Profile and Phenotypes of Chronic Kidney Disease-Mineral and Bone Disorders in Chronic Haemodialysis Patients

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ABSTRACT

Background: Chronic kidney disease-mineral and bone disorder (CKD-MBD) significantly affects haemodialysis patients, impacting prognosis and quality of life. This study examines CKD-MBD profiles and phenotypes to guide intervention strategies.

Methods: We conducted a cross-sectional study at Dr. Soetomo Hospital, Surabaya, from August to October 2023, involving 111 haemodialysis patients. Data collected included demographic characteristics, CKD etiology, nutritional status, and bone mineral markers (calcium, phosphate, parathyroid hormone, and vitamin D3). Statistical analyses are used to assess relationships between bone mineral biochemistry and factors like age, dialysis duration, and diabetes presence.

Results: The study found a balanced gender distribution and median age consistent with global CKD trends. Hypertension was the most common CKD cause (48.6%). The prevalence of high turnover, low turnover, and mixed turnover is 54.95%, 23.42%, and 21.62%, respectively. Longer dialysis duration and absence of diabetes correlated with higher levels of calcium, iPTH, and ALP. Older patients showed significantly lower iPTH and ALP levels.

Conclusions: CKD-MBD in chronic haemodialysis patients shows varied and complex patterns, highlighting the need for personalized treatment approaches.

1. Introduction

Chronic kidney disease (CKD) encompasses a range of conditions characterized by lasting kidney damage or diminished kidney function, specifically an estimated glomerular filtration rate (eGFR) under 60 ml/min/1.73 m² for at least three months, regardless of the underlying cause [1]. Major contributing factors to CKD include type 2 diabetes mellitus, affecting 30% to 50% of cases, and hypertension, responsible for approximately 27.2% [2]. Previous research indicates varying prevalence rates across CKD stages, with stage 1 at 3.5%, stage 2 at 3.9%, stage 3 at 7.6%, stage 4 at 0.4%, and stage 5 (end-stage renal disease) at 0.1% [3]. Globally, an estimated 843.6 million individuals suffer from CKD stages 1 through 5 [4], [5]. For those progressing to ESRD, the primary therapeutic approach is maintenance haemodialysis, though options also include peritoneal dialysis and kidney transplantation [6], [7].

Chronic kidney disease-mineral and bone disorder (CKD-MBD) is a significant complication that arises from CKD, profoundly impacting the prognosis for patients undergoing hemodialysis by substantially increasing the risks of cardiovascular and all-cause mortality [7], [8]. This disorder encompasses a variety of metabolic and bone mineral disturbances, including alterations in calcium, phosphorus, and hormones like parathyroid hormone (PTH) and calcitriol (1.25 (OH) 2D3), often leading to secondary hyperparathyroidism [9]. CKD-MBD significantly worsens both the prognosis and the quality of life for patients [7]. Among individuals undergoing hemolysis, depression is prevalent, and studies have consistently reported a decline in their overall quality of life [10], [11]. It is crucial, therefore, to address CKD-MBD effectively to ensure that patients can maintain a better quality of life and achieve a more favorable prognosis.

Although addressing CKD-MBD is important, traditional diagnostic methods like bone biopsy are invasive and not widely available, especially in developing countries. Similarly, bone mineral density assessments via dual-energy X-ray absorptiometry, while useful, are not universally accessible or economically feasible [12]. Instead, monitoring changes in serum levels of calcium, phosphorus, PTH, and alkaline phosphatase offers a practical

approach for evaluating CKD-MBD. The research on profiling and phenotyping CKD-MBD in chronic hemolysis patients aims to gain insights to guide the prevention and intervention strategies for CKD-MBD in those dependent on long-term hemolysis, helping to identify patient characteristics that may exacerbate the disorder's biochemical markers.

2. Methods

This study employs an observational, analytical approach with a cross-sectional design, which was conducted in Dr. Soetomo Hospital, Surabaya, on August–October 2023. The inclusion criteria for the study are as follows: participants must be aged 18 years or older, have been undergoing hemolysis twice weekly for at least three months, and must provide consent to participate in the study. The exclusion criteria are designed to eliminate potential confounders and include patients who are currently hospitalized for any reason, patients in emergency medical conditions, patients with acute infections, patients with co-existing active malignancies, patients with known primary bone diseases such as osteoporosis or Paget's disease, patients with histories of liver diseases, and patients with dialysis access complications such as infections or thrombosis.

The collected descriptive data encompass gender distribution, age, duration of hemolysis, and the etiologies of CKD, which include hypertension, diabetes mellitus, kidney stones, combinations of these, and other causes like polycystic kidney disease, nephrotic syndrome, or autoimmune disorders. Nutritional assessment is conducted using serum albumin levels and a 7-point Subjective Global Assessment (SGA). The duration of the study was from January 2022 to, categorizing patients as well-nourished or mildly to moderately malnourished [13]. Based on the serum level of iPTH, patients were classified into: 1. Low turnover: iPTH < 150 pg/ml 2. Mixed: iPTH 150-300 pg/ml 3. High turnover > 300 pg/mL. This study also evaluates the phenotypic characteristics of CKD-MBD through comprehensive analyses of calcium, phosphate, and parathyroid hormone levels, assigning patients to specific phenotype groups. Further analysis is aimed at exploring the association between the bone metabolic profile—comprising calcium, phosphate, intact parathyroid hormone (iPTH), vitamin D3, and alkaline phosphatase (ALP)—and demographic factors such as age, hemolysis duration, and the presence of diabetes mellitus. Appropriate statistical analysis was conducted using SPSS 29.0 (IBM Corp., Armonk, NY, USA). Normally distributed data were analyzed with a t-test, and those not normally distributed were analyzed with a Mann-Whitney test.

3. Results and Discussion

The results from our study, involving 111 participants undergoing long-term haemodialysis, and the subjects' characteristics are shown in Table 1.

Table 1. Subjects' characteristics

Characteristics	Statistics (n = 111)
Men/women (%)	57/54 (51.4/46.8)
Age, years (median [IQR])	51 (14)
Haemodialysis duration, months (median [IQR])	50 (64)
CKD etiology	
Hypertension (%)	54 (48.6)
Diabetes mellitus (%)	5 (4.5)
Kidney stones (%)	7 (6.3)
Combination (%)	30 (27.0)
Other (%)	15 (13.5)
Nutritional status	
Albumin, g/dL (mean±SD)	3.89±0.38
Well-nourished (%)	108 (97.3)
Mildly to moderately malnourished (%)	3 (2.7)
Bone mineral markers	
Phosphorus, mg/dL (median [IQR])	5.34 (2.73)
Calcium, mg/dL (median [IQR])	9.00 (1.30)
iPTH, pg/mL (median [IQR])	380.00 (670.20)
Total ALP, u/L (median [IQR]) (n = 95)	142.00 (132.00)
Vitamin D3, ng/mL (median [IQR])	17.00 (12.70)

ALP: alkaline phosphatase; iPTH: intact parathyroid hormone; IQR: interquartile range; SD: standard deviation

We observed a nearly balanced gender distribution (51.4% men and 46.8% women), which contrasts slightly with broader data from a study of 206,374 patients across 12 developed countries, where a higher proportion of men (59%) were receiving hemodialysis. This difference might be reflective of the specific demographics and health care practices within the regions studied [14]. Our participants had a median age of 51 years, aligning

closely with the mean age of 52.76 years reported in Indonesian patients, suggesting that the onset of CKD necessitating haemodialysis occurs predominantly in the early fifties [15]. This age distribution is crucial for planning healthcare resources and interventions, especially in regions with similar demographic profiles.

Hypertension was identified as the most common cause of CKD in our study group, accounting for 48.6% of cases. This is consistent with global findings that highlight hypertension as a significant risk factor for CKD development [3], [5]. In a study conducted in the Japanese general population [16], individuals with hypertension (HT) alone had a hazard ratio (HR) of 1.56, significantly increasing their risk compared to those without HT. Diabetes mellitus (DM) alone presented a lower risk increase (HR of 1.22), but the combination of HT and DM significantly heightened the risk (HR of 2.83). This aligns with our results, where HT was the most common cause of CKD, found in 48.6% of cases, and emphasizes the importance of managing hypertension as a primary intervention point. Our findings also indicated a substantial portion of our cohort (27.0%) suffering from multiple comorbidities, reinforcing that combined HT and DM might drastically amplify CKD risk. Nutritional status among our participants was predominantly good, with 97.3% being well-nourished. This finding is notably better than that reported by Agboton et al. [17], where 36.24% of patients experienced moderate malnutrition. Regarding albumin levels, our study found a mean level of 3.89 g/dL, indicating slight hypoalbuminemia but still better than the >60% of HD patients reported in the DOPPS data with levels below 4.0 g/dL [18]. Albumin levels are a significant concern as they are indicative of nutritional status and are influenced by factors like hyperparathyroidism, which affects albumin homeostasis.

In this study, the median phosphorus level was found to be above the normal range (3.4–4.5 mg/dL [19]), indicating hyperphosphatemia among the participants. The calcium levels, however, remained within the normal range (8.5–10.5 mg/dL [20]). The intact parathyroid hormone (iPTH) levels were significantly elevated (normal levels range from 10 to 65 pg/mL [21]), suggesting the presence of secondary hyperparathyroidism. Additionally, the total alkaline phosphatase (ALP) was slightly higher than usual (20–140 U/L), which could be attributed to increased bone turnover associated with chronic kidney disease-mineral and bone disorder (CKD-MBD), although it could also be influenced by liver function [22]. The study also noted low levels of vitamin D3, indicative of vitamin D insufficiency, a common condition in CKD that can further complicate parathyroid hormone dynamics and overall bone health. According to guidelines from the Endocrine Society, along with the National and International Osteoporosis Foundation and the American Geriatric Society, a vitamin D deficiency is classified when the level of 25-hydroxyvitamin D (25 OH D) falls below 30 ng/mL [23]. The Endocrine Society advises that an optimal concentration of vitamin D should be between 40 and 60 ng/mL [24].

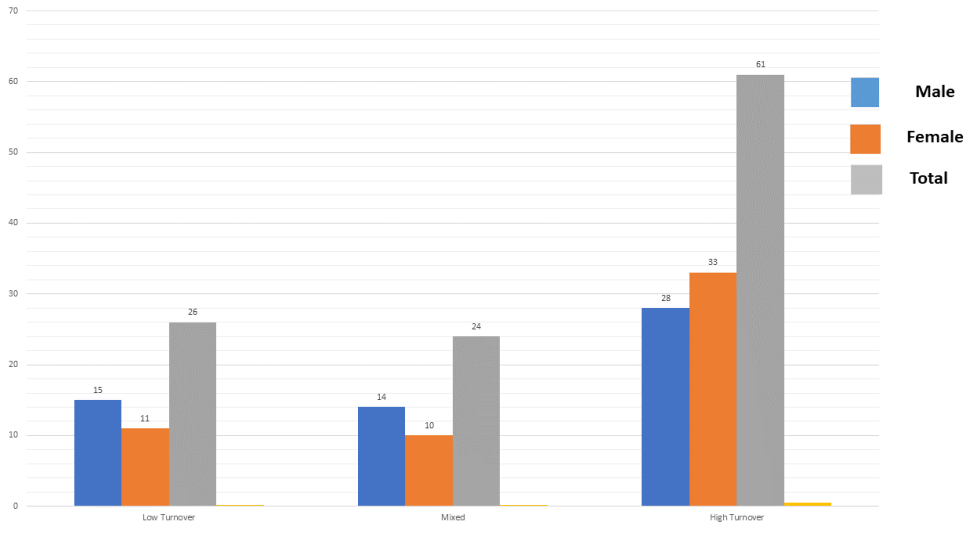

Figure 1. Proportion patients with different forms of CKD-MBD

This study found high turnover (osteitis fibrosa cystica) at 54.95%, low turnover (adynamic bone disease and osteomalacia) at 23.42%, and mixed turnover at 21.62% (Figure 1). This aligns with the findings of Leelavathi et al., who reported a prevalence of high-turnover conditions at 45.45% [25]. Maschio et al. and Stanbury et al. in Santoso et al., indicated that osteomalacia was prevalent in Italy and certain regions of the UK. Conversely, fibrous osteitis was more prevalent in Germany, the Netherlands, and the United States. The various types and

frequency of bone lesions in patients with kidney disease result from a range of dynamic factors that fluctuate annually. Aluminum poisoning (found in osteomalacia and aplastic or adynamic bone disease), diabetes, continuous ambulatory peritoneal dialysis (CAPD), removal of the parathyroid gland, the use of calcium-based phosphate binders, and the availability of vitamin D analogs are some of these [26].

In our analysis, we evaluated the relationship between age and key bone mineral biochemistry parameters in patients undergoing long-term haemodialysis, as outlined in Table 2.

Table 2. Correlation between age and bone mineral markers

Parameters	Age		P
	<60 years old (n = 95)	≥60 years old (n = 16)	
Phosphorus, mg/dL	5.88±2.21	4.76±1.67	0.389
Calcium, mg/dL	8.95±0.93	8.73±0.53	0.282
iPTH, pg/mL	700.99±718.97	480.34±614.32	0.020*
Total ALP, u/L (n = 95)	205.39±197.40	125.23±99.95	0.039*
Vitamin D3, ng/mL	18.31±8.44	18.72±6.08	0.465

ALP: alkaline phosphatase; iPTH: intact parathyroid hormone

Notably, older patients (≥60 years old) demonstrated significantly lower levels of iPTH and total ALP compared to younger patients (<60 years old). The lower iPTH levels in older patients align with findings from previous studies, such as those by Kiss et al. [27], who observed similar trends in a Hungarian dialysis cohort, where serum iPTH was significantly higher in younger patients. This reduction in older patients could be influenced by factors including a heightened inflammatory state or previous treatment regimens involving aluminum-based phosphate binders, which reduce phosphate absorption and consequently, iPTH secretion [27]. Furthermore, significant differences in total ALP levels between age groups in our study are consistent with the literature. For instance, Wu et al. [28] reported that younger patients typically had higher ALP levels, which Yang et al. [29] attributed to greater bone formation capability and increased osteoblastic activity in younger individuals. High ALP might indicate high bone turnover states or dysregulated mineral metabolism, which are key concerns in the management of CKD-MBD [28].

Our study also examined the impact of haemodialysis duration on bone mineral biochemistry parameters, categorizing patients based on whether they had been undergoing dialysis for less than five years or for five years and longer (Table 3).

Table 3. Correlation between haemodialysis duration and bone mineral markers

Parameters	Dialysis duration		P
	<5 years (n = 60)	≥5 years (n = 51)	
Phosphorus, mg/dL	5.62±2.45	5.84±1.85	0.214
Calcium, mg/dL	8.66±0.76	9.17±0.94	0.016*
iPTH, pg/mL	382.78±442.43	964.95±803.48	<0.001*
Total ALP, u/L (n = 95)	145.48±123.79	244.40±228.20	0.002*
Vitamin D3, ng/mL	19.54±8.58	17.17±7.56	0.418

ALP: alkaline phosphatase; iPTH: intact parathyroid hormone

Interestingly, despite recent trends towards managing dialysis patients with lower serum calcium levels through various interventions such as reducing dialysate calcium concentrations, using calcimimetics, switching to less calcaemic vitamin D analogues, and promoting non-calcium-based binders [30], our results indicated an increase in serum calcium levels with longer dialysis duration. This observation could be attributed to several factors. If the dialysate's calcium concentration exceeds that in the patient's blood, calcium diffusion into the bloodstream occurs, which can raise serum calcium levels [31]. This mechanism might be more pronounced in settings where the dialysate calcium is not adjusted to lower levels or individual patient needs. Sustained high levels of iPTH, as evidenced in patients undergoing long-term dialysis (964.95 pg/mL in ≥5 years vs. 382.78 pg/mL in <5 years), can stimulate extensive bone resorption. This process releases calcium from bone stores into the bloodstream, contributing to higher circulating calcium levels. The ongoing high PTH levels suggest that the body's initial response to correct perceived low calcium states becomes a persistent condition, further compounded by the reduced renal response to PTH due to chronic kidney damage [32]. Corresponding with high iPTH levels, elevated ALP levels were noted in long-term dialysis patients (244.40 U/L in ≥5 years vs. 145.48 U/L in <5 years). ALP is involved in bone turnover processes; higher levels indicate increased bone turnover or resorption, which typically accompanies prolonged elevated iPTH levels [33]. This increased bone metabolic activity can also contribute to higher serum calcium. A cut-off of 5 years was chosen as the representative time, which

increased the risk of CKD MBD development in dialysis patients.

The analysis of the influence of diabetes mellitus on bone mineral markers, as detailed in Table 4, demonstrates significant associations between the absence of diabetes and elevated levels of calcium, iPTH, and total ALP.

Table 4. Correlation between diabetes mellitus and bone mineral markers

Parameters	Diabetes mellitus		P
	Present (n = 21)	Absent (n = 90)	
Phosphorus, mg/dL	6.33±2.15	5.62±2.17	0.403
Calcium, mg/dL	8.46±0.49	9.00±0.92	0.039*
iPTH, pg/mL	270.47±256.53	745.86±739.22	<0.001*
Total ALP, u/L (n = 95)	107.20±55.04	210.78±200.32	0.014*
Vitamin D3, ng/mL	18.06±8.01	18.43±8.21	0.886

ALP: alkaline phosphatase; iPTH: intact parathyroid hormone

Our results are consistent with those reported by Schiller et al. [34], who observed significantly lower PTH levels in patients with DM. Poor glycaemic control and elevated levels of advanced glycation end products (AGEs), which suppress parathyroid cell function and inhibit PTH synthesis, are responsible for this reduction in PTH. Chronic hyperglycemia in diabetes exacerbates these effects, negatively impacting osteoblast activity, reducing bone formation, and leading to decreased ALP levels [34]. Conversely, in non-diabetic individuals, the absence of hyperglycemia and AGE-related inhibition allows for more robust PTH secretion, supporting effective calcium and phosphate homeostasis. This includes the activation of vitamin D by PTH, which improves calcium absorption in the intestines and raises serum calcium levels in people who don't have diabetes [34].

Luo et al. [7]had previously demonstrated that health-related quality of life was affected by CKD MBD phenotype. While the KDOQI CKD–MBD guideline had recommended the normocalcemia-normophosphatemia-normoparathyroidism phenotype as the target, Luo observed that the hypoocalcemia-hyperphosphatemia-normoparathyroidism phenotype had better quality of life scores compared to the recommended group. The quality of life of our study subjects would also probably vary.

4. Conclusion

Our study revealed a balanced gender distribution and an age profile consistent with global CKD data, identifying hypertension as the primary CKD cause. The prevalence of high turnover, low turnover, and mixed is 54.95%, 23.42%, and 21.62%. Notably, older patients displayed significantly lower iPTH and ALP levels compared to younger ones. Additionally, longer hemodialysis duration and absence of diabetes were linked to higher levels of calcium, iPTH, and ALP, underscoring the need for personalized management strategies in CKD-MBD.

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