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" *Prevalence and pattern of Mineral Bone Disorders in patients with end-stage renal disease and the impact of diabetic status and type of phosphate binders on these disorders* "

Authors

Naglaa Hamed Fadel [1], Islam Ali Elsayed [2], Dina Mostafa [3], Fatima Al-Taher Taha Morsi [4]

[1] Department of internal medicine, faculty of medicine, Port-Said University

[2] Lecturer of internal medicine, Department of Internal Medicine, Faculty of Medicine Zagazig University, Zagazig, Egypt.

[3] Department of clinical pathology, Faculty of Medicine Zagazig University, Zagazig, Egypt.

[4] Lecturer of nephrology, Department of Internal Medicine, faculty of Medicine, Zagazig University.

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https://muj.journals.ekb.egdean@med.psu.edu.eg

vice_dean_postgraduate@med.psu.edu.eg

ABSTRACT:

Mineral and bone disorders are considered one of the most common disorders affecting renal patients that are associated with great mortality and morbidity. Also, diabetes as a metabolic disorder could affect the bone mineralization per se. As hyperphosphatemia is the key factor of such a pathogenic process, most management is directed toward lowering phosphate levels and correcting such metabolic derangements, one of them is the use of phosphate binders. The aim is to measure the prevalence of bone mineral disorders in patients with end-stage renal disease on regular hemodialysis in diabetics and non-diabetics and to assess the pattern of bone disorders and the effect of the use of different types of phosphate binders on the assessed biochemical markers

Methods: a cross-section study included 116 patients with end-stage renal disease on regular hemodialysis (26 due to diabetes, 90 due to other causes), 50% used calcium-based phosphate binders and 50% used non-calcium binders. the prevalence and pattern of bone mineral disorders and the effect of different binders on biochemical markers are studied.

Results: bone mineral disease is prevalent in 59.6% (low and high bone turnover 38.8%,20.7% respectively), with the same pattern in diabetics (low and high bone turnover 30.8%, 23.1% respectively). A significantly lower phosphate level and intact parathyroid hormone in non-calcium phosphate binder users (p=0.013, 0.039, respectively).

Conclusion: low bone turnover is more prevalent in renal patients with hemodialysis and patients with diabetic nephropathy. Non-calcium-based phosphate binders are associated with lower phosphate and parathyroid levels with less risk of hypercalcemia.

Keywords: chronic kidney disease–mineral and bone disorder, diabetic nephropathy, phosphate binders

Introduction

Chronic kidney disease (CKD) roughly affects 11–13% of the general population, which continues to be a global health concern. One typical consequence of CKD is a mineral and bone disorder (CKD-MBD), which develops early in the illness and worsens as kidney function declines [1].

CKD-MBD is a systemic disorder affecting the metabolism of bone and minerals in CKD patients. The definition is settled by kidney disease: Improving Global Outcomes (KDIGO) as the presence of 1 or more of 3 elements: biochemical abnormalities (involving calcium, phosphorus, PTH, or vitamin D metabolism), bone turnover abnormalities, soft tissues, and vascular calcifications. This is considered a broad-spectrum definition replacing the term renal osteodystrophy (ROD) which describes only one component “bone pathology “of the previously mentioned 3 items and necessitates bone biopsy for diagnosis [2].

Diagnosis of CKD-MBD is based on the evaluation of one or more of the previously mentioned pillars. Bone turnover abnormalities need performing bone biopsy which is an invasive strategy, especially in end-stage renal disease (ESRD) and it is indicated only in certain selected patients' criteria (e.g., confusing biochemical abnormalities). Also, bone histomorphometry is not easily available in certain developing countries for precise histological examination. Furthermore, imaging modalities such as soft tissue images for diagnosis of tissue calcifications and bone density scans are not affordable tools to be done routinely for all patients. Thus, clinical and biochemical assessments remain the widely accepted tools in diagnosis, especially in low-income countries [2,3].

Many previous studies have investigated the influence of CKD-MBD on overall morbidities and mortalities as well as the quality of life. CKD-MBD is associated with increased bone fragility, cardiovascular calcifications, and cardiovascular mortalities with a magnification of the risk, especially in hemodialysis patients [4]. Also, the disturbed markers in MBD are associated with more deterioration of the renal function especially phosphate disturbance which drives other biomarkers derangement (e.g., iPTH, Fibroblast growth factor 23(FGF-23), Calcium, and Vitamin D) and seems to exert a pivotal role in the pathogenic process. Thus, it is judicious to target the phosphate level during the management of CKD-MBD [5].

MBD in patients with diabetic nephropathy seems to have a different profile as patients with diabetes mostly have bone mineral disorder even in the absence of CKD, the issue that becomes aggravated by developing diabetic nephropathy [6].

Phosphate binders are one of the major strategies for coping with the problem. Phosphate binders are located in one of 3 types: calcium-based (e.g., calcium carbonate), aluminum-based, and non-calcium-based (e.g., sevelamer, lanthanum, and sucroferric oxyhydroxide). The first 2 are cheap and available options but still have certain drawbacks such as gastrointestinal upsets and constipation for the former and the risk of

aluminum intoxications in long-term use especially on dialysis patients for the latter. Non-calcium-based phosphate (non-CBPB) binders have higher costs and vary in their efficacy. Sevelamer is effective but needs a high pill burden which may affect patient compliance, in contrast, lanthanum carbonate needs a few pills burden with double the efficacy than calcium-based and sevelamer. Iron-based non-CBPB is not widely available in some developing countries (e.g., Egypt) [7]. The efficacy and safety of different forms of phosphate binders on different aspects of MPD are widely evaluated with variable outcomes [8].

The current study aims to determine the prevalence and the pattern of CKD-MBD in patients with ESRD on regular hemodialysis based on biochemical biomarkers and the difference in this pattern between diabetic nephropathy patients and CKD due to other causes. We studied also the effects of different phosphate binders on biochemical biomarkers in different patterns of MBD in the studied population.

2. Participants and Method:

2.1.Study design and participant

This cross-section study was carried out at Zagazig University Hospitals and included 116 patients who have end-stage renal disease on regular hemodialysis (3 sessions per week).

The inclusion criteria include all Patients with ESRD on regular hemodialysis, on treatment with either calcium-based (CBPB) or non-calcium-based phosphate binders, with ages above 18y. The exclusion criteria include Age < 18 years, patients with known CKD-MBD on conservative management, and patients with a known history of other metabolic bone diseases (e.g., Paget disease of bone, osteopetrosis, etc...)

The included patients were divided into 2 groups:

- Diabetic Group with diabetic nephropathy as a cause of ESRD (included 26 patients). Diagnosis of diabetic nephropathy was considered in a known diabetic with any type of diabetes of more than 5 years duration, with persistent albuminuria (>300mg/dL) in 2 of 3 sessions with concomitant retinopathy, hypertension, azotemia, and normal or enlarged kidneys on ultrasound, in the absence of the following: rapidly progressing or nephrotic-range albuminuria (>2500 mg/g), rapid deterioration of GFR, active urinary sediment, refractory hypertension, and symptoms or signs of other systemic illness [9,10].
- Non-diabetic group (included 90 patients) diagnosed with ESRD due to causes other than diabetes.

All patients after fulfilling the inclusion criteria were subjected to thorough history taking for age, sex, duration of DM, current therapy, compliance, complete medical history for medications, chronic medical condition, duration and frequency of hemodialysis, and the type of phosphate binders used. Full clinical examination was performed including general examination and complete systemic examination.

Investigations were done in the form of **r**outine investigations such as CBC, Na, K, serum albumin, and bicarbonate, Biochemical markers of MBD include intact PTH (iPTH), total and ionized calcium, phosphorus level, total alkaline phosphatase (ALP), and 25OHD level. The pattern of MBD was studied based on the iPTH level: [3]

- iPTH >400pg/ml: high turnover MBD
- iPTH 65-400pg/ml: Normal
- iPTH < 65pg/ml: low turnover MBD

The effect of different types of phosphate binder on markers of MBD was studied in diabetic and non-diabetic groups. The patients used calcium carbonate tablets as calcium-based phosphate binders (CBPB) or sevelamer as non-CBPB.

2.2.Statistical Analysis

Data collected throughout history, basic clinical examination, laboratory investigations, and outcome measures were coded, entered, and analyzed using Microsoft Excel software. Data were then imported into Statistical Package for the Social Sciences (SPSS version 20.0) (Statistical Package for the Social Sciences) software for analysis. According to the type of data qualitative represented by number and percentage, and the quantitative continues group is represented by mean ± SD, the following tests were used to test differences for significance: *Chi-square Test (χ2);* used to study comparison and association between qualitative variables, *Fisher's Exact;* used for Correction for chi-square when more than 20% of the cells have an expected count less than 5, *ANOVA (f) test;* a test of significance used for comparison between three or more groups having quantitative variables, Kruskal-Wallis test (nonparametric test); a test of significance used for comparison between three or more groups not normally distributed having quantitative variables, *t-test*; used for comparison between two groups having quantitative variables (normally distributed), *Mann-Whitney (nonparametric test),* used for comparison between two groups not normally distributed having quantitative variables. *A P-value of ≤ 0.05* was considered statistically significant and *p≤ 0.001* for highly significant results for two-tailed tests.

3. Results

The current study was planned as a two-stage study: initially, we evaluated the prevalence of different MBD among our population and the impact of diabetic status on the pattern of MBD. We found high turnover MBD in 24 patients (20.7%), low turnover in 45 patients (38.8%), and normal iPTH in 47 patients (40.5%). A comparison of this pattern between the diabetic (26 patients) and non-diabetic groups (90 patients) revealed no significant difference (P=0.634) with high turnover percentage (23.1 and 20%, respectively), low turnover percentage (30.8 and 41.1% respectively), and normal percentage (46.2 and 38.9% respectively). (**Table 1)**

Table 1: Prevalence of MBD among the studied groups

Variable (MBD)	*Total patients*		*Diabetic group*		*Non-diabetic group*		*χ 2*	*P*
	N=116	*Percentage*	*N=26*	*Percentage*	*N=90*	*Percentage*		
No	**47**	40.5	12	46.2	35	38.9	**0.911**	**0.634**
Low turnover	**45**	38.8	8	30.8	37	41.1		
High turnover	**24**	20.7	6	23.1	18	20		

MBD: mineral bone disorder, χ 2 chi-square test

No statistically significant differences were found between diabetic and non-diabetic groups as regards the prevalence of BMD (p>0.05).

Regarding the demographic characteristics of the studied populations, the mean ± SD of age was 54 ± 13.2, with no significant difference in age with different patterns of MBD (52.3± 16.2, 53.7 ±11.9, 57 ±11.7 in non, low, high MBD groups respectively). 68 patients (58.6%) were male and 48 (41.3%) were females with no significant difference in the pattern of MBD (P-value=0.184). The mean hemodialysis vintage was 3.7 ± 2.7. 65% of patients were anuric while 35% were not. No significant difference was found regarding the use of phosphate binders and the pattern of MBD. **(Table 2).**

Table 2: Comparison of demographic characteristics, dialysis vintage, clinical and laboratory data among different MBD groups

Variable	**No MBD (N=47)**		**Low MBD (N=45)**		**High MBD (N=24)**		**f-test**	**P-value**	**LSD**
Age (years): Mean ± SD	**52.3± 16.2**		**53.7 ±11.9**		**57 ±11.7**		**0.95**	**0.389**	
HD vintage (years): Mean ± SD	**3.9± 2.7**		**3.9± 2.7**		**3.5 ±2.8**		**0.24 (KW)**	**0.787**	
Variable	***N***	***%***	***N***	***%***	***N***	***%***	**χ 2**	**P-value**	**LSD**
Sex:									
Male	**26**	**53.3**	**24**	**53.3**	**18**	**57**	**1.3**	**0.184**	
Female	**21**	**44.7**	**21**	**46.7**	**6**	**25**			
Non-Anuria Patient:	**17**	**36.2**	**14**	**31.1**	**9**	**37.5**	**0.382**		
Anuric patients	**30**	**63.8**	**31**	**68.9**	**15**	**62.5**		**0.826**	
Non-CBPB	**24**	**51.1**	**24**	**53.3**	**10**	**41.7**	**0.888**	**0.641**	
CBPB	**23**	**48.9**	**21**	**46.7**	**14**	**58.3**			
Laboratory data	**No BMD (N=47)**		**Low BMD (N=45)**		**High BMD (N=24)**		**f-test**	**P-value**	**LSD**

	(Mean ± SD)	*(Mean ± SD)*	*(Mean ± SD)*			
CBC						
Hb(gm/dL)	**9.9 ±1.3**	**9.9± 1.1**	**9.9 ±1.1**	**0.021**	**0.789**	
Platelets (cell/mm^3)	**225.3 ±56.6**	**220.4 ± 60.1**	**210.5 ±52.9**	**0.532**	**0.589**	
Leucocytes(cells/mm^3)	**7.1 ±1.6**	**6.7± 1.5**	**7.3 ±1.3**	**1.8**	**0.174**	
Calcium (mg/dL)						
Total	**9.8 ±1.1**	**9.7 ± 1.2**	**10.1 ±1.1**	**1**	**0.370**	
Ionized	**4.4±0.37**	**4.4 ± 0.73**	**4.6 ±0.39**	**1.1**	**0.355**	
Phosphorus (PO_4) (mg/dl)	**6.2 ±1.7**	**6.5 ± 1.9**	**6.6 ±1.2**	**0.562**	**0.572**	
iPTH ((pg./mL)	**284.8 ±84.9**	**35.8 ±16.3**	**722.9 ± 191.3**	**212.3**	**0.000*** **(HS)**	***P1,0.000 P2,0.000 P3,0.000***
ALP (IU/L)	**143.5 ± 96.6**	**124.5 ±76.9**	**194.4 ± 83.4**	**1.7 (KW)**	**0.179**	
Albumin (gm/dL)	**3.9 ±0.43**	**3.9± 0.62**	**3.7 ±0.46**	**1.2**	**0.306**	
25(OH)D(ng/ml)	**9.6 ±4.6**	**10.4 ± 4.2**	**9.5 ±4.5**	**0.462 (KW)**	**0.613**	
Bicarbonate (meq/L)	**19.9 ±2.3**	**19.9 ± 2.2**	**19.7 ±2.1**	**0.048**	**0.953**	
Urea (mg/dL)						
Predialysis	**160.4±63.6**	**165.8 ± 44**	**173 ±92.1**	**0.868**	**0.423**	
Post dialysis	**76.7 ±31.5**	**74.8 ± 28.3**	**77.2±14.8**	**0.080 (KW)**	**0.923**	

CBPB: calcium-based phosphate binders, iPTH: intact parathyroid hormone, ALP alkaline phosphatase

f- test: Anova test, KW: Krussle Wallas test, LSD: least significant difference.

P1: No BMD Vs Low BMD P2: No BMD Vs High BMD P3: Low BMD Vs High BMD.

Comparison of biochemical markers on 3 different patterns of MBD revealed a significant difference in iPTH level with mean ± SD 722.9 ± 191.3, 35.8 ±16.3, 284.8 ±84.9 in high turnover, low, and non-MBD respectively. Total calcium levels were within normal in all groups with mean ± SD 10.1 ±1.1, 9.7 ± 1.2, and 9.8 ±1.1 in high, low, and non-MBD groups respectively with no significant difference (P=0.370). Also, hyperphosphatemia was prevalent in most of the studied populations with no significant difference between MBD group patterns (6.6 ±1.2, 6.5 ± 1.9, and 6.2 ±1.7 in high, low, and non-MBD groups respectively) (P= 0.572). Comparison of serum albumin, 25(OH)D level, alkaline phosphatase, urea, and bicarbonate level revealed no significant difference between the MBD group pattern (P value= 0.306, 0.613, 0.179, 0.423, and 0.953 respectively). **(Table 2)**

In the second stage of our study, we classified the patients into two groups according to the type of phosphate binders administrated where 58 patients were using CBPB (9 were diabetics and 49 were nondiabetics), while the other 58 patients were using non-CBPB (17 were diabetics and 41 were nondiabetics). A comparison of the effect of different phosphate binders on biochemical markers was studied in both diabetic and non-diabetic groups. In the diabetic group, no significant difference was found regarding total calcium, iPTH, or ALP between non-CBPB and CBPB (9.1 ±1.1 vs 9.3± 0.78 with P value 0.677, 297.3 ±194.3 vs 305.3± 172.2 with p value 0.919, and 83.6 ±27.5 vs 118.7 ± 109.3 with p value 0.216 respectively). However, a significant difference was found regarding phosphorus levels with lower levels in non-CBPB users than calcium-based (5.2 ±1.3 vs 6.8± 1.7 respectively with P=0.013) **(Table 3).**

Table 3: Comparison of different forms of phosphate binders on biochemical markers in a diabetic and non-diabetic group

Variable	***Diabetic nephropathy group (N=26)***			
mean± SD	***Non-CBPB (N=17)***	**CBPB (N=9)**	**t-test**	**P-value**
Calcium (mg/dL)				
Total	**9.1 ±1.1**	**9.3± 0.78**	**0.42**	**0.677**
Ionized	**4 ±0.52**	**4.7± 1.4**	**1.8**	**0.075**
Phosphorus (PO_4) (mg/dl)	**5.2 ±1.3**	**6.8± 1.7**	**-2.7**	**0.013 *(S)**
iPTH ((pg./mL)	**297.3 ±194.3**	**305.3± 172.2**	**0.103(MW)**	**0.919**
ALP (IU/L)	**83.6 ±27.5**	**118.7 ± 109.3**	**-1.3(MW)**	**0.216**
	Non-diabetic group (N=90)			
	Non-CBPB (N=41)	**CBPB (N=49)**	**t-test**	**P-value**
Calcium (mg/dL)				
Total	**8.9 ±1.1**	**9.3± 0.92**	**-1.2**	**0.222**
Ionized	**4.8 ±0.46**	**4.8± 0.41**	**-0.87**	**0.385**
Phosphorus (PO_4) (mg/dl)	**6.4 ±1.5**	**6.4± 1.2**	**-0.007**	**0.994**
iPTH ((pg./mL)	**390.8 ±258.6**	**406± 278.6**	**-0.27(MW)**	**0.270**
ALP (IU/L)	**127.4 ±99.5**	**157.3 ± 145.6**	**-1.1(MW)**	**0.268**

A comparison of phosphate binders in the nondiabetic group revealed nonsignificant differences regarding calcium, phosphorus, iPTH, or ALP (8.9 ±1.1 vs 9.3± 0.92, P=0.222, 6.4 ±1.5 vs 6.4± 1.2, p=0.994, 390.8 ±258.6 vs 406± 278.6, p =0.270, and 127.4 ±99.5 vs 157.3 ± 145.6, p= 0.268 with Non-CBPB and CBPB respectively) **(Table 3).**

The comparison of the effect of phosphate binders was applied to the 3 bone turnover subgroups and revealed a significantly lower iPTH in non-CBPB users (517.6 ±254.5 vs 668.9± 217.9, P=0.039) in the high turnover group only, with non-significant lower calcium, phosphorus, and ALP in non-CBPB users (8.9 ±1 vs 9.1± 0.59, 6.1 ±1.4 vs 6.2± 0.9, and 131.7 ±113.9 vs 189.9 ± 142.9) respectively. Similarly, in the low turnover group and the group with normal iPTH, no significant difference was found between calcium-based and non-calcium-based phosphate binder users. **(Table 4)**

Table 4: Comparison of different forms of phosphate binders on biochemical markers in different patterns of MBD

Variable	***Low MBD group (N=45)***			
mean± SD	***Non-CBPB (N=24)***	**CBPB (N=21)**	**t-test**	**P-value**
Calcium (mg/dL)				
Total	**9.2 ±1.1**	**9.3± 1.1**	**-0.54**	**0.588**
Ionized	**4.6 ±0.35**	**4.7± 1**	**0.35**	**0.727**
Phosphorus (PO_4) (mg/dl)	**6.2 ±1.6**	**6.3± 1.4**	**-0.39**	**0.693**
iPTH ((pg./mL)	**65.1 ±34.3**	**65.3± 38.9**	**-0.02 (MW)**	**0.984**
ALP (IU/L)	**82 ±20.9**	**102.9 ± 100.6**	**-6.4 (MW)**	**0.528**
Variable	***high MBD group (N=24)***			
mean± SD	***Non-CBPB (N=10)***	**CBPB (N=14)**	**t-test**	**P-value**
Calcium (mg/dL)				
Total	**8.9 ±1**	**9.1± 0.59**	**0.52**	**0.607**
Ionized	**4.9 ±0.61**	**4.9± 0.63**	**0.03**	**0.976**
Phosphorus (PO_4) (mg/dl)	**6.1 ±1.4**	**6.2± 0.9**	**-0.35**	**0.733**
iPTH ((pg./mL)	**517.6 ±254.5**	**668.9± 217.9**	**-2.1(MW)**	**0.039*(S)**
ALP (IU/L)	**131.7 ±113.9**	**189.9 ± 142.9**	**-1.5(MW)**	**0.142**

Variable	***Non- MBD group (N=47)***			
mean± SD	***Non-CBPB (N=24)***	**CBPB (N=23)**	**t-test**	**P-value**
Calcium (mg/dL)				
Total	**8.9 ±1.2**	**9.3± 0.87**	**-1.1**	**0.273**
Ionized	**4.8 ±0.52**	**4.8± 0.33**	**0.33**	**0.477**
Phosphorus (PO_4) (mg/dl)	**5.9 ±1.6**	**6.7± 1.4**	**-1.8**	**0.078**
iPTH ((pg./mL)	**312.1 ±169.6**	**291.1± 100.1**	**0.51(MW)**	**0.610**
ALP (IU/L)	**110 ±69.1**	**145.6 ± 153.8**	**-1(MW)**	**0.309**

MW: Mann-Whitney

4. Discussion:

In the current study, the prevalence of MBD in the overall patients was 59.6% (38.8 % with low bone turnover disease and 20.7% with high turnover) confirming the high disease burden demonstrated in most of the previous studies with a variation in the percentages based on the stage of renal impairment, different localities, populations, and criteria used for diagnosis. A study by Choudhary et al found a prevalence of 81.6 % of overall patients with CKD with a prevalence of 63.4%, 76.9%, 87.6%, and 91.3% in patients with stage 3,4,5 and stage 5 on dialysis respectively [11].

Another study assessed the prevalence of MBD in the Nigerian population has found that 58% of the patients had CKD-MBD, with about 31% with a high turnover pattern and 27% with a low turnover pattern [3]. Chuang et. al. estimated the prevalence of MBD in patients with peritoneal dialysis based on either Kidney Disease Outcomes Quality Initiative (KDOQI) or Kidney Disease: Improving Global Outcomes (KDIGO) guidelines. The study found moderate prevalence based on (KDIGO) criteria compared to (KDOQI) (54.7% vs 86% respectively) [12].

Diabetes can affect bone mineral density (BMD) even in the presence of normal kidney function, especially in type 1 patients who seem to have a low bone formation rate compared to healthy control [13]. Although Type 2 diabetes has a less clear relation with BMD, it is associated with increasing the risk of fractures mostly due to causes related to concomitant metabolic derangement associated with disease pathogenesis [14]. As the stage of renal impairment progresses, the risk of MBD increases and bone changes occur in almost all patients with diabetes and CKD [15].

The pattern of MBD in the diabetic group showed no significant difference from non-diabetics in the current research with 23.1% showing high turnover and 30.8% showing low turnover MBD. These results agree with the study by Ray et.al. evaluating the pattern of MBD in diabetic patients with advanced Predialysis CKD. The study has found that adynamic bone disease in diabetes is more prevalent than secondary hyperparathyroidism, especially with advanced stages of CKD [16]. Another study conducted on Brazilian populations with heterogeneous races has found that 39% of patients with low iPTH have diabetes, concurring with low remodeling bone disorders in diabetics [17].

Hyperphosphatemia is observed in most of the studied population in our study regardless of the iPTH levels. It is considered a common finding in CKD patients with increasing prevalence with the advancing CKD stage and in dialysis patients and could be found in association with either high, low, or normal iPTH [18]. Hyperphosphatemia is considered one component of the recent "3Ps" hypothesis for the progression of CKD accompanied by proteinuria and blood pressure [19]. Furthermore, hyperphosphatemia is considered the spark of starting the overall pathogenic process in CKD-MBD in the form of activation of iPTH, FGF23, suppression of calcium and vitamin D with a subsequent cascade of deleterious effects [20].

In the current study, it was observed that most of the patients suffer from vitamin D deficiency with serum levels < 20 ng/ml based on Endocrine Society guidelines [21]. No significant difference was observed regarding the 3 MBD patterns. A previous Indian study by Bansal et al found a prevalence of vitamin D deficiency in about 88.9 % of the studied patients with hemodialysis and about 65% of those patients suffering severe vitamin D deficiency with no correlation with iPTH or the duration of dialysis [22]. Most patients with CKD and ESRD receive an active supplement of vitamin D due to impairment of activation of native form by the diseased kidneys, however, an active conversion of native form to $1,25(OH)_2$ D seems to occur in other tissues such as the prostate, breast, colon, and macrophages [23].

Deficiency of the native form of vitamin D is prevalent even in normal populations and in sunny countries (e.g., Egypt), mostly due to changes in outdoor life activities, covering clothes, and increased awareness of the use of sun-blocking agents during daytime activities [24]. In CKD patients, the presence of native vitamin D deficiency was linked to decreased BMD, increased risk of fractures, and secondary activation of iPTH. Thus, clear recommendations have emerged by KDIGO to achieve a 25OHD level above 30 ng/ml for any stage of CKD [2].

In the current study, total alkaline phosphatase (ALP) was 194.4 ± 83.4, 124.5 ±76.9, and 143.5 ± 96.6 which showed non-significance differences in high, low, and nonbone turnover groups respectively. ALP is used mostly as a complementary marker of bone turnover or an alternative when iPTH is not available, but it is less associated with the pattern of MBD [3]. This is proved by many previous studies that discriminated a mismatch between ALP and iPTH in dialysis patients [25]. On the other side, many previous studies focused on the predictive role of high ALP on overall and cardiovascular mortalities [26].

A comparison of different forms of phosphate binders in the current study revealed a significantly lower phosphate level in the non-CBPB group (in the diabetic group only), with non-significant higher calcium in the CBPB users in all studied groups, and nonsignificant lower levels of iPTH, and ALP with non-CBPB. In the high bone turnover group only significantly lower iPTH levels with non-CBPB.

As hyperphosphatemia is considered the cornerstone of CKD-MBD, the effect of phosphate binders on lowering phosphate levels and the subsequent effect on metabolic parameters were investigated in many previous studies with multiple conflicting results. One example is the study of Udomkarnjananun et al investigated the effect of phosphate binders on bone turnover parameters in hemodialysis patients. The study found no significant difference regarding serum phosphate and iPTH between the 2 groups of phosphate binder users which suggests that the effect of phosphate binders was achieved through the medications themselves and independent of serum iPTH or serum phosphate. The BMD was higher in CBPB users evaluated by dual-energy X-ray absorptiometry (DEXA scan) compared to non-CBPB, also bone turnover markers were higher in the non-CBPB than calcium-based group suggesting the role of non-CBPB in preventing low turnover MBD [27].

A meta-analysis study by Sekercioğlu et al has found that CBPBs are associated with higher mortality in CKD-MBD patients [28]. On the contrary, another meta-analysis conducted on stage 5 CKD on dialysis found that sevelamer can lower all-cause mortality, however, there is no significant benefit of any type of phosphate binder on cardiovascular mortality or other co-morbidities [29].

Another retrospective study on CKD patients with hemodialysis comparing the efficacy and safety of different types of phosphate binders found a significant lowering of phosphorus level, iPTH, and ALP after 3 months of the use of either type of phosphate binders however, CBPB use was associated with probable elevation of serum calcium with subsequent risk of vascular calcifications [30].

In conclusion, CKD-MBD is prevalent in hemodialysis patients with a higher prevalence of low bone turnover compared to high turnover disease. Diabetic CKD patients showed a similar prevalence and pattern of CKD-MBD compared to non-diabetics. Vitamin D deficiency is observed in almost all of the included subjects regardless of the pattern of MBD. Hyperphosphatemia was present also irrespective of the level of iPTH. A comparison of phosphate binders revealed a significantly lower phosphate level with non-CBPB in the diabetic group which is absent in the overall population. A significantly lower iPTH with non-CBPB in the high turnover group. Also, a non-significant higher calcium level was observed in all CBPB users in both diabetics and non-diabetics and all MBD group patterns.

This study has several limitations, such as the small number of the included subjects. Also, we classify the pattern of MBD based on iPTH only, with no information available regarding other parameters of MBD such as the assessment of BMD by DEXA scan, or the use of bone markers such as FGF 23, total procollagen type 1 N-terminal propeptide, bone-specific alkaline phosphatase, and tartrate-resistant acid phosphatase 5b due to

financial restrictions. Furthermore, the included subjects use 2 types of phosphate binders (calcium carbonate and sevelamer) due to the coverage of these 2 types only by insurance and the unavailability of other types of phosphate binders. Finally, due to the observational nature of the study, we can't assess the difference in the biochemical parameters before and after the use of different phosphate binders, thus further prospective studies are needed.

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Ethical approval: the study was approved by an International Review Board (IRB) at Zagazig University (on July 2023/No ZU-IRB # 10944, and the study was performed following the declaration of Helsinki.

Consent to participate: Informed consent was obtained from all individual participants included in the study.

Author contributions: All authors contributed to the study's conception and design. All authors shared in material preparation, data collection, and analysis and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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