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Phospho-Calcic Phenotypes in Chronic Hemodialysis Patients and Associated Mortality Risk: A Single-Center Retrospective Study

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ABSTRACT

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Background: Mineral and bone disorder (MBD) is a major contributor to cardiovascular mortality in end-stage kidney disease (ESKD). Classifying hemodialysis patients into phospho-calcic phenotypes may help identify those at highest risk.

Methods: A retrospective single-center study of 54 chronic hemodialysis patients at CHU Ibn Rochd (Casablanca), conducted over 12 months (January–December 2023). Patients were classified into 12 groups (36 phenotypes) based on averaged calcium, phosphorus, and PTH levels. Logistic regression was used to assess phenotype-mortality associations.

Results: Mean age was 46.9 years; mean HD vintage 13.31 years. Mean PTH was markedly elevated at 774.9 pg/mL. The largest group (38%) was Group 2 (high PTH, normal calcium, variable phosphorus). Six deaths occurred (11.1%), distributed across six different groups. No statistically significant association was found between phospho-calcic phenotype and mortality.

Conclusion: The limited sample size precluded the detection of a significant phenotype-mortality relationship. Larger multicenter studies are warranted to validate a phenotypic classification approach to MBD-related mortality risk in hemodialysis.

KEYWORDS:

hemodialysis; mineral and bone disorder; phospho-calcic phenotype; PTH; cardiovascular mortality; CKD-MBD.

1. INTRODUCTION

End-stage kidney disease (ESKD) carries a cardiovascular mortality risk 10 to 30 times higher than that of the general population, even after adjustment for age and traditional risk factors [1,2]. While classic cardiovascular risk factors — hypertension, diabetes, dyslipidemia, and left ventricular hypertrophy — are highly prevalent in hemodialysis patients, they fail to fully account for this excess mortality. Over the past two decades, growing evidence has implicated chronic kidney disease–mineral and bone disorder (CKD-MBD) as an independent and modifiable contributor to cardiovascular events and death in this population [3,4].

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CKD-MBD encompasses a triad of biochemical disturbances — elevated phosphorus, dysregulated calcium, and abnormal parathyroid hormone (PTH) — alongside bone disease and vascular calcification. Hyperphosphatemia is associated with endothelial dysfunction, vascular smooth muscle cell osteoblastic transformation, and accelerated arterial calcification [5]. Excess PTH — a hallmark of secondary hyperparathyroidism — exerts direct toxic effects on the myocardium, promotes fibrosis, and is associated with increased all-cause and cardiovascular mortality [6,7]. Hypercalcemia, often iatrogenic in the dialysis setting, further promotes soft-tissue and coronary calcification, particularly when the calcium-phosphorus product is elevated [8].

Despite KDIGO guidelines providing target ranges for each individual biochemical parameter, the clinical reality is that patients rarely present with isolated single-parameter abnormalities. More commonly, they exhibit simultaneous derangements across two or three axes (calcium, phosphorus, PTH), creating distinct "phospho-calcic phenotypes" that may confer differential prognostic

significance. Several observational analyses have attempted to categorize dialysis patients by their combined biochemical profiles, suggesting that phenotypic clustering may be more informative than individual biomarker thresholds alone [9,10].

To our knowledge, few studies from the North African/Maghrebi population have systematically explored the distribution of phospho-calcic phenotypes and their relationship with mortality in hemodialysis. The present study aims to (1) describe the prevalence of distinct phospho-calcic phenotypes in a cohort of chronic hemodialysis patients at a tertiary center in Casablanca, Morocco, and (2) assess the association between these phenotypes and all-cause mortality over a one-year observation period.

2. PATIENTS AND METHODS

2.1 Study Design and Population

This was a single-center, retrospective, descriptive, and analytical study conducted at the Department of Nephrology, Dialysis and Renal Transplantation of CHU Ibn Rochd, Casablanca, Morocco. The study period extended from January 1 to December 31, 2023 (12 months). The study was conducted in accordance with the Declaration of Helsinki. Patient data were anonymized prior to analysis.

Inclusion criteria: All adult patients on chronic hemodialysis who had at least three complete phospho-calcic biochemical assessments during the study period. Each assessment comprised serum calcium, serum phosphorus, and intact PTH, performed at the biochemistry laboratory of CHU Ibn Rochd.

Exclusion criteria: Patients with fewer than three biochemical assessments during the study period, those who initiated hemodialysis within the study period (incident patients), and those with missing clinical data.

2.2 Biochemical Assessments and Phenotypic Classification

For each patient, mean values for calcium, phosphorus, and PTH were calculated across all available assessments during the study period. Patients were then classified according to a pre-defined three-parameter grid, yielding 12 groups (G1–G12), each encompassing three phosphorus sub-phenotypes (high, normal, or low), for a total of 36 distinct phenotypes. Classification thresholds, based on KDIGO 2017 CKD-MBD guidelines and adapted for the local laboratory reference ranges, were defined as follows:

Table 1. Biochemical classification thresholds for phospho-calcic phenotyping.

Parameter	Threshold	Classification
PTH (pg/mL)	0–140	**Low**
PTH (pg/mL)	150–300	**Normal-low**
PTH (pg/mL)	301–600	**Normal-high**
PTH (pg/mL)	> 600	**High**
Phosphorus (mg/L)	< 35	**Low**
Phosphorus (mg/L)	35–55	**Normal**
Phosphorus (mg/L)	> 55	**High**
Calcium (mg/L)	< 84	**Low**
Calcium (mg/L)	84–102	**Normal**
Calcium (mg/L)	> 102	**High**

It should be noted that PTH target ranges in hemodialysis remain a subject of ongoing debate. KDIGO 2017 recommends maintaining PTH between 2 and 9 times the upper limit of normal (ULN) of the assay used, which corresponds approximately to the 150–600 pg/mL range with most second-generation assays. We adopted a four-tier PTH classification (low, normal-low, normal-high, high) to allow greater granularity in phenotypic assignment.

2.3 Outcome Definition

The primary outcome was all-cause mortality occurring during the 12-month study period. Deaths were identified from medical records and dialysis unit registers. Cause of

death was not systematically adjudicated due to the retrospective nature of the study.

2.4 Statistical Analysis

Descriptive statistics were used to characterize the study population. Continuous variables are expressed as mean ± standard deviation; categorical variables as frequency and percentage. Phenotype distribution was described as the proportion of patients in each of the 12 groups. To evaluate the association between phospho-calcic phenotype and mortality, binary logistic regression was performed with death as the dependent variable and phenotypic group as the independent variable. Given the small sample size, no multivariate adjustment was performed. All statistical analyses were conducted using SPSS version 25.0. Statistical significance was set at $p < 0.05$.

3. RESULTS

3.1 Patient Characteristics

Fifty-four patients met the inclusion criteria and were enrolled in the study. Baseline demographic and clinical characteristics are summarized in Table 2. The mean age was 46.9 years, with a male-to-female sex ratio of 1.3. The mean hemodialysis vintage was 13.31 years, reflecting a predominantly long-term dialysis population. Undetermined nephropathy was the leading etiology of ESKD, accounting for 50% of cases — a finding consistent with regional epidemiological data in Morocco, where late nephrology referral often precludes etiological diagnosis [11]. A total of 9.2% of patients had previously undergone parathyroidectomy.

Table 2. Baseline demographic and biochemical characteristics (n = 54).

Characteristic	Value
Total patients, n	**54**
Mean age (years)	**46.9 ± SD**
Sex ratio (M/F)	**1.3**
Mean HD vintage (years)	**13.31 ± SD**
Undetermined nephropathy (%)	**50%**
Prior parathyroidectomy (%)	**9.2%**
Mean calcium (mg/L)	**88.12**
Mean phosphorus (mg/L)	**44.73**
Mean PTH (pg/mL)	**774.9**
Total deaths, n (%)	**6 (11.1%)**

Biochemically, the mean serum calcium was 88.12 mg/L (within the normal range of 84–102 mg/L), the mean serum phosphorus was 44.73 mg/L (within normal range of 35–55 mg/L), and the mean PTH was markedly elevated at 774.9 pg/mL — well above the KDIGO upper target of 600 pg/mL. This suggests a high burden of severe secondary hyperparathyroidism in this cohort.

3.2 Phenotypic Distribution

Patients were distributed across 12 phenotypic groups as described in Table 3. The most prevalent group was Group 2 (G2), comprising 38% of all patients. G2 is defined by high PTH, normal calcium, and variable phosphorus (high, normal, or low). This phenotype is consistent with poorly controlled secondary hyperparathyroidism in the setting of adequate phosphate and calcium management — a pattern reflective of the clinical challenge of achieving simultaneous PTH control without inducing hypercalcemia.

Table 3. Distribution of 12 phenotypic groups by PTH, calcium, and phosphorus status.
N = normal; H = high; N-H = normal-high; N-L = normal-low; B = low.

Group	PTH	Ca	Ph	Group	PTH	Ca	Ph
G1	High	High	*High/N/Low*	**G7**	N-Low	High	*High/N/Low*
G2	High	Normal	*High/N/Low*	**G8**	N-Low	Normal	*High/N/Low*

G3	High	Low	*High/N/Low*	**G9**	N-Low	Low	*High/N/Low*
G4	N-High	High	*High/N/Low*	**G10**	Low	High	*High/N/Low*
G5	N-High	Normal	*High/N/Low*	**G11**	Low	Normal	*High/N/Low*
G6	N-High	Low	*High/N/Low*	**G12**	Low	Low	*High/N/Low*

3.3 Mortality and Phenotype-Mortality Association

Six deaths were recorded during the study period, corresponding to a one-year all-cause mortality prevalence of 11.1%. The six deceased patients were distributed across six distinct phenotypic groups, with no single group showing clustering of deaths. Logistic regression analysis did not identify any statistically significant association between phospho-calcic phenotype and all-cause mortality ($p > 0.05$ for all group comparisons). The small number of events ($n = 6$) and the broad distribution of deaths across groups fundamentally limited the statistical power of this analysis.

4. DISCUSSION

This study represents, to our knowledge, the first attempt to systematically classify hemodialysis patients from a Moroccan tertiary center into comprehensive phospho-calcic phenotypes and to assess their relationship with mortality. While no statistically significant phenotype-mortality association was identified, the study provides important descriptive data on the CKD-MBD landscape in this population and highlights the feasibility and potential value of a phenotypic classification approach.

4.1 The Case for Phenotypic Classification

The management of CKD-MBD in dialysis has traditionally relied on sequential optimization of individual biochemical targets — phosphate control, calcium correction, and PTH suppression — guided by KDIGO and KDOQI recommendations [3,12]. However, this siloed approach fails to capture the interactions between these parameters. As Karaboyas et al. demonstrated in the DOPPS study, simultaneous consideration of calcium, phosphorus, and PTH categories yields more nuanced mortality risk stratification than any single parameter alone [9]. Similarly, Floege et al., in the ARO multinational study, showed that mortality risk peaks in the quintiles of both very low and very high PTH, reinforcing the concept of a "U-shaped" relationship that a simple "PTH in range/out of range" classification would miss [10].

The phenotypic approach adopted in our study — creating a 3×3×4 classification matrix — is consistent with this paradigm shift toward integrated biomarker profiling. By defining 12 groups (each with three phosphorus sub-phenotypes), we aimed to capture clinically meaningful combinations, such as the high-PTH/normal-calcium profile of Group 2 (the dominant phenotype in our cohort), which differs prognostically from the high-PTH/high-calcium/high-phosphorus profile of Group 1, even though both represent forms of poorly controlled CKD-MBD.

4.2 Prevalence of Secondary Hyperparathyroidism

The mean PTH of 774.9 pg/mL in our cohort is strikingly elevated and deserves specific comment. KDIGO 2017 recommends a target PTH of 2–9 times the ULN (approximately 150–600 pg/mL for most second-generation intact PTH assays) [3]. A mean of 774.9 pg/mL suggests that a substantial proportion of patients had PTH values well above the upper target. This level of secondary hyperparathyroidism is not atypical in low- and middle-income country dialysis settings, where access to cinacalcet, active vitamin D analogs, and parathyroidectomy may be constrained by cost or availability [13]. The 9.2% parathyroidectomy rate in our cohort further reflects this context — in some high-resource settings, surgical rates for refractory hyperparathyroidism can reach 15–20% in long-vintage dialysis populations [14].

Importantly, the long mean dialysis vintage of 13.31 years in our cohort may itself contribute to the elevated PTH levels. Progressive parathyroid gland hyperplasia over years of uremic stimulus results in nodular transformation and autonomous ("tertiary") hyperparathyroidism, which is increasingly refractory to medical therapy and associated with higher mortality [15].

4.3 Interpretation of Null Findings

The absence of a statistically significant phenotype-mortality association in our study should be interpreted cautiously and not construed as evidence of no relationship. Several factors limit the interpretability of this negative result. First, the sample size of 54 patients with only six deaths provides minimal statistical power — a well-designed study to detect a moderate association (OR ~2.5) between phenotype and mortality with 80% power and a baseline mortality of ~10% would require several hundred patients. Second, the one-year observation window may be too short to capture the full impact of phospho-calcic disturbances on cardiovascular mortality, which typically accumulates over years of sustained biochemical derangement. Third, the retrospective use of mean biochemical values, while practical, does not capture longitudinal variability or the duration of time spent in each phenotypic state — factors that emerging evidence suggests may be critical [16].

4.4 Strengths and Limitations

The strengths of this study include its systematic phenotypic classification approach, the use of a real-world dialysis cohort with long HD vintage, and its originality in the North African clinical context. Limitations include the small single-center sample, the retrospective design with its inherent selection and information biases, the absence of cause-specific mortality data, and the inability to account for important confounders such as dialysis adequacy (Kt/V), nutritional status, comorbidity burden (CCI score), inflammatory markers (CRP), and medication use (phosphate binders, vitamin D analogs, calcimimetics). Future studies should incorporate these variables in a multivariate framework.

5. CONCLUSION

This study presents a novel phenotypic classification of CKD-MBD in chronic hemodialysis patients at a Moroccan tertiary center, characterized by a high prevalence of severe secondary hyperparathyroidism. While no statistically significant association between phospho-calcic phenotype and one-year mortality was demonstrated — likely due to limited sample size — the phenotypic framework developed here provides a conceptually robust foundation for future investigation. Multicenter prospective studies with larger sample sizes, longer follow-up, and comprehensive adjustment for confounders are needed to validate the prognostic utility of phospho-calcic phenotyping in hemodialysis and to guide individualized CKD-MBD management strategies.

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Conflicts of Interest

The authors declare no conflicts of interest.

Ethical Approval

This study was conducted in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments. Patient data were anonymized prior to analysis.

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