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Assessment Of Mineral-Bone Diseases & Osteoporosis Among Hemodialysis Patients In Aswan

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ABSTRACT

Objective
Chronic kidney disease is linked to presence of mineral bone disorder (MBD), fragility fractures and osteoporosis. It results from reduced bone mineral density as well as abnormalities in bone turnover. This study aimed to assess MBD and osteoporosis among hemodialysis patients.

Methods
This study adopted a cross-sectional design. It was performed in Aswan-Egypt; from December 2022 until December 2023. The study comprised 100 patients on hemodialysis. All patients underwent general examinations and a full medical history. Investigations included complete blood count, urea, creatinine, parathyroid hormone (PTH), calcium, phosphorus, vitamin D level (vit D) , Dual-energy x-ray absorptiometry and Fracture risk score (FRAX)

Results
Mean± SD of patients' age was 49.4 ± 13.32 years. There were 36 males and 64 females, 45 of them were menopause. The incidence of osteoporosis was 66%, while the incidence of osteopenia was 72% among our patients. 19 patients had moderate fracture risk, while 6 patients had high fracture risk. Our study revealed that 18 patients had low PTH and 71 had high PTH. Also, 65 patients suffered from vit D deficiency and 14 suffered from vit D insufficiency. Finally, FRAX was significantly increased in females than males (P

=0.002), in menopause females than non-menopause females (P <0.001), in osteoporotic patients than non- osteoporotic patients (P<0.001) and in subjects with vit D deficiency than those without vit D deficiency (P =0.039).

Conclusion
The study identified a significant prevalence of vit D deficiency, osteoporosis and osteopenia among our hemodialysis patients.

Keywords: Osteoporosis, MBD, Hemodialysis, fracture risk

Key Points:

- This study was to investigate the risk factors linked to BMD and osteoporosis and to determine these factors to facilitate the timely development of appropriate treatment strategies
- In patients with CKD-MBD, the utilization of either DXA or FRAX for fracture risk assessment should be contemplated
- patients on HD experience a greater risk of osteoporosis and fractures relative to the general population, particularly in the elderly, postmenopausal women, malnourished individuals and those with vitamin D deficiency

INTRODUCTION

Bone disease is prevalent among chronic kidney disease (CKD)
patients undergoing hemodialysis (HD). It may lead to significant issues regarding bone health, particularly fragility fractures. Bone disease in HD patients arises from a reduction in bone mineral density (BMD) as well as abnormalities in bone turnover. Bone biopsy is considered the definitive method for diagnosing abnormalities in bone turnover. Nonetheless, this method is invasive and repeated evaluations of bone status are not feasible [1]

CKD–mineral bone disorder (CKD-MBD) represents a complex syndrome marked by alterations in parathyroid hormone (PTH), phosphorus (ph), vitamin D (vit D), calcium (ca) and fibroblast growth factor-23 concentrations. These alterations result in changes to systemic effects and bone morphology, leading to elevated mortality rates, mainly attributed to cardiovascular diseases. CKD-MBD may present through one or more of the following manifestations: (i) Disruptions in ph, ca, PTH or vit D metabolism
(ii) abnormalities in bone linear growth, strength, mineralization, turnover or volume (iii) vascular or other soft tissue calcification [2]

High bone turnover states are defined by elevated rates of bone formation and resorption. High PTH levels play a crucial role in the pathogenesis of these conditions, manifesting as secondary or tertiary hyperparathyroidism [3]

Low bone turnover states mainly comprise adynamic bone disease and osteomalacia. Adynamic bone disease primarily arises from suppressed PTH levels, leading to inadequate bone mineralization and decreased bone turnover [4]

Osteoporosis is defined as a skeletal condition identified by reduced density (mass/volume) of normally mineralized bone, resulting in an elevated fracture risk. Osteoporosis occurs in a significant proportion of hemodialysis patients, with prevalence rates between 23% and 41%. Osteoporosis must be considered in managing hemodialysis patients to alleviate burdens on both patients and the healthcare system [5]

According to the World Health Organization (WHO) criteria, osteoporosis is “a disease characterized by low bone mass and micro architectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk. [6]

Numerous factors have been linked to an elevated risk of osteoporosis in patients with CKD, including advanced age, low BMI, female sex, smoking, fragility fracture history, alcohol, abnormal biochemical markers (e.g., PTH, ph, ca, and vit D), glucocorticoid treatment, inflammatory cytokines status, lifestyle and sarcopenia [7]

Kidney Disease Improving Global Outcomes (KDIGO) advised against routine Dual-energy x-ray absorptiometry (DXA) measurements in CKD stages 3-5, due to the diminished

predictive value of BMD for risk of fractures. However, studies by Yenchek et al. and Iimori have established BMD as an independent risk factor for fragility fractures in elderly patients with CKD stages 3-5. Consequently, a working group has recently proposed revising the original KDIGO recommendation concerning routine DXA testing in this patient population. [8]

In patients with CKD-MBD, the use of Fracture risk score (FRAX) or DXA for screening fracture risk is advisable. Bone alkaline phosphates and intact PTH serve as markers for evaluating bone turnover. Prior to the commencement of anti-resorptive agents (Bisphosphonate, Denosumab) or anabolic agents (Teriparatide) for osteoporosis management in CKD patients, it is essential to implement lifestyle modifications such as exercise, avoidance of excessive alcohol intake and smoking cessation. Calcium and vitamin D supplementation with effective management of secondary hyperparathyroidism and hyperphosphatemia is essential [9]

Study Design, Setting, and Patients:
The current study is a cross-sectional study of 100 subjects from the dialysis unit (Aswan University Hospital-Egypt) from December 2022 to December 2023. All Patients above 18 years on regular HD were included in the study, while Bone diseases like (Paget's disease, rheumatoid arthritis osteogenesis imperfect and osteomyelitis), malignancy, pregnancy, renal transplantation and medications that affect the bone as corticosteroid, calcinurin inhibitors, methotrexate and warfarin were excluded

Data collection:
Data were collected from each eligible patient: full medical history, which includes sex, BMI, age and duration of dialysis. Investigations included complete blood count(CBC), urea, creatinine, PTH, ca, ph and vit D level, as well as assessment of nutritional state utilizing Subjective Global Assessment score (SGA).

Assessment of fracture risk

BMD Measurements
DXA scan was conducted to evaluate BMD, which was expressed in gm/cm². It was assessed at the lumbar spine, hip, femoral neck and total body. We employed WHO criteria for identifying osteoporosis. Osteopenia is defined by a T-score > −2.5 SD and
< − 1 SD. Osteoporosis is characterized by a T-score ≤ − 2.5 SD at least in one of the

following sites: total hip, femoral neck or lumbar spine.

Fracture risk assessment tool
FRAX is a computer-based algorithm designed to estimate the 10-year risk of experiencing a major fracture, which includes wrist, clinical spine, humerus or hip fractures, as well as the 10-year risk of a hip fracture specifically. If the score is below 10% there is Low Fracture Risk, if it is greater than 10% but less than 20% there is Moderate Fracture Risk and if it is greater than 20% there is High Fracture Risk. Numerous risk factors for fractures were used in FRAX, including sex, age, family history, rheumatoid arthritis, alcohol use, BMI, glucocorticoid and smoking. [10]

Study Outcomes:
The study's primary outcomes were the prevalence of fracture risk, low bone mass and bone mineral diseases among hemodialysis patients. The secondary outcomes were the association between CKD-MBD and various variables.

Statistical Analysis:

The SPSS v26 software (IBM Inc.-Armonk-NY-USA) was utilized for data analysis. Quantitative parametric data were expressed as mean and SD and analyzed utilizing an unpaired student t-test. Quantitative non-parametric data were expressed as inter quartile range (IQR) and the median, followed by analysis using the Mann Whitney- test test. Qualitative data were expressed as percentages and frequency, followed by analysis utilizing Fisher's exact or Chi-square tests when appropriate. Pearson's correlation was performed to determine the degree of correlation between two quantitative parametric variables. Spearman's correlation was conducted to determine the degree of correlation between two quantitative non-parametric variables. A two-tailed P value ≤ 0.05 was considered statistically significant.

Sample size calculation

N: Population Size (135)

Z: z-score at confidence level 95 %(1.96)

e: margin of error (0.05)

P: standard of deviation (50%)

$$\text{Sample size (n)} = \frac{\frac{Z^2 \times p\,(1-p)}{e^2}}{1 + \left(\frac{Z^2 \times p\,(1-p)}{e^2 N}\right)}$$

This means that a minimum of 100 patients are needed to have a confidence level of 95% that the real value is within ±5% of the measured value.

RESULTS

The present study comprised 100 subjects from Aswan University Hospital. The mean± SD of patients' age was 49.4 ± 13.32 years. There were 36 males and 64 females; 45 of them were in menopause and did not receive any hormonal therapy. The mean± SD of their BMI was 26.7 ± 6.55. The mean duration of dialysis was 3 – 7 years. Twenty patients were diabetic, 83 were hypertensive, 8 patients with cerebrovascular stroke, 6 patients with peripheral vascular disease and 19 patients suffered from cardiovascular disease.

Our study revealed that 18 (18%) patients had low PTH (A dynamic bone disease) and 71 (71%) had high PTH (hyperparathyroidism). Also, 65 (65%) patients suffered from vitamin D deficiency and 14 (14%) suffered from vitamin D insufficiency (**Table 1).**

Among the studied patients 66% had osteoporosis, while 72% had osteopenia. 19 (19%) patients had moderate fracture risk, while 6 (6%) patients had high fracture risk

The mean ± SD of the SGA score was 13.55 ± 3.99. Thirteen (13%) patients were well-nourished, 74 (74%) patients exhibited mild to moderate malnutrition and thirteen (13%) patients suffered from severe malnutrition.

Table1 Laboratory investigations of the studied patients

Hb (g/dL)		**9.51 ± 1.43**
WBCs (x10^9/L)		6.87 ± 2.21
Platelets (x10^9/L)		228.66 ± 74.36
Creatinine (mg/dL)		9.63 ± 2.16
Urea (mg/dL)		117.49 ± 26.13
PTH (ng/L)		556 (247 – 981.25)
PTH	**Low PTH <150** pg/ml	18 (18%)
	High PTH >300 pg/ml	71 (71%)
Ca (mg/dL)		8.68 ± 0.85
Ph (mg/dL)		5.41 ± 1.67
Vit D (ng/mL)		15 (9.8 – 24.85)
Vitamin D	**Vit D deficiency<20 ng\ml**	65 (65%)
	Vit D insufficiency<30ng\ml	14 (14%)

Hb: haemoglobin, WBCs: white blood cells, PTH: parathyroid hormone, Ca: calcium, Ph: phosphorus, Vit: vitamin

Regarding predictors of osteoporosis, age and SGA score were significantly different in patients with osteoporosis compared to those without (P = 0.020 and 0.003, respectively), whereas sex, BMI, menopause, duration of dialysis, DM, PTH and Vit D showed no significant differences between the two groups (Table 2,3).

The FRAX score was evaluated for all participants, revealing a significant elevation in females compared to males (P = 0.002), in postmenopausal females relative to premenopausal females (P< 0.001), in osteoporotic patients versus non-osteoporotic patients (P < 0.001) and in patients with vitamin D deficiency compared to those without (P = 0.039), as depicted in (Table 4), (Fig 1).

A notable positive association existed between the FRAX score and age (r=0.393, P<0.001), as well as the SGA score (r=0.292, P=0.003). FRAX score demonstrated an insignificant correlation with BMI, duration of dialysis and PTH level. (Fig 2)

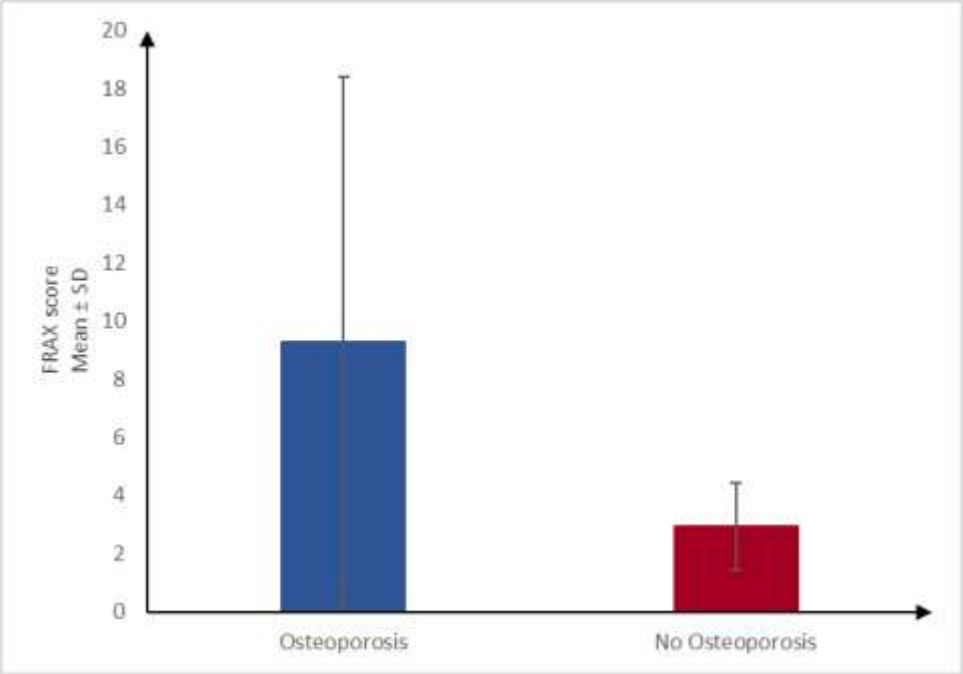

Fig 1 Osteoporosis according to FRAX score

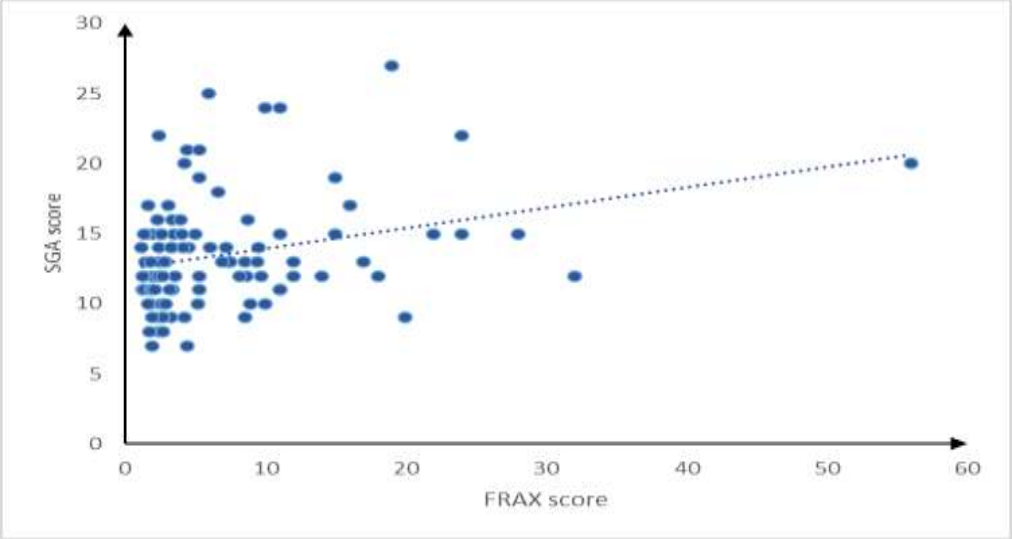

Fig 2 Correlation between FRAX and SGA score

Table 2 Patients-related data according to osteoporosis

		Osteoporosis		P value
		Yes (n=66)	No (n=34)	
Age (years)		51.61 ± 14.35	45.12 ± 9.9	0.020*
Sex	**Male**	23 (34.85%)	13 (38.24%)	0.738
	Female	43 (65.15%)	21 (61.76%)	
BMI (kg/m^2)		26.33 ± 6.34	27.41 ± 6.97	0.439
Menopause		33 (50%)	12 (35.29%)	0.161
Duration of dialysis (years)		4 (3 - 8)	3 (2 –4.75)	0.066
DM		14 (21.21%)	6 (17.65%)	0.673
PTH (ng/L)		618 (196.75–1098.5)	481.5 (335.75–784.5)	0.434
Low PTH		13 (19.7%)	5 (14.71%)	0.538
High PTH		45 (68.18%)	26 (76.47%)	0.387
Vit D (ng/mL)		15 (9.35–24.35)	14 (10 - 25)	0.741
SGA score		14.38 ± 4.33	11.94 ± 2.63	0.003*

BMI: body mass index, **DM:** diabetes mellitus, **Hb:** haemoglobin, **PTH:** parathyroid hormone, **SGA:** subjective global assessment, *: significant P value

Table 3 Multiple logistic regression analysis predicting osteoporosis

Predictor	OR	P value	95% CI Lower	95% CI Upper
Age (years)	1.056	0.009*	1.014	1.101
BMI (kg/m^2)	0.958	0.275	0.886	1.035
Duration of dialysis (years)	1.043	0.636	0.876	1.242
Hb (g/dl)	1.067	0.713	0.755	1.509
PTH (ng/L)	1.001	0.164	1.000	1.002
Vit D (ng/mL)	0.989	0.474	0.960	1.019
SGA score	1.196	0.029*	1.019	1.404

BMI: body mass index, Hb: haemoglobin, PTH: parathyroid hormone, SGA: subjective global assessment, OR: odds ratio, CI: confidence interval, *: significant P value

Table 4 Patients-related data according to FRAX score

		FRAX score	P value
Sex	**Male**	4.42 ± 3.52	0.002*
	Female	8.63 ± 9.38	
Menopause	**Yes**	11.02 ± 10.22	<0.001*
	No	3.37 ± 2.53	
DM	**Yes**	9.97 ± 8.55	0.101
	No	6.32 ± 7.71	
Osteoporosis	**Yes**	9.28 ± 9.12	<0.001*
	No	2.92 ± 1.5	
Low PTH	**Yes**	7.83 ± 6.96	0.678
	No	6.96 ± 8.28	
High PTH	**Yes**	6.68 ± 8.35	0.396
	No	8.19 ± 7.23	
Vit D deficiency	**Yes**	8.09 ± 9.47	0.039*
	No	5.31 ± 3.73	

FRAX: fracture risk assessment tool, DM: diabetes mellitus, PTH: parathyroid hormone,

*: significant p value.

DISCUSSION

CKD impacts multiple biochemical parameters, such as PTH, vit D, ph and ca.
Therefore, patients on HD experience a greater risk of osteoporosis and fractures relative to the general population. [11] The main aim of this study was to investigate the risk factors linked to BMD and osteoporosis and to determine these factors to facilitate the timely development of appropriate treatment strategies.

Our study indicated that the majority of our patients were female, with high prevalence of

vitamin D deficiency and hyperparathyroidism

Beena et al. [12] found that vitamin D deficiency and insufficiency were present in 88.9 and 6.7%, respectively, of the patients undergoing HD. Kim et al. [13] demonstrated that vitamin D deficiency is frequently observed in the CKD population, with prevalence rates of 40.7% in stage 3, 61.5% in stage 4 and escalating to 85.7% in stage 5. In Nigeria, Sanusi et al. [14] reported that 11.8% of patients with ESRD exhibited secondary hyperparathyroidism. In Senegal, Seck et al. [15] reported that 57 out of 118 cases exhibited high turnover disease, while 22 cases demonstrated low turnover bone disease. The causes of this statistical disparity may include varying population characteristics, sample size and other confounding variables.

Regarding the prevalence of low bone mass, specifically osteopenia (72%) and osteoporosis (66%), in patients undergoing HD. We selected DXA to assess BMD in HD patients, which is regarded as the gold standard for osteoporosis evaluation. Our study further highlights the importance of FRAX in HD patients, revealing that 19% exhibited moderate fracture risk and 6% demonstrated severe fracture risk. The FRAX score indicates a substantial elevation in fracture risk among older, malnourished individuals, those with vit D deficiency and patients with osteoporosis. This is evident particularly in females compared to males, especially postmenopausal women, which may be attributed to the hormonal changes that contribute to increased bone loss in females.

Avramovski et al. [16] established that the rate of bone mass deterioration was markedly higher in CKD patients compared to the general population, osteopenia prevalence rate ranged from 33.3% to 81%, averaging 45.91%. Huang et al. [17] reported the greatest incidence of osteopenia in a study conducted in Taiwan involving 63 HD patients. Maroua et al. [18] reported that 23% of patients have osteoporosis and45% have osteopenia, osteoporosis predominantly impacts the hip rather than the spine; 56% of patients exhibit normal PTH, while 19% of had diminished PTH levels; vit D insufficiency and deficiency were identified in 41.11% and 44.44% of cases, respectively. Paúl et al. [19] demonstrated that patients at elevated risk of major fractures according to the FRAX were older and had been on HD for a longer period.
FRAX was studied in relation to CKD stages by Reid et al. [20] who discovering that out of 10,099 subjects, 772 sustained a major osteoporotic fracture, while 226 experienced a hip fracture over a 5-year observation interval, revealing that FRAX was the most significant independent risk factor for major bone fractures.

Concerning osteoporosis, SGA score and age were markedly elevated in patients with osteoporosis compared to those without. Malnutrition significantly contributes to the risk of osteoporosis in patients receiving HD [21]. Kunutsor et al. [22] found that hypoalbuminemia was associated with a higher risk of osteoporosis and future fractures. Numerous studies, such as those by Ersoy FF [23] and Huang et al. [17] are consistent with our findings, indicating that BMD diminishes with advancing age. Three studies reported the association of body weight or BMI with BMD; two provided a positive correlation between body weight and BMD [17], [24].

Most included studies detected no association between vit D levels and BMD or bone loss among CKD patients, which contradicts prior research findings that a negative association between vit D and bone loss [25]. Conversely, Yong et al. [26] indicated that BMD significantly declined in stage 3 and 4 CKD patients with vit D deficiency, these subjects exhibited elevated levels of PTH and a greater incidence of sarcopenia. Six studies assessed the relationship between PTH levels and BMD; two indicated a negative association between PTH and BMD [27], [28]. Four studies found no association and reported statistically no significant differences in BMD scores among CKD patients with varying PTH levels [29] ,[30] . This insignificant association, in contrast to prior literature, may be attributable to the younger patients or other confounding

variables.

The current study has some limitations; thus, additional multi-center research with larger sample sizes is necessary to evaluate osteoporosis, fracture risk and their correlation with other variables. Additionally, other factors potentially linked to osteoporosis, such as heparin dosage, inflammatory markers and hypogonadism, were not examined.

CONCLUSION

This review identified a significant prevalence of osteoporosis, osteopenia, high turnover disease and vitamin D deficiency among our hemodialysis patients. We found that fracture risk and osteoporosis are common in hemodialysis patients, particularly in the elderly, postmenopausal women, malnourished individuals and those with vitamin D deficiency. In patients with CKD-MBD, the utilization of either DXA or FRAX for fracture risk assessment should be contemplated. Failure to adequately assess CKD patients for BMD may elevate the risk of osteoporosis and fractures.

Statements and Declarations

Availability of data and materials

The datasets used during the current study may be made available from the corresponding author upon reasonable request.

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Authors contribution

Aml Ahmed Sayed; writing the main manuscript text & collection of data & analysis and interpretation of data
Hanaa Mohammed Eid El sayed; analysis and interpretation of data
Weaam Mohamed Mohamed Ali; analysis and interpretation of data All authors reviewed the manuscript.

Conflict of interest

All authors declare that they have no conflict of interest

Ethics declarations

Ethical approval and consent to participate

All procedures were performed in accordance with the Declaration of Helsinki and have been approved by the Ethics Committee of Faculty of Medicine, Aswan University, Egypt (Asw.uni./523/3/21). An informed written consent was obtained from all participants before conducting the research.

Consent for publication

Not applicable.

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