

# Hyperphosphatemia in Dialysis Patients National Multicenter Study

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## Abstract

**Introduction:** Hyperphosphatemia (HPFT) is a complication that is exacerbated proportionally to the degree of kidney damage, and leads to vascular calcification and increased cardiovascular risk. The objective of the present study is to determine the frequency of hyperphosphatemia in patients with chronic dialysis treatment.

**Material and methods:** This is a cross-sectional, observational, retrospective and analytical study. Real-life national multicenter study, conducted from January 1 to March 31, 2022. It includes subjects with chronic dialysis (>3 months stay), >16 years, from the public and private sectors. Does not include patients treated with phosphate binders or vitamin D receptor analogs; only treated with calcium derivatives in different formulations. Gender, age, causes of kidney failure, serum phosphorus values (mg/dL), calcium (mg/dL) and parathyroid hormone (pg/mL) are identified.

**Results:** 2,176 subjects, 1,205 from the public sector (55%) and 971 private (45%). 1,063 (49%) male and 1,113 female (51%), with a mean age of 51.4 years (range 16-88). 794 with diabetes (36%), 559 arterial hypertension (26%) and 823 unknown (38%). The mean serum calcium values were 8.75 mg/dL (SD  $\pm$  1.01; range: 6.1-12.7) and phosphorus 5.15 mg/dL (SD  $\pm$  3.04; range: 2.5-18.1). 1,435 subjects presented HPFT (66%), 903 mild (41%), 450 moderate (21%, mean 5.7 mg/dL) and 82 severe (4%, mean: 9.2 mg/dL). Parathyroid hormone was determined in 33% (mean 614.87 pg/mL, SD 628.64; range: 53.3-3,803).

**Conclusions:** HPFT is frequent in patients with chronic dialysis, it affects regardless of gender, age, primary cause of kidney disease and even after receiving adequate dialysis treatment. Significant increase in HPFT was observed in peritoneal dialysis patients.

**Keywords:** Epidemiology; Chronic kidney disease; Dialysis; Hyperphosphatemia; Sevelamer; Cardiovascular risk

## Introduction

Chronic Kidney Disease (CKD) represents the outcome of various metabolic and hypertensive disorders that mainly affect the adult population [1], evolves progressively and disabling, mortality is increased by the associated cardiovascular risk. [2] The epidemiological data of CKD in each report exceed previous figures, thus in 2017 the global prevalence was estimated at 9.1% (8.5-9.8%),

with some 700 million affected subjects; in 2019 of 11%, with 850 million and currently, it is estimated at 13.4% (11.7-15.1%), with the existence of one billion cases; and the number of dialysis patients ranges from 4.9 to 7 million. [3,4]. Derived from the renal tubular inability to eliminate phosphorus, hyperphosphatemia (HPFT) becomes a frequent complication, which is expressed proportionally to the degree of kidney damage, also affecting the normal behavior of calcium and parathyroid hormone (PTH). These alterations are

included in a set of biochemical and clinical variants in the term Mineral and Bone Metabolism Disorders, where calcium, phosphorus, vitamin D and parathyroid hormone participate together; which converge and lead to develop predominantly vascular and musculoskeletal disorders characterized by calcium deposits in the vascular middle layer [5]. In the pathophysiology of HPFT, phosphorus stimulates the production of PTH and fibroblast growth factor 23 (FGF23), promoting the excretion of phosphorus in the urine; however, renal synthesis of vitamin D is also suppressed, causing decreased absorption of intestinal calcium and phosphorus, parathyroid overstimulation and a vicious circle given by the triad hyperphosphatemia, hypocalcemia and hyperparathyroidism. In addition to the mineral and bone metabolism disorders that HPFT causes, it also participates in other biochemical alterations of chronic kidney disease, for example, HPFT, is the second cause of resistance to erythropoietic agents and perpetuates the degree of anemia [6].

## Material and Methods

### Type of study

This is a cross-sectional, observational, retrospective and analytical study. Real-life national multicenter study.

### Site and study period

Includes public and private sector hospitals that perform dialysis therapies. The participating medical units were Nephrology Service of the La Raza Medical Center Specialty Hospital of the Mexican Social Security Institute, Mexico City. Nephrology Service Hospital Civil Guadalajara, University Center for Health Sciences and Pharmaceutical PiSA, SANEFRO, México. IGSA Medical Services Hemodialysis Unit Río Verde, San Luis Potosí, México. Health University of México City. Department of Nephrology and Renal Transplantation of the High Specialty Medical Unit of Western National Medical Center, Guadalajara Jalisco, México; Emergency Service General Hospital of Zone 2-A Troncoso, Mexican Social Security Institute, México City. Clinical Coordination of Peritoneal Dialysis General Hospital of Mexico Dr. Eduardo Liceaga, Mexico City and various medical offices for private medical care. Data were collected from January 1 to March 31, 2022.

**Inclusion criteria:** Patients with chronic dialysis (peritoneal modality or hemodialysis, stay >3 months), >16 years of age. Hemodialysis was of high efficiency (minimum 3 hours of treatment, 3 times a week and use of a high-flux dialyzing membrane, minimum Kt/V of 1.2); in peritoneal dialysis, automated dialysis (10 to 12 liters/day) and continuous ambulatory (8 liters/day) modalities were included.

**Non-inclusion criteria:** Not include patients treated with phosphate binders or vitamin D receptor analogs; only treated with calcium derivatives in different formulations, <16 years of age, history of parathyroidectomy.

**Elimination criteria:** Patients with phosphorus value <2.5 mg/dL.

### Sample size

Obtained for convenience.

### Study variables

Gender, age, presence of diabetes, arterial hypertension or unknown causes, serum values of creatinine (mg/dL), calcium (mg/dL), phosphorus (mg/dL), parathyroid hormone (pg/mL), Kt/V.

## Classification of hyperphosphatemia

Normal value: 2.5 to 4.4 mg/dL; mild hyperphosphatemia: 4.5 to <7.5 mg/dL; moderate hyperphosphatemia: 7.5 to <9.0 mg/dL; severe hyperphosphatemia >9 mg/dL.

### Data analysis

Descriptive statistical measures were applied, the difference of two independent means were obtained, the t test was applied, accepting a value of  $p < 0.05$  for statistical significance at a confidence interval of 95%.

## Results

2,176 subjects were included, 1,063 (49%) male, 1,113 female (51%), with a mean age of 51.4 years (range: 16-88). 794 with diabetes mellitus (36%), 559 arterial hypertension (26%) and unknown 823 (38%). 1,205 from the public sector (55%) and 971 private (45%) (Table 1).

The mean serum values for calcium were 8.75 mg/dL (SD  $\pm$  1.01, range 6.2-12.7) and for phosphorus 5.15 mg/dL Mild HPFT was found in 903 cases (41%), moderate in 450 (21%) and severe in 82 (4%) (Figure 1). Parathyroid hormone was determined in 33% of the patients, the mean values were 614.87 pg/mL (SD 628.64, range: 53.3-3,803) (Figure 2).

Phosphorus values according to the cause of kidney disease were in diabetes 5.27 mg/dL (range: 2.5-9.29), in hypertension 5.04 mg/dL (range: 2.5-18.1) and in unknown causes 5.09 mg/dL (range: 2.5-11.8).

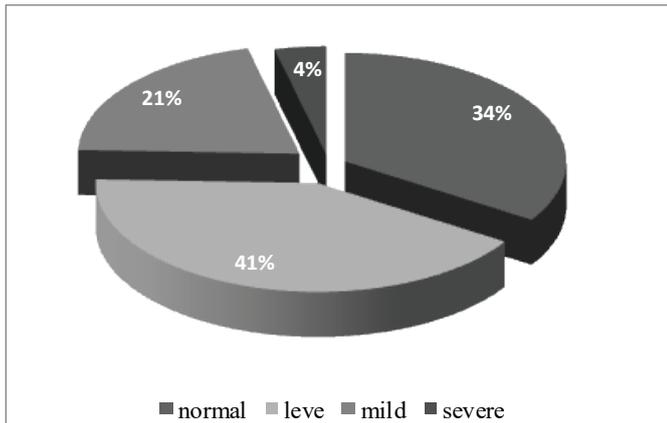
According to the dialytic modality, the phosphorus values were 5.57 mg/dL in peritoneal dialysis (SD: 3.05, range: 2.5-17.6) and 4.98 mg/dL in hemodialysis (SD: 3.07, range: 2.5-18.1);  $p < 0.0014$  (Table 2).

## Discussion

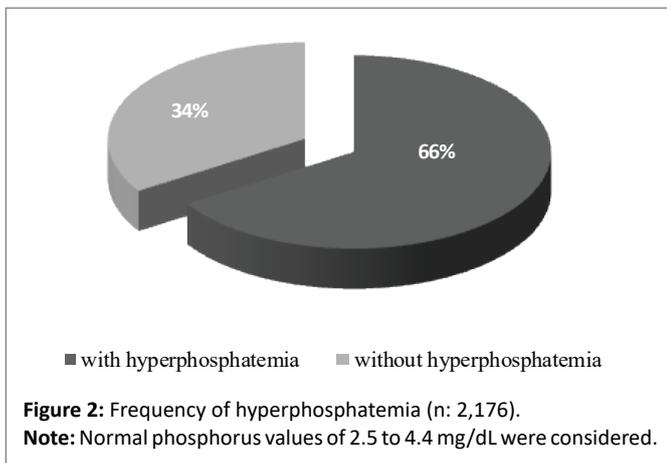
More than a decade after it was shown that both high and low serum levels of phosphorus, calcium and PTH are associated with an increased risk of mortality, as well as the direct relationship of risk with the highest concentration, the therapeutic is not fully known. Up to 50% of deaths in chronic kidney disease are attributed to cardiovascular causes, being the coronary disease the first place. Other series have found coronary calcification in more than 90% of cases in patients receiving dialysis; however, the calcification process is also observed in peripheral arteries, which constitutes a multisystem pathophysiological process [7,8]. In 2003, the Kidney Disease Outcomes Quality Initiative (K/DOQI) Clinical Practice Guideline recommended maintaining phosphorus between 3.5 and 5.5 mg/dL

**Table 1:** General characteristics of the population.

Variable	Value
Male	1,063 (49%)
Female	1,113 (51%)
Average age (years)	51.4 (range: 16-88)
Mellitus diabetes	794 (26%)
Arterial hypertension	559 (24%)
unknown	823 (50%)
Public sector	1,205 (55%)
Private sector	971 (45%)
Calcium (mg/dL)	8,75 (DS+1.01; range: 6,1-12,7)
Phosphorous (mg/dL)	5,15 (DS+3.04; range: 2.5-18,1)
Parathyroid hormone (pg/mL)	614.87 pg/mL (DS 628.64; range: 53.3-3,803)



**Figure 1:** Degree of hyperphosphatemia (n: 2,176).  
**Note:** Phosphorous values: 2.5 to 4.4 mg/dL, normal; 4.5 to <7.5 mg/dL, leve hyperphosphatemia, 7.5 to <9.0 mg/dL, mild hyperphosphatemia and >9 mg/dL, severe hyperphosphatemia.



**Figure 2:** Frequency of hyperphosphatemia (n: 2,176).  
**Note:** Normal phosphorus values of 2.5 to 4.4 mg/dL were considered.

in dialysis patients, calcium-corrected albumin between 8.4 and 9.5 mg/dL and PTH values between 150 and 300 pg/mL [9-11]. This study allowed us to identify that the frequency of mild HPFT affected the largest number of patients and that the phosphorus values found in this series are similar to those described in most reports in the literature, unlike of PTH that observed higher values. In the generation of HPFT, nutritional advice and support in chronic treatment have a decisive role. Periodic evaluation of nutritional status allows the patient to properly select foods with lower content of elements that harm their health and contribute to reducing the serum level of phosphorus and maintaining control, which will lead to a reduction in the risk of complications, hospital expenses and improve survival rates. Unfortunately, in México, obesity represents a highly prevalent disorder, which is a consequence of the eating disorder that affects them, which does not exempt kidney patients. This public health problem requires effective strategies to help reduce the prevalence of associated metabolic and hypertensive diseases [12,13]. Changes in lifestyle and diet transgression in the general population and in the population receiving dialysis, contribute decisively to increase the levels of phosphorus, sodium and potassium, which definitely expedite vascular damage and increase cardiovascular risk [14,15].

Disorders of mineral and bone metabolism are still issues with great opportunity to be approached by the specialist and by the

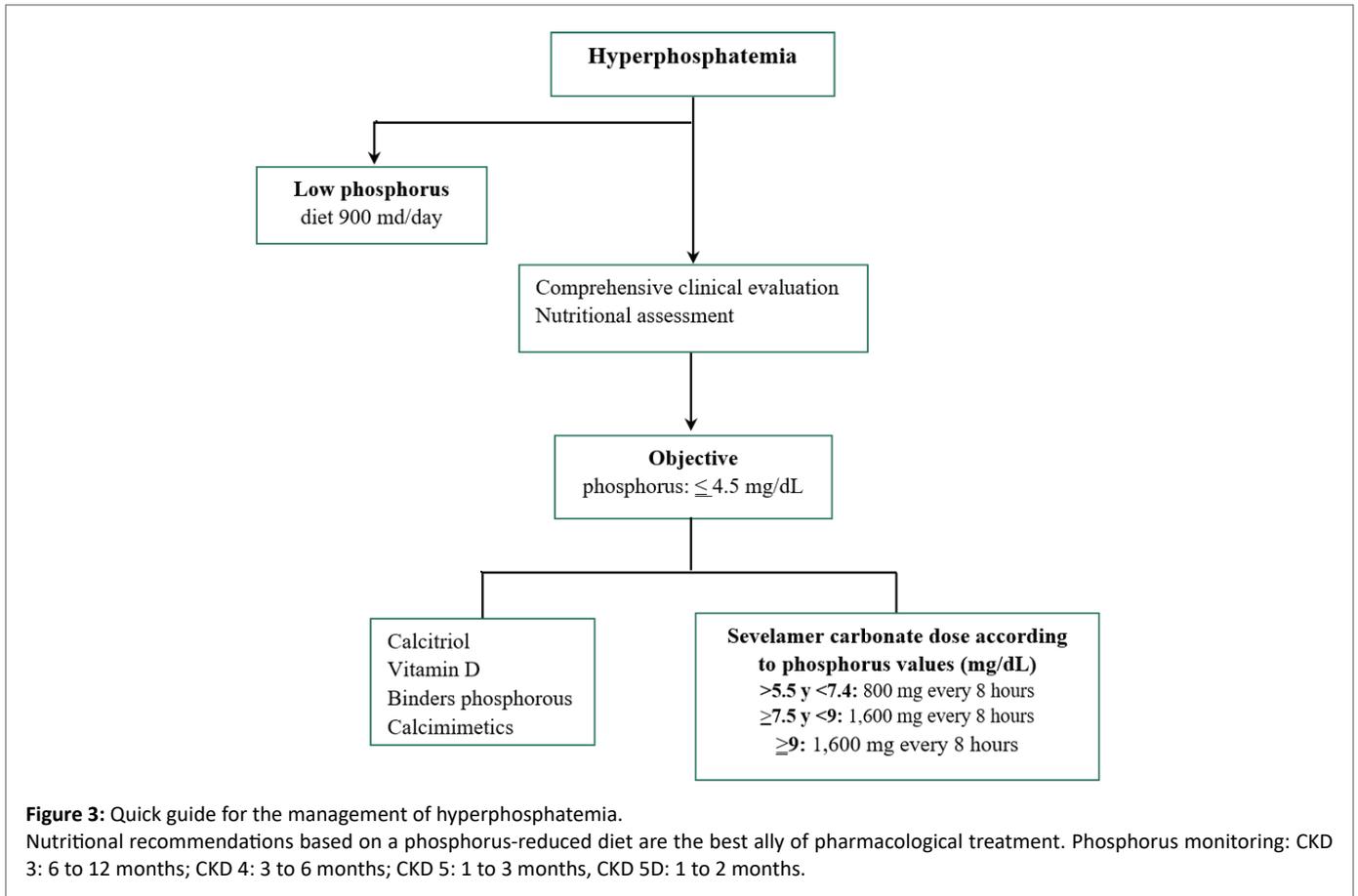
**Table 2:** Phosphorus values (mg/dL) according to cause of CKD and age group-range.

Variable	Values	p
<b>Causes</b>		
Diabetes	5.27 mg/dL (range: 2.5-9.29)	ns
Arterial hypertension	5.04 mg/dl (range: 2.5-18.1)	
Unknown	5.09 mg/dL (range: 2.5-11.8)	
<b>Dialysis modality</b>		
Peritoneal Dialysis	5.57 mg/dL (DS: 3.05, range: 2.5-17.6)	p <0.0014
Hemodialysis	4.98 mg/dL (DS: 3.07, range: 2.5-18.1)	

Statistical estimate: difference of two independent means, test t: 208, IC 95%, p<0.05.

multidisciplinary team; the identification of cardiovascular problems is usually detected late, when the relevance of the complication becomes important. [16-18]. The diagnostic and therapeutic inertia in mineral metabolism disorders and particularly in the identification of HPFT is due to multiple factors. Emphasizing the lack of knowledge of the alteration, the late presentation of its manifestations that are generally not clinically identified, the asymptomatic course of the pathophysiological process, the lack of supplies to perform serum biochemical determinations of calcium, phosphorus, albumin and parathyroid hormone, the lack of specific medications to combat HPFT and HPPT [19]; among others. As well of a normative or institutional nature, as is the case in Mexico where the Official Norm for the Practice of Hemodialysis, being an official document, does not contemplate the determination of blood markers that allows the identification of mineral and bone metabolism disorders [20]. Current evidence shows that hyperphosphatemia is directly proportional to the degree of kidney damage, which is given by the own loss of renal mass and tubular incapacity for the reabsorption of phosphorus; and that the and that phosphate binders such as sevelamer carbonate are of greater benefit, by allowing elimination through the digestive tract, which occurs both in advanced stages of kidney damage and in patients undergoing dialysis treatment [9,21]. Figure 3 Mineral metabolism disorders are associated with the development of heart valve disease, with prevalence from 20 to 59% of aortic, mitral valve disease or both; they include hypercalcemia, hyperphosphatemia, hypomagnesemia, metabolic alkalosis, hyperparathyroidism, increased trophoblastic growth factor 23, as well as decreased levels of the co-receptor klotho [22,23]. HPFT generates arterial hypertension, which is caused by increased activity of the sympathetic nervous system, augmented serum renin level, acute dysfunction of the endothelium, incremented expression of endothelin 1, decreased expression of the protein khloto and deterioration of renal function itself. Khloto is a trans membrane protein that is expressed in the kidney and other tissues and acts as a co-receptor for FG 23 [24]. HPFT also contributes to the increase in oxidative stress, the release of proinflammatory cytokines, alterations in the regulation of osteogenic transcription factor, decreased fetuin A, alpha-khloto deficiency and extracellular matrix remodeling are factors related to atherosclerosis and the ventricular growth [25-27].

There is sufficient evidence to demonstrate the direct relationship between serum phosphorus concentration and the onset of the pathophysiological process of vascular calcification and increased cardiovascular risk, as well as the benefit of different calcium and non-calcium drugs used to control hyperphosphatemia, which are usually higher after the use of sevelamer carbonate [28,29]. This real-world study was able to identify the frequency of hyperphosphatemia in



patients receiving hemodialysis in both public and private healthcare settings and has provided different opportunities for improvement to be applied to patients in order to interrupt the pathophysiological cascade of hyperphosphatemia. Risk and death of cardiovascular origin, where the reduction of phosphorus in the diet plays a determining role in the control of phosphatemia; on the other hand, phosphorus control and hyperphosphatemia have a favorable effect on reducing anemia, vascular calcification, atherogenesis, and endothelial dysfunction; consequently, improve rate survival [30].

### Conclusion

HPFT is frequent in patients with chronic dialysis, it affects regardless of gender, age, primary cause of kidney disease and even after receiving adequate dialysis treatment. Significant increase in HPFT was observed in peritoneal dialysis patients. The biochemical detection of mineral metabolism disorders represents a great opportunity to reduce cardiovascular risk in patients with chronic dialysis.

### Study Limitations

This is a real-life study, where a single measurement of the variables is made, the nutritional aspect, adherence to diet recommendations or adherence by the patient was not explored.

### Ethical Responsibilities

Protection of people and animals. The authors declare that no experiments have been performed on humans or animals for this research.

### Interest Conflict

The authors declare that there is no conflict of interest.

### Author's Contributions

All authors participated in the clinical study design, data collection, processing, reading the manuscript and agreed to the submission of the final version. The analysis of the data was performed by a statistical engineer; and the writing of the final manuscript and publication project by the research leader.

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