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Which Is the Predominant Pattern of Mineral & Bone Disease (High vs Low Turnover) Among Dialysis Patients in Baghdad Teaching Hospital

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Abstract: Background: A common complication of CKD is a metabolic bone disease. It is one of a wide range of mineral metabolism disorders that can occur in clinical sitting and have both skeletal and non-skeletal implications. Abnormalities found in laboratory examinations, parathyroid gland dysfunction, abnormality in bone metabolism, and abnormality in soft tissue calcification are the three components of CKD-MBD. Objective: The study's goal is to find out which are the most common. Common type of CKD-MBD among dialysis patients in Baghdad Teaching Hospital based on laboratory parameters. Materials and methods: The study included 100 ESRD patients who underwent HD treatment at an outpatient dialysis center (Baghdad Teaching Hospital) if they have three months or more of dialysis vintage. Level of PTH, ALP, calcium, and phosphorus Normal laboratory procedures were used to assess the results. Results: 80% of the sample had CKD-MBD, and the high turnover bone disease was 38%, while the low turnover bone disease was 19%. There was no significant association between MBD and pattern and each of age or gender. No significant association was found between MBD pattern and each of the causes of CKD, type of access, and associated disease. Conclusion: MBD are very prevalent in our patients (80%), and the most common pattern of MBD is a high turnover bone disease

Keywords: MBD, Patients, CKD, Turnover, Pattern, Parameters

INTRODUCTION

Chronic kidney disease (CKD) is a major global health problem affecting 5-10% of the world population, particularly those on maintenance hemodialysis (HD). Patients with CKD have a higher mortality rate and an increased incidence of hip fractures. Metabolic bone disease is a common complication of CKD, affecting calcium and phosphorus hemostasis control [Andress, D.L. *et al*., 2006; Miller, P, 2014; Liu, Z. *et al*., 2019]. CKD-MBD is a growing concern associated with secondary hyperparathyroidism, mineral abnormalities, increased risk of cardiovascular disease, and alteration in fibroblast growth factor [Pavolic, D. *et al*., 2015]. CKD-MBD is characterized by abnormal metabolism of calcium, phosphorous, parathyroid hormone, vitamin D, bone turnover, mineralization, volume, linear growth, or strength. Factors associated with CKD-MBD include age, sex, dialysis form, duration, use of phosphate binders, calcimmetics, parathyroidectomy, diabetes, hypertension history, kidney failure duration, and dietary habits [Waziri, B. *et al*., 2019; Yamomoto, S. *et al*., 2018; Sista, K. *et al*., 2016].

CKD-MBD continues to be a therapeutic dilemma for practicing nephrologists. The mechanisms for its development are both multifactorial and controversial. Not surprisingly, the most appropriate treatment are conjectural (15).

The pathogenesis of CKD MBD is not fully understood, but based on broad basic and clinical research, it is accepted that a central role in pathogenesis is phosphorus retention [15]

Secondary hyperparathyroidism develops in high turnover patients with chronic kidney disease (CKD), resulting from phosphate retention, low plasma calcium, and elevated FGF-23. Factors contributing to this include phosphate retention, calcitriol deficiency, intrinsic changes, increased parathyroid gland development, skeletal resistance to PTH action, and hypocalcemia. PTH levels increase when eGFR falls below 60ml/min/1.73m. [Yun, H. *et al*., 2020; Martin, K. *et al*., 2007; Pazianas, M. *et al*., 2020]

Low turnover bone disease is commonly observed in patients with kidney disease, especially in patients who are on dialysis and is characterized by an extremely slow rate of bone formation. [Mussler, S. *et al*., 2018; Kazama, J. *et al*., 2015] Adynamic bone disease (ABD) is being found in increasing frequency. The pathogenesis of ABD is

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not well defined, but it seems that a number of factors might be involved [Martin, K. *et al*., 2007]. ABD is due to either resistance of PTH on bone metabolism or the over-suppression of PTH release, though several events precede this event [Sista, K. *et al*., 2016]

CKD-MBD is asymptomatic and requires diagnosis through biochemistry, radiology, and bone biopsy. Initial evaluation includes laboratory tests for calcium, phosphate, PTH, ALP, and bicarbonate. Bone biopsy is the gold standard for bone turnover assessment [Vervloet, M. *et al*., 2017; Morrone, L. *et al*., 2011] but has limitations like sampling errors, invasiveness, cost, and availability. Circulating biomarkers are attractive alternatives. Biochemical assessment of bone and mineral metabolism is the mainstay of diagnosis and treatment. Routine monitoring starts at an early stage [Mungulluh, F. *et al*., 2020; Lima, F. *et al*., 2019; Shalhoub, V. *et al*., 2013].

MATERIALS AND METHODS

Study material:

The study was conducted in February 2021. The study included 100 ESRD patients who underwent HD treatment at an outpatient dialysis center (Baghdad Teaching Hospital) if they have three months or more of dialysis vintage.

Patients who were hospitalized and/ or suffered from acute systemic infection at the time point of study initiation were excluded.

Levels of ALP, calcium, and phosphorus were determined by standard laboratory methods. PTH levels were measured by Electrochem-luminescence immunoassay (ECLIA) by Cobas e411 system (Roche Diagnostic Elecsys).

Normal value of calcium is 8.5-9.5 mg/dl, and phosphorus is 3.5-5 mg/dl. The PTH level target is 300-500 pg/ml.

STATISTICAL ANALYSIS:

Data were entered, managed, and analyzed using the statistical package for Social Sciences version 26 (SPSS 26). Variables are presented as frequencies (N0.), percentages, mean, median, standard errors, and ranges accordingly. Chi-square test was used to assess the association between categorical variables (frequencies), and Fisher's exact test was used as an alternative when the chi-square was inapplicable. The nonparametric Kruskal Wallis Test is used to assess the differences in the levels of continuous variables that have means and standard errors. However, this test is based on one way analysis of variances (ANOVA) on ranks of values. Level of significance is set at 0.05 and less to be a significant difference or association.

RESULTS

Table 1: Age and gender distribution of the studied group

Variable		No.	%
Age (year)	≤ 40	16	16.0
	41 - 50	27	27.0
	51 – 60	19	19.0
	61 – 70	30	30.0
	> 70	8	8.0
Gender	Male	60	60.0
	Female	40	40.0

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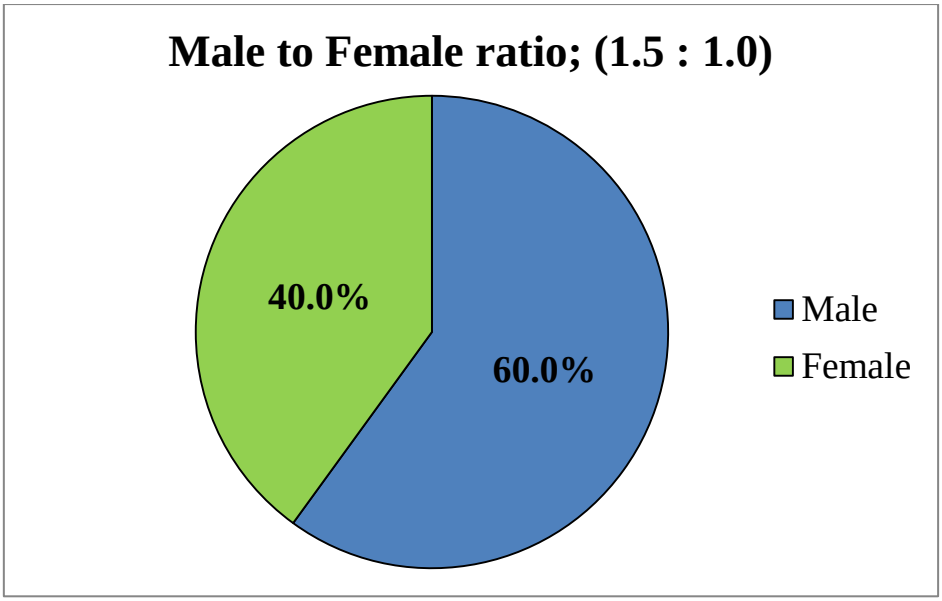

Figure 1: Pie-chart showing gender distribution of the studied group with male-to-female ratio

Table 2 demonstrates the clinical characteristics of the studied group; regarding the cause of CKD, Diabetes mellitus was the more frequent cause, contributed for 40%, followed by unknown 28%. Other causes were less frequent, ranged between 7% for hypertension, and the least cause was FSGS 3% and SLE3%

Table 2: Clinical characteristics of the studied group

Variable	No.	%
Cause of CKD		
Diabetes Mellitus	40	40.0
Hypertension	7	7.0
APKD	5	5.0
Con dysplasia	4	4.0
FSGS	3	3.0
SLE	3	3.0
Others	10	10.0
Unknown	28	28.0
Comorbidities*		
Yes	87	87.0
No	13	13.0
Duration on HD		
Median (year)	2.7	-
Range	Three months – 14 years	
No. of sessions/week		
Two sessions	82	82.0
Three sessions	18	18.0
Followed up by nephrologist		
Yes	32	32.0
No	68	68.0
Virology		
HCV	46	46.0
Negative	54	54.0

The more frequent type of access was arterio-venous fistula (AVF), which was reported in (77%) of patients; a central venous catheter (CVC) was applied in the remaining 23% of patients (Figure 2)

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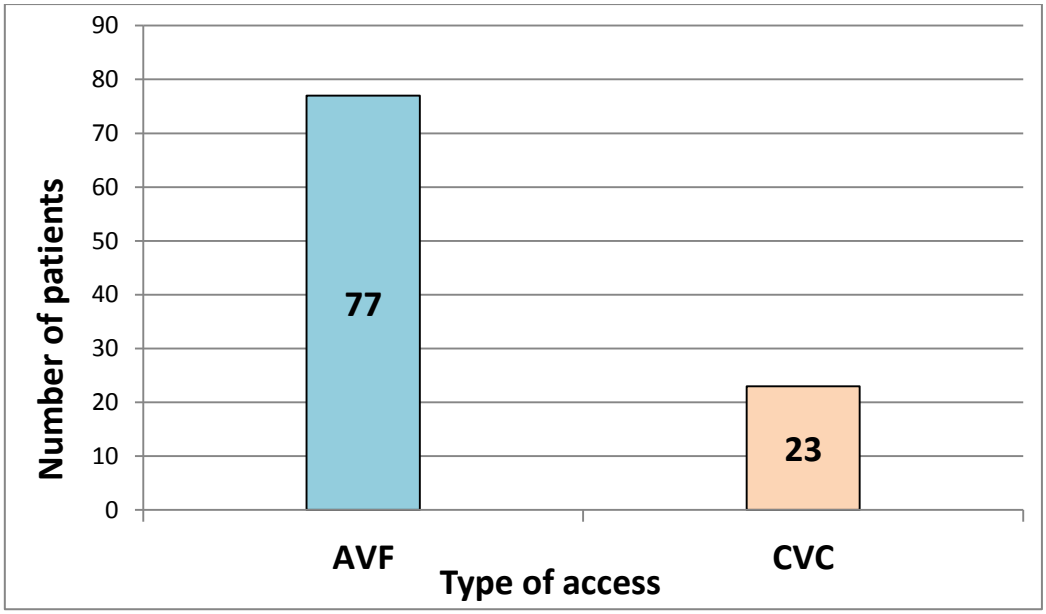

Figure 2: Bar chart showing the Types of access

Table 3: Medications and agents used among the studied group

Item		No.	%
Calcium tab*	S	36	36.0
	C	9	9.0
	S, C	22	22.0
	None	33	33.0
Vit D		35	35.0
sevelamer		31	31.0
Cinacalcit		6	6.0
Iron		63	63.0
Eprex		92	92.0
Folate		100	100.0
S: supplement, C: chelating			

Table 7 shows the mean values, standard error of the mean, minimum and maximum values of laboratory findings and Kt/V ratio, wide ranges reported in Ferritin (32 – 2000) ng/ml, Ca x Po4 product (16.6-80) mg^2/dL^2 and PTH (28 – 2600) pg/ml.

From other point of view, the Kt/V ratio was ≥ 1.4 in 22 patients while < 1.4 in the remaining 78 patients. Level of Ca x Po4 product was < 55 in 85 patients and ≥ 55 in 15 patients. PTH level was high in 33 patients, low in 34, and normal in 33 patients. High levels of ALP were reported in 53 patients (Table 8).

Table 4: Laboratory parameters of the studied group

	Mean	SE of Mean	Minimum	Maximum
Hb (mg/dl)	**9.16**	0.14	5.0	12.0
Phosphate (mg/dl)	**5.19**	0.17	2.1	9.8
Calcium (mg/dl)	**7.98**	0.09	5.1	9.8
Albumin (g/dL)	**3.80**	0.05	2.3	5.0
Ferritin (ng/ml)	**521.94**	38.83	32	2000
Kt/V	**1.17**	0.02	0.45	1.70
Creatinine	**8.44**	0.24	3.2	14.0
Ca x Po4 product (mg^2/dL^2)	**41.21**	1.50	16.60	80.00
PTH (pg/ml)	**475.50**	51.21	28.0	2600.0

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Table 5: Levels of Kt/V ratio Ca x Po4 product, PTH, and ALP of the patients

		No.	%
Kt/V ratio categories	≥ 1.4	22	22.0
	< 1.4	78	78.0
Ca x Po4 product	< 55	85	85.0
	≥ 55	15	15.0
PTHlevel	High	33	33.0
	Low	34	34.0
	Normal	33	33.0
ALP	High	53	53.0
	Normal	47	47.0

As shown in Figure 3, a high turnover pattern of MBD was found in 38 patients, low turnover in 19, and mixed in 23 while 20 patients had none.

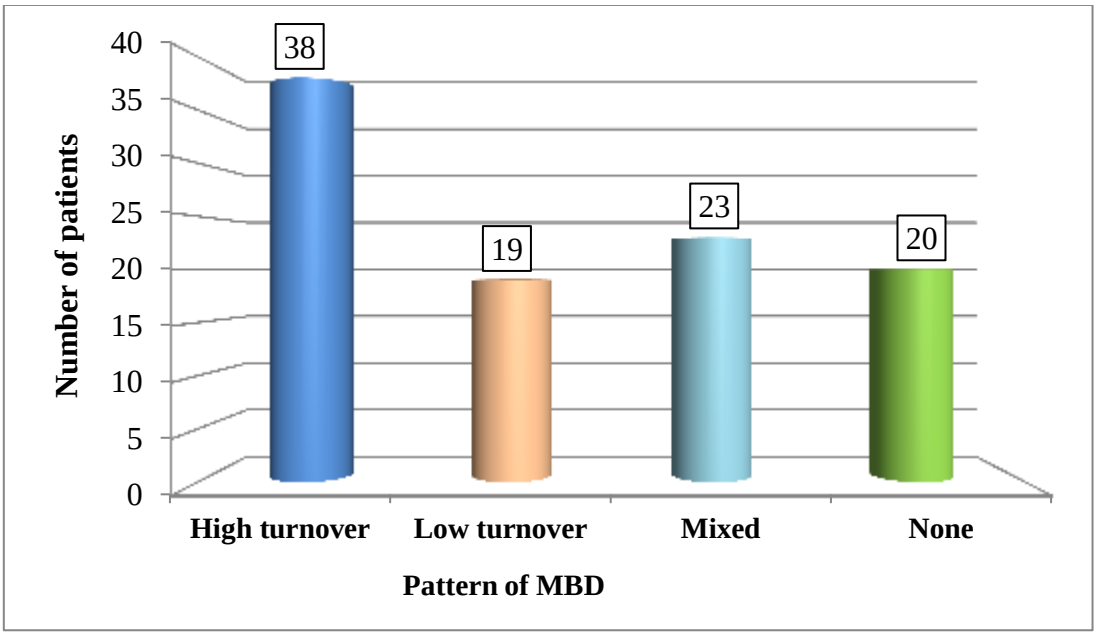

Figure 3: Distribution of pattern of MBD among the studied group

To assess the association between the Pattern of MBD and other variables, cross-tabulation was performed between the MBD pattern as a dependent variable against other variables as independent ones. Results of these analyses revealed the following findings:

1. No significant association between the MBD pattern and each of age or gender of the patients; in both comparisons, the P-value > 0.05 (Table 9).
2. No significant association was found between MBD pattern and each of Cause of CKD, type of access, and associated disease in all comparisons, P-value > 0.05
3. A statistically significant association was found between using calcium tab supplementation and high turnover MBD pattern, where 61.1% of patients using calcium supplements had high turnover, compared to 33.3% of those used chelating, 36.4% of those used to supplement and chelating and only 15.2% among those who did not used any calcium tab, (P-value < 0.05). On the other hand, users of vitamin D were more likely to have high turnover MBD, 68.6%, compared to those who did not use it (P-value < 0.05).

Other items and Cax PO4 products showed no significant association with MBD pattern (P>0.05) (Table 6)

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Table 6: Cross-tabulation for the association between MBD pattern and each of age and gender of the patients

Variable	MBD pattern								P-value
	High turnover (n = 38)		Low turnover (n = 19)		Mixed (n = 23)		None (n = 20)		
	No.	%	No.	%	No.	%	No.	%	
Age (year)									
≤ 40	8	50.0	4	25.0	2	12.5	2	12.5	0.733 ns
41 – 50	10	37.0	4	14.8	6	22.2	7	25.9	
51 – 60	6	31.6	4	21.1	4	21.1	5	26.3	
61 – 70	12	40.0	5	16.7	10	33.3	3	10.0	
> 70	2	25.0	2	25.0	1	12.5	3	37.5	
Gender									
Male	18	30.0	12	20.0	18	30.0	12	20.0	0.122 ns
Female	20	50.0	7	17.5	5	12.5	8	20.0	

Table 7: Cross-tabulation for the association between MBD pattern and each of Cause of CKD, type of access, and Associated Disease

Variable	MBD pattern								P-value
	High turnover (n = 38)		Low turnover (n = 19)		Mixed (n = 23)		None (n = 20)		
	No.	%	No.	%	No.	%	No.	%	
Cause of CKD									
Diabetes Mellitus	13	32.5	3	7.5	14	35	10	25	0.198 ns
Hypertension	2	28.6	5	71.4	0	0	0	0	
APKD	3	60	1	20	1	20	0	0	
Con dysplasia	2	50	1	25	0	0	1	25	
FSGS	1	33.3	0	0	1	33.3	1	33.3	
SLE	1	33.3	1	33.3	0	0	1	33.3	
Other	4	40	3	30	1	10	2	20	
Unknown	12	42.9	5	17.9	6	21.4	5	17.9	
Type of access									
AVF	33	42.9	14	18.2	16	20.8	14	18.2	0.325 ns
CVC	5	21.7	5	21.7	7	30.4	6	26.1	
Associated disease									
Yes	32	36.8	17	19.5	20	23	18	20.7	0.914 ns
No	6	46.2	2	15.4	3	23.1	2	15.4	

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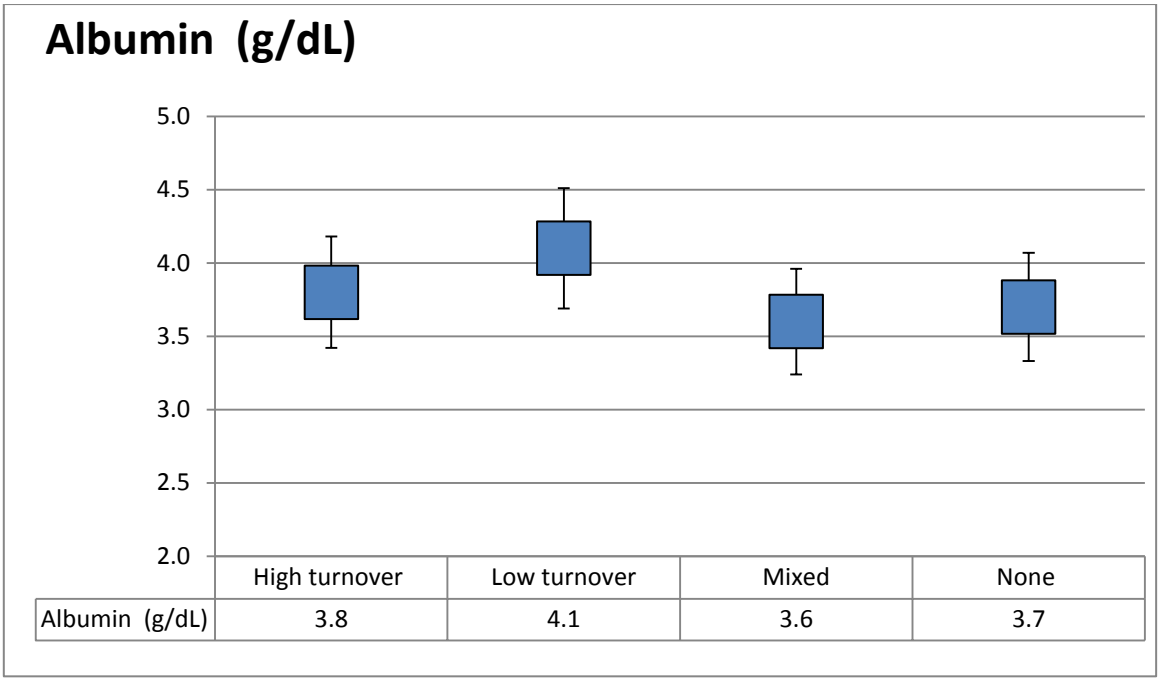

Figure (4): Markers-line-plot comparing the levels of Albumin across the MBD patterns

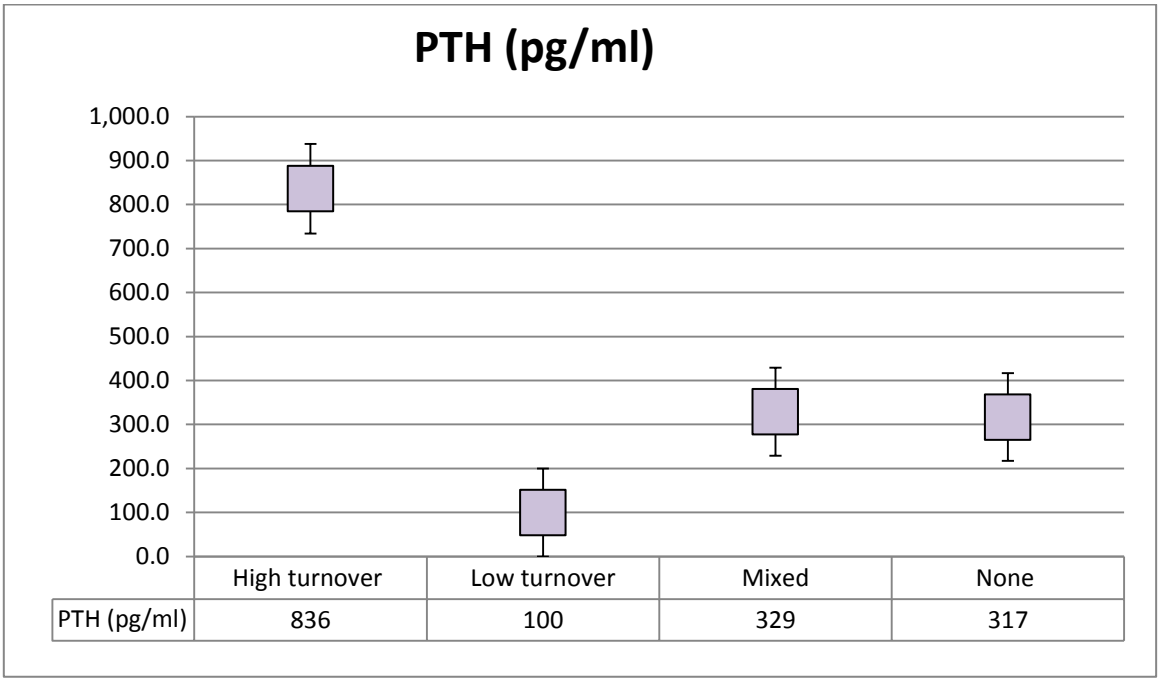

Figure 5: Markers-line-plot comparing the levels of PTH across the MBD patterns, the highest PTH level associated with high turnover and the lowest PTH level associated with low turnover.

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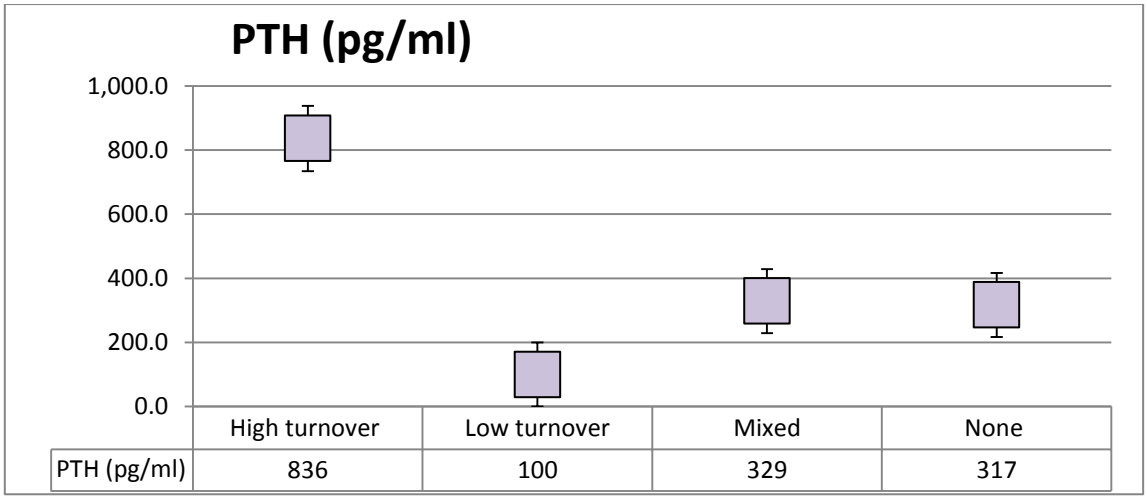

Table 8: Cross-tabulation for the association between MBD between pattern and cach of cause CKD, Type of access

Variable	MBD pattern								P. value
	High turnover (n = 38)		Low turnover (n = 19)		Mixed (n = 23)		None (n = 20)		
	No.	%	No.	%	No.	%	No.	%	
Cause of CKD									
Diabetes Mellitus	13	32.5	3	7.5	14	35	10	25	
Hypertension	2	28.6	5	71.4	0	0	0	0	
APKD	3	60	1	20	1	20	0	0	
Con dysplasia	2	50	1	25	0	0	1	25	0.198 ns
FSGS	1	33.3	0	0	1	33.3	1	33.3	
SLE	1	33.3	1	33.3	0	0	1	33.3	
Other	4	40	3	30	1	10	2	20	
Unknown	12	42.9	5	17.9	6	21.4	5	17.9	
Type of access									
AVF	33	42.9	14	18.2	16	20.8	14	18.2	0.325 ns
CVC	5	21.7	5	21.7	7	30.4	6	26.1	
Associated disease									
Yes	32	36.8	17	19.5	20	23	18	20.7	0.914

DISCUSSION

The CKD-MBD was identified approximately a century ago, prior to the conception of dialysis therapy. Remarkably, around 70% to 90% of patients with chronic kidney disease (CKD) experience alterations in mineral and bone homeostasis (20).

Our study likewise observed the same outcome, with 80% of the patients exhibiting MBD. This finding aligns with the findings reported by Ahmed, H. *et al*., 2017.

Out of the 100 patients participating in the study, 38% had high turnover bone disease, 19% had low turnover bone disease, and 23% had mixed patterns of mineral bone disorder (MBD). In their study, Bansal et al. also note that the prevalence of CKD-MBD is mostly characterized by high turnover bone disease (Bansal, B. *et al*., 2016). Sharma S states that adynamic bone disease is the most prevalent of the mineral bone disorders linked with chronic kidney illness (Sharma, S. *et al*., 2021).

The high incidence of CKD-MBD in our patients can be attributed to insufficient dialysis, as evidenced by a low Ktv in 78% of cases. Additionally, 68% of the sample population is not under the care of nephrologists.

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Our investigation found that individuals with low turnover mineral bone disorder (MBD) had significantly elevated levels of albumin compared to other subgroups. This finding contradicts previous studies that have identified malnutrition as a risk factor for low-turnover bone disease (Hou, Y. *et al*., 2018; Sherrard, D. *et al*., 1993).

In conclusion, in our study, the prevalence of CKD-MBD is 80%, with the most frequent kind of bone disease being high turnover (38%), followed by low turnover bone disease (19%). Additionally, a significant proportion of the sample is inadequately dialyzed.

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