

Management of Calcium and Phosphorus Metabolism in Hemodialysis Patients in Tehran Province, Iran

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Keywords: bone metabolism,
chronic kidney disease,
calcium, phosphorus,
parathyroid, hemodialysis

Introduction. Our aim was to evaluate the degree of achievement of the recommended values in National Kidney Foundation Dialysis Outcomes Quality Initiative (K/DOQI) guidelines for the laboratory indicators of bone metabolism in patients undergoing hemodialysis (HD) in Tehran province.

Materials and Methods. We evaluated the laboratory information of 2630 HD patients in Tehran province. Demographic data of the patients and the clinical information including the duration of dialysis session, dialysate calcium concentration, Kt/V, and serum values of calcium, phosphorus, and intact parathyroid hormone (PTH) were recorded. The laboratory values were compared to the recommended ranges by the K/DOQI work group in patients with end-stage renal disease.

Results. Only 1.8% of the patients could enjoy a successful management according to the K/DOQI recommendations for the 4 target laboratory tests of serum calcium, phosphorus, intact parathyroid hormone, and calcium-phosphorus product. Hypocalcemia was diagnosed in 33.2% of the patients, whereas 13.6% were diagnosed with hypercalcemia. Hypophosphatemia and secondary hyperparathyroidism were diagnosed in 6.8% and 24.2% of the patients, respectively.

Conclusions. Our findings proved that complying with the recommendations established by the K/DOQI work group in the clinical management of mineral metabolism is very demanding. Phosphate binders frequently lead to untoward toxicities and imbalance in bone metabolism of patients on HD, warranting new cost-effective therapies with fewer side effects. It would be of great interest to analyze, in the future, the benefits derived from the effect of new therapies such as calcimimetics or new phosphate binders regarding the achievement of the K/DOQI guidelines.

IJKD 2007;1:25-8
www.ijkd.org

INTRODUCTION

Chronic kidney disease (CKD) is accompanied by profound disturbances in calcium, phosphate, vitamin D, and intact parathyroid hormone (PTH) homeostasis that play a crucial role in the pathophysiology of renal bone disease. Despite

remarkable advances in the technical ability to provide maintenance dialysis, the mortality rate of patients on long-term dialysis has remained unacceptably high and not significantly improved over the past decade. The control of phosphorus and calcium metabolism is one of the objectives

in an adequate dialysis protocol. Treatment of renal osteodystrophy is essential for prevention of musculoskeletal disorders and cardiovascular calcifications, and ultimately for reduction of morbidity and mortality rates in patients with end-stage renal disease (ESRD).¹⁻³

The pathogenesis of bone metabolism disorders in ESRD is complicated and of multifactorial origin. In 2003, the National Kidney Foundation Dialysis Outcomes Quality Initiative (K/DOQI) guidelines were published, recommending serum levels of phosphorus between 3.5 mg/dL and 5.5 mg/dL; serum calcium, between 8.4 mg/dL and 9.5 mg/dL; calcium-phosphorus product, less than 55 mg²/dL²; and serum intact PTH, between 150 pg/mL and 300 pg/mL.⁴ The objective of this study was to determine the degree of achievement of the recommended limits established in the K/DOQI guidelines for bone metabolism in patients undergoing hemodialysis (HD) in Tehran province.

MATERIALS AND METHODS

As a routine, all patients receiving HD undergo monthly laboratory assessments in the country. In a cross-sectional study, we evaluated the laboratory information of the patients in Tehran province (with 13.5 million inhabitants). In December 2005, an investigation was performed including the entire HD population (2630 patients) from 56 dialysis units. The data were collected on a form specifically designed for the study. The considered variables were the demographic data of the patients and the clinical information including the duration of dialysis session, dialysate calcium concentration, KT/V, and serum values of calcium, phosphorus, and intact PTH.

Results of the descriptive statistical analyses were shown as proportional frequencies and means ± standard deviations, where appropriate.

RESULTS

Table 1 shows the characteristics of the 2630 patients on HD in Tehran province. The mean duration of dialysis sessions was 3.90 ± 0.29 hours. The mean Kt/V, a measure of dialysis adequacy, was 0.97 ± 0.25. The mean values for serum calcium, phosphorus, and PTH, as well as the recommended ranges by the K/DOQI work group are presented in Table 2. Dialysate calcium concentration was 2.5 mEq/L.

Table 1. Demographic and Clinical Characteristics of Patients on Hemodialysis in Tehran Province in December 2005*

Characteristic	Value
Mean age (range), y	53.4 ± 17.1 (6 to 90)
Sex	
Male	1505 (57.2)
Female	1125 (42.8)
Illiterate patients	737 (28.0)
ESRD etiology	
Diabetic nephropathy and hypertension	1567 (59.6)
Chronic glomerulopathies	224 (8.5)
Adult renal polycystic kidney disease	114 (4.3)
Urologic diseases	113 (4.3)
Congenital diseases	53 (2.0)
Unknown and other etiologies	559 (21.3)
Dialysis duration, mo	51.1 ± 58.7 (2 to 336)
Dialysis sessions per week	
3	2376 (90.3)
2	236 (9.0)
1	18 (0.7)

*Values in parentheses are percents unless otherwise indicated. ESRD indicates end-stage renal disease.

Table 2. Laboratory Tests Results in Patients on Hemodialysis in Comparison With K/DOQI Target Ranges*

Factor	Value
Phosphorous, mg/dL	
Mean (range)	5.43 ± 1.51 (1.7 to 10.9)
K/DOQI ranges	
< 3.5	149 (6.8)
3.5 to 5.5	1141 (52.2)
> 5.5	896 (41.0)
Calcium, mg/dL	
Mean (range)	8.98 ± 1.23 (3.1 to 14.4)
K/DOQI ranges	
< 8.5	731 (33.2)
8.5 to 10.2	1170 (53.2)
> 10.2	300 (13.6)
Calcium-phosphorus product, mg ² /dL ²	
Mean (range)	48.70 ± 14.89 (11.2 to 129.6)
K/DOQI ranges	
< 55	1548 (75.1)
> 72	167 (7.8)
Intact PTH, pg/mL	
Mean (range)	205.52 ± 190.21 (7.0 to 992.0)
K/DOQI ranges	
< 150	240 (48.1)
150 to 300	138 (27.7)
> 300	121 (24.2)

*Values in parentheses are percents unless otherwise indicated. K/DOQI indicates the National Kidney Foundation Dialysis Outcomes Quality Initiative; and PTH, parathyroid hormone.

Only 1.8% of the patients could enjoy a successful management according to the K/DOQI recommendations for the 4 target laboratory tests

(Table 3). Hypocalcemia (serum calcium < 8.4 mg/dL) was diagnosed in 33.2% of the patients, whereas 13.6% were diagnosed with hypercalcemia (serum calcium >10.2 mg/dL). Hypophosphatemia (serum phosphorous < 3.5 mg/dL) and secondary hyperparathyroidism (serum intact PTH > 300 pg/mL) were diagnosed in 6.8% and 24.2% of the patients, respectively.

Table 3. Achievement of K/DOQI Guideline Targets for Mineral Metabolism

Status	Patients (%)
None of the targets achieved	64 (2.4)
At least one target achieved	1881 (96.7)
At least two targets achieved	1288 (75.0)
At least three targets achieved	526 (34.2)
All four targets achieved	34 (1.8)

DISCUSSION

This study illustrated the difficulty in the management of calcium and phosphorus metabolism, and showed that less than 2% and 35% of the population achieved all the 4 or 3 K/DOQI guideline targets for the laboratory tests, respectively (Table 3). It is worth pointing out that other published studies on the subject have proved the failure to comply with the guideline, too.⁵⁻⁸ Data from the International Dialysis and Practice Patterns Study (DOPPS),⁶ which included 8611 and 6864 patients studied in 2001 and 2004, showed that only 4.6% and 5.5% of patients, respectively, achieved all the 4 goals of the K/DOQI for mineral metabolism. Yokoyama and colleagues observed that 9% of the 1341 Japanese patients enjoyed all the 4 targets.⁷ In their well designed study, Maduell and associates highlighted that 7.3% (out of 2392 dialysis patients) achieved all the targets.⁵

The strict maintenance of serum calcium and phosphorus levels within the ranges recommended by the K/DOQI guidelines is difficult to achieve due to multifactorial reasons. Two main obstacles are the patient's noncompliance and the use of phosphate binders that contain calcium.^{1,3,5,6}

Based on the national protocol, calcium carbonate is administered as the phosphate binder and calcitriol as the active vitamin D for patients on maintenance dialysis in Iran. Other specific drugs for calcium and phosphorus management are not covered by the insurance companies because of the budget limitations.

Hyperphosphatemia is one of the major factors responsible for alterations in mineral and bone metabolism in dialysis patients. In our study, the control of serum phosphorus values was adequate in 52% of patients, while 41% of the patients presented with hyperphosphatemia. These findings are not better than those published in the DOPPS; they showed that fewer than 50% of patients met the target value for serum phosphorus and this proportion had not changed substantially since 1999.^{3,6} The results yielded by Maduell and colleagues showed hyperphosphatemia in only 29% of patients.⁵ Regarding serum calcium levels, although it exceeded the recommended values in less than 14% of our patients, it seems that the risk of vascular calcification is high because of the high levels of serum phosphorous.

Achievement and maintenance of the target for serum intact PTH is the most difficult task. The majority of the patients (48.1%) presented with low values and 27.7% had values within the target range. The DOPPS and Yokoyama and coworkers' study represented similar results; 26% of patients achieved the targets and 26% and 27% had elevated values, respectively.^{6,7}

However, Al Aly and colleagues showed that 72% of their patients had values greater than 300 pg/mL.⁸ In another research in South India, it was shown that the PTH level remained relatively suppressed in the majority of randomly selected patients with ESRD.⁹ While it is clear that elevated PTH levels are associated with a higher mortality rate,^{2,3,10-13} it has been noted that levels below 65 pg/mL (found in 30% of the patients in this study), in comparison with moderately high levels, could be associated with decreased survival.^{11,12} In this study, we did not assess the mortality or morbidity among these high-risk groups.

In line with the opinion-based recommendations of K/DOQI work group, it is recommended in our country that the dialysate calcium concentration be 2.5 mEq/L. Nevertheless, in many dialysis units, 3 mEq/L is the most frequently used dialysate calcium concentration with the aim of obtaining a nil or slightly positive calcium balance. In the study by Al Aly and coworkers,⁸ in which all patients received 2.5-mEq/L dialysate calcium concentrations, 72% of the patients had an intact PTH level higher than 300 pg/mL, while this rate was 24.2% in our patients. This is in contrast with

the concept that a 2.5-mEq/L dialysate calcium concentration tends to result in a negative calcium balance and stimulating PTH secretion.⁵ However, when Maduell and colleagues analyzed the data of their 925 and 1123 patients who received 2.5-mEq/L and 3-mEq/L dialysate calcium concentration, respectively, they found that 41.8% of former group showed intact PTH levels higher than 300 pg/mL versus 24.9% of the latter group.⁵ Opposing to our findings, it seems that mineral metabolism was better controlled when 3-mEq/L dialysate calcium concentrations were used, compared to 2.5 mEq/L with a similar use of vitamin D.

CONCLUSIONS

This epidemiologic study proved that the current clinical management of mineral metabolism and achieving the recommendations established in the K/DOQI guidelines is precluded by a multitude of challenges, both practically and scientifically. Unfortunately, the most often relied-on therapeutic agents, phosphorus binders, have repeatedly led to untoward toxicities. It would be of great interest to analyze, in the future, the benefits or consequences derived from the effect of new therapies such as calcimimetics, new vitamin D analogs, or new phosphate binders regarding the K/DOQI guidelines. Lastly, this question remains unanswered: How can the goal of achieving tight control be achieved within the framework of cost-effectiveness and the reality of limitations in financial resources available to long-term HD patients, especially in developing countries?

CONFLICT OF INTEREST

None declared.

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Received April 2007

Revised May 2007

Accepted June 2007