain this observation. However, previous studies showed a significant relationship; increasing serum phosphorus level and the subsequent increase in PTH level have destructive effects on bone mass.[59,60]

Correlations (OR) analyses suggested that normal BMI, older age, longer dialysis duration, female gender, DM and low serum Vitamin D could be potentially stronger risk factors compared to the other factors studied. However logistic regression (backward) analysis revealed that age, dialysis duration and BMI remained significantly associated with bone mass status.

The current study was a cross-sectional two-center study with a relatively small sample size. Another major limitation was the unavailability of some patients' medical records, as some patients did not comply sufficiently with the study set up. The mentioned limitations prevented us from drawing firm conclusions from the current study, as measured and/or unmeasured confounders may have had a critical role. Thus, the generalizability of our results may be confined by the above-mentioned limitations. Our cross-sectional study introduced some risk factors of low bone mass density in HD patients. Prospective studies might be required to establish the effects of these factors on bone mass status.

In Conclusion, older age, low serum vitamin D and probably longer duration of HD are linked with a higher incidence of osteoporosis, while increased BMI could possibly have a positive effect on bone mass density resulting in higher BMD.

More similar and prospective studies with larger sample sizes seem to be necessary to investigate the mentioned osteoporosis-related factors, particularly the link between osteoporosis and gender, diabetes, hypertension and also HD duration in patients under HD, as the correlations were not firmly established for these factors.

Finally, we recommend at least annual assessments of BMD in patients undergoing HD.

Authors' Contributions

SA and GR did definition of intellectual content, data analysis manuscript editing and manuscript review. MA, HM, SST, SM, PZ, MA and FA did study design, data collection, manuscript editing and manuscript review. SMH proposed the study concept, design, definition of intellectual content, literature search, data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript editing and manuscript review.

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