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Difficulties in achieving the K/DOQI (NKF) laboratory target values for bone and mineral metabolism in haemodialysis patients

Chelioti Eleni[1], Mamali Vassiliki[2], Papatzikos Lambros[3] and Stavianoudakis George[4]

[1]Renal Unit, Athens Medical Group "Dafni" Clinic, Athens, Greece, [2]Department of Nephrology and Renal Unit, "NIMITS" Veterans Administration Hospital, Athens, Greece

Abstract

Background. Increased serum phosphorus (PO_4^-) and elevated calcium phosphorus product (CaxP) levels have been recognized as risk factors for increased cardiovascular mortality in haemodialysis (HD) patients. However, an increasing number of studies report difficulties in meeting K/DOQI guidelines for bone and mineral metabolism, raising questions regarding the management of HD patients. The aim of this study was to evaluate our ability to meet K/DOQI guidelines for bone and mineral metabolism in HD patients.

Methods. We reviewed laboratory parameters of bone and mineral metabolism in 103 patients over a period of 16 months. Serum calcium (Ca) and PO_4^- levels were determined monthly using standard assays, calcium phosphorus product (CaxP) was calculated every month and intact parathyroid hormone (iPTH) levels were determined every three months using chemiluminescence immunoassay (CLIA). Patients requiring phosphate-binding agents received calcium carbonate, sevelamer or a combination of these. 76/103 patients required an analog of vitamin D (41/76 received alfacalcidol, 35/76 received paricalcitol).

Results. Serum Ca ranged from 5.8 to 12.4 (mean ± SD; 8.8 ± 0.7) mg/dl, serum PO_4^- ranged from 1.7 to 10.9 (mean ± SD; 5.5 ± 1.35) mg/dl, CaxP product ranged from 22 to 101 (mean ± SD; 49 ± 12) mg^2/dl^2 and iPTH levels ranged from 9 to 1750 (mean ± SD; 294 ± 286) pg/ml. The average percentage of serum Ca, serum PO_4^- determinations and CaxP product which met the K/DOQI target levels was 64 ± 6%, 52 ± 9% and 74± 7% respectively. In regards to iPTH, 33 ± 8% of the determinations were within the recommended range. Only 8± 7% met all four recommended guidelines simultaneously. In regards to the number of patients who achieved the K/DOQI guidelines for Ca, PO_4^-, CaxP product or iPTH target levels the corresponding percentages were 55%, 44%, 63% and 12% respectively. Notably, only 3% of the patients met the target for all four parameters simultaneously.

Conclusion. Our data indicate that with current medication the achievement of K/DOQI guidelines for the management of bone and mineral metabolism in haemodialysis patients is very difficult in clinical practice.

Keywords: bone metabolism; K/DOQI targets; chronic kidney disease; secondary hyperparathyroidism

Correspondence and offprint request to: Eleni Chelioti; hhelioti@hotmail.com

Introduction

Chronic kidney disease (CKD) is linked with increased morbidity [1], is associated with a wide range of causes of mortality [2,3] and recent reports about all cause mortality attributable to CKD, and escalating figures of prevalence and incidence of the disease, raise CKD at the levels of global epidemic [4,5]. Although the percentage of CKD patients who require haemodialysis (HD) treatment (stage 5 CKD) is small, this group is characterised by high rate of morbidity and mortality and much shorter life expectancy [4]. The prevalence of coronary heart disease (CHD) in HD patients is 40%, and in peritoneal dialysis patients 60% [6] while CVD – related mortality in this group is 10 to 30 times higher compared to the general population [7]. The National Kidney Foundation (NFK) – published the Kidney Disease Outcomes Quality Initiative (K/DOQI) Clinical Practice Guidelines for HD patients, regarding bone and mineral metabolism recommending tight control of serum calcium (Ca) and phosphorus (PO_4^-) levels, calcium-phosphorous product (CaxP) and intact parathyroid hormone (iPTH). These guidelines anticipate adjusted Ca level: 8.4-9.5 mg/dl, serum PO_4^-: 5-5.5 mg/dl, CaxP: < 55 mg^2/dl^2 and iPTH: 150-300 pg/ml [8]. These recommended cut-off points and range are in line with the accumulated evidence that the presence of plasma Ca, PO_4^- and CaxP product at concentrations greater than, or outside the suggested K/DOQI ranges, is associated with increased all-cause mortality risk, risk for fracture-related hospitalization, and fatal and non fatal cardiovascular events [9-11].

Unbalanced mineral homeostasis, is also implicated in the pathogenesis of hyperparathyroidism [12-15] occurring at the very early stages of renal failure. A decrease in 1,25 dihydroxycholecalciferol (the active form of hydroxyvitamin D) accompanied by increased PTH levels are the earliest mineral metabolism alterations occurring in CKD with calcium and phosphorus changes appearing at a later stage [16]. PTH levels are inversely related to glomerular filtration rate (GFR), showing considerable variability at GFR < 60 ml/min [16] while the incidence and severity of secondary parathyroidism increases as renal function is deteriorating [17].

Notwithstanding the clinical importance of maintaining calcium and phosphorus homeostasis and preventing or controlling secondary hyperparathyroidism in patients with CKD, there are an increasing number of reports recognizing difficulties in maintaining K/DOQI guidelines in HD patients despite optimal therapy [16,18-22]. Most of these studies report an alarmingly small percentage of patients that manage to maintain all four guidelines, raising questions about aspects of clinical practice such as treatment strategies and level of patients' compliance.

In the present study we evaluated our ability to meet K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease and present laboratory results of serum Ca, PO_4^-, CaxP product and iPTH in a group of HD patients. In addition the percentage of patients that maintained laboratory values within the recommended ranges was evaluated.

Patients and methods

We reviewed laboratory parameters of bone and mineral metabolism of 103 patients (71 males, 32 females, patient characteristics are presented in Table 1, over a period of 16 months (April 2004 to August 2005). The study was approved by the Institutional Ethical Committee and all patients signed and dated an informed consent form, endorsing access to their medical information. The study was conducted in accordance to the Helsinki Declaration of 1975, as revised in 2000.

Table 1. Demographic characteristics of the study population

Patients	103
Age (years)	65± 15*
Sex, % (n)	
Male	69 (71)
Female	31 (32)
Standart HD°/Haemodiafiltration %(n)	61.2 (63)/38.8 (40)
Diabetes % (n)	33 (34)
Time on HD° (months)	20 ± 10*
Kt/V	1.4 ± 0.2*
Calcium dialysate (mEq/L)	3 ± 0.5*

*Data are expressed as mean ±SD values, °HD: Haemodialysis

Patients remained in the haemodialysis unit for a mean of 20.3 ± 10.4 months and received either standard haemodialysis (HD) or haemodiafiltration (HD). Demographic characteristics and medical history of concomitant diseases were recorded. Serum calcium and phosphorus levels were determined using standard assays every month. The level of serum calcium was corrected for albumin. Calcium phosphorus product was calculated every month. Intact PTH levels were determined every three months using chemiluminescence immunoassay (CLIA). There were a total of 1648 determinations for serum calcium, phosphorus and Ca x P and 550 determinations for iPTH. Kt/V was calculated every 5 months. Patients requiring phosphate-binding agents received calcium salts, sevelamer or a combination of these and those requiring vitamin D compounds received alfacalcidol or paricalcitol. The physicians taking care of the patients managed the parameters of bone and mineral metabolism according to standard practice and adhering to K/DOQI guidelines.

Values are presented as means ± SD, except were otherwise indicated. Categorical variables are described by relevant frequencies. Differences between categorical variables over the observed period were analysed using the χ^2 analysis test. Level of significance was set at $p \leq 0,05$.

Results

A total of 103 patients were included in the study. The demographic characteristics of the study population are detailed in table 1. The average age was 65± 15 years; 69% were male and 31% were female. Thirty three percent of patients were diagnosed with diabetes mellitus. Sixty three patients (61.2%) received standard HD and 40 (38.8%) patients received haemodiafiltration The average time on HD was 20±10 months, the average Kt/V was 1.4 ± 0.2 and calcium dialysate was 3 ± 0.5 mEq/L.

The percentages of patients who received calcium salts, sevelamer, combination of calcium salts and sevelamer, aluminum hydroxide in combination with other phosphate-binding agents were 59%, 30%, 17.5% and 20% respectively. The percentage of patients that required a vitamin D analogue was 73% (76/103) in which 54% (41/76) received alfacalcidol and 46% (35/76) received paricalcitol (Table 2).

Table 2. Phosphate binders and vitamin D analogues treatment of HD patients

Treatment	Frequency *% (n)*	Dose *Mean ± SD (range)*
Calcium carbonate	59 (61/103)	1.5 ± 05grams/day (0.5-2.5)
Sevelamer	30 (31/103)	4±1.6 grams/day (1.6-8)
Calcium carbonate + sevelamer	17.5 (18/103)	0.5 ± 0.5 / 4 ± 8 grams/day
Aluminum Hydroxide $Al(OH)_3$*	20 (21/103)	1.9±0.5 grams/day (0.9-2.8)
Alfacalcidol	54 (41/76)	2±0.5 mcg/HD° (0.5 - 3)
Paricalcitol	46 (35/76)	7±2.5 mcg/HD° (2.5 - 12)

Concomitant administration with other phosphate binders.
°HD: every session of haemodialysis

Serum Ca ranged from 5.8 to 12.4 (mean ± SD; 8.8 ± 0.7) mg/dl, serum PO_4^- ranged from 1.7 to 10.9 (mean ± SD; 5.5 ± 1.35) mg/dl, CaxP product ranged from 22 to 101 (mean ± SD; 49 ±12) and iPTH ranged from 9 to 1750 (mean ± SD; 294 ± 286) pg/ml, (Table 3).

The average percentage of serum Ca, serum PO_4^- determinations and CaxP product which met the K/DOQI target levels was 64 ± 6%, 52 ± 9%, and 74 ± 7% respectively (Fig. 1). In regards to iPTH, 33 ± 8% of the determinations were within the recommended range. Only 8 ± 7% of all determinations met all four recommended targets simultaneously (Figure 2).

Table 3. Bone mineral metabolism parameters during the haemodialysis treatment

Parameter	Mean ± SD	Range
Serum calcium (mg/dl)	8.8 ± 0.7	5.8 – 12.4
Serum phosphorus (mg/dl)	5.5 ± 1.3	1.7 -10.9
CaxP (mg^2/dl^2)	49 ± 12	22 - 101
iPTH (pg/ml)	294 ± 286	9 - 1750

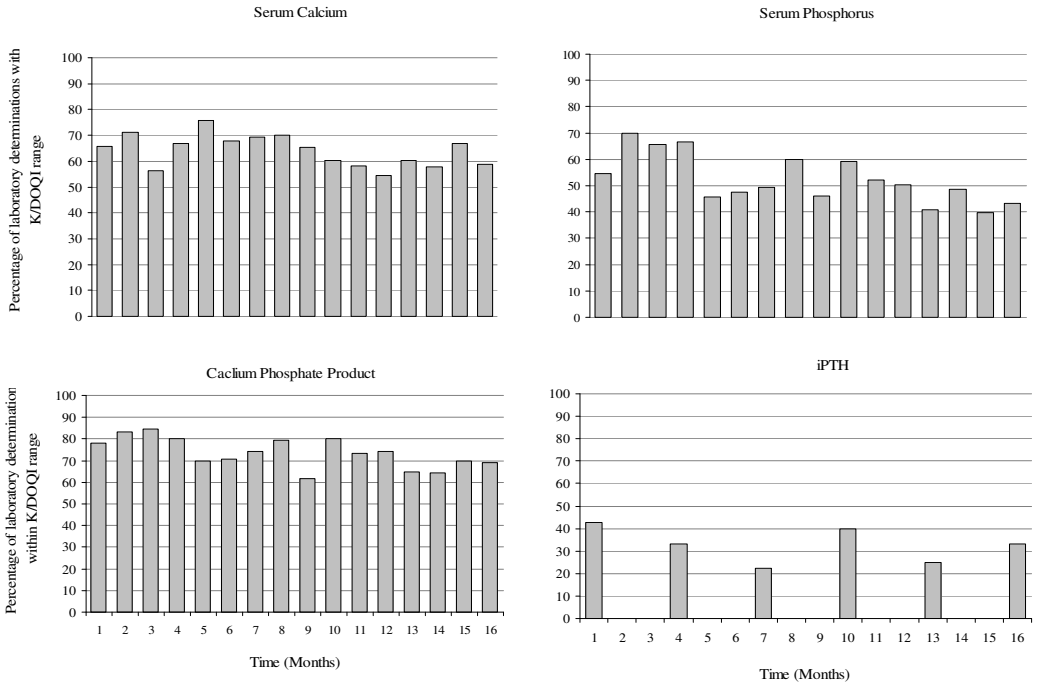

Fig. 1. Percentage of laboratory determinations of serum calcium, phosphorus, calcium – phosphate product, and iPTH within K/DOQI targets during the 16 months of HD treatment

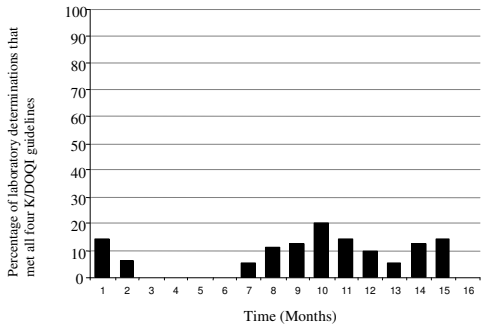

Fig. 2. Percentage of laboratory determinations that met all four K/DOQI guidelines during the 16 months of HD treatment

In regards to the number of patients who achieved the K/DOQI guidelines for Ca, PO_4^-, CaxP product or iPTH the corresponding percentages were 55%, 44%, 63% and 12% respectively. Notably, only 3% of the patients met the target for all four parameters simultaneously (Figure 3). Intact parathyroid hormone levels after 16 months of treatment with phosphate binders were significantly more likely to fall within (150-300 pg/ml) or below (<150 pg/ml) range ($p \leq 0.001$).

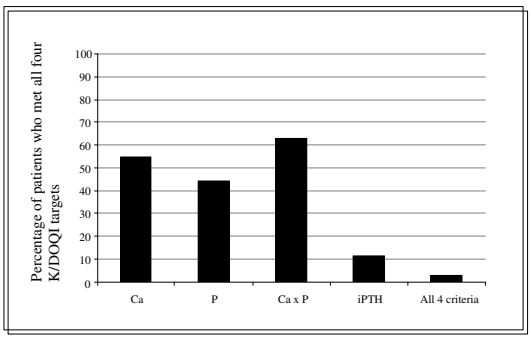

Fig. 3. Percentage of patients who met all four K/DOQI targets during the 16 months of HD treatment

Discussion

A surprisingly low percentage (3%) of HD patients managed to achieve and maintain K/DOQI guidelines for bone and mineral metabolism in the present study. This result is in line with previous, recent observations that

report very low percentages of success [16,18-20]. This low level of achievement in our study was obtained despite optimum supportive therapy with phosphate binders, calcium carbonate, and vitamin D analogues, administered as clinically indicated.

Recent investigations have also reported difficulties in achieving and maintaining K/DOQI guidelines. Wei *et al.* [22] reported that the in-target percentages of patients for Ca, PO_4^-, CaxP product and PTH were 46%, 53%, 77% and 28% in HD patients respectively, whereas the percentage of patients with simultaneous achievement of all 4 guidelines was only 4.3%. Similarly low percentages have been reported by Aly *et al.* [18], were only the 4% of patients managed to achieve K/DOQI guidelines in all four parameters, and Young *et al.,* 4.6% [23], whereas a study from Craver *et al*. which investigated stage 3, 4, and 5 CKD patients during 12 months of HD treatment reported that patients who had all four parameters within recommended ranges where 34.9%, 18.4% and 21.6%, for stage 3, 4 and 5 CKD respectively [16].

Several factors have been considered to contribute to the increased difficulty seen in attempting to attain guidelines' cut-off levels and ranges. Simultaneous achievement of serum Ca and PO_4- and maintenance of PTH levels within ranges of normal, in many cases have been proven problematic. Abnormal increases in Ca and PO_4^- levels have deleterious effects in CKD patients and play an active role in the pathophysiology of extrasceletal calcification [24]. Hyperphosphataemia for example is one on the main factors contributing to secondary hyperparathyroidism [25], manifested as increased parathyroid hormone secretion and activity, and is also associated with increased risk of all-cause mortality and mortality due to cardiovascular events, such as myocardial infraction and heart failure [11,17]. The recommended clinical approach in treating secondary hyperparathyroidism and hyperphosphataemia, is the administration of vitamin D analogues (calcitriol, paricalcitol, alfacalcidol) and phosphate binders (calcium carbonate, sevelamer, lanthamum carbonate). The main goal of administering these agents is to suppress PTH levels and reduce hyperphosphataemia and so attenuate the systematic stimulus for increased PTH secretion. However, the administration of such agents, especially of calcium based phosphate binders, is associated with a range of adverse events including hypercalcaemia and hyperphosphataemia. Moreover, vitamin D analogues such as calcitriol and paricalcitol have been implicated [24] and may contribute in the in vivo development of vascular calcification [26]. The introduction of calcium free phosphate binders, such as sevelamer and lanthanum carbonate seems to be effective in maintaining parathyroid hormone levels and also to be associated with reduced cardiovascular risk compared to calcium carbonate [27,28] [29,30]. However despite the possible beneficial effects of sevelamer on the progression of vascular calcification, it is still unknown whether this agent is likely to improve the long-term survival outcome of dialysis patients. [31]. This, taken together with reports regarding the financial impact of sevelamer treatment, raises questions about the effectiveness of sevelamer as an anti-hyperphosphataemic agent [32].

Nonetheless, parathyroid hormone seems to be the parameter of bone and mineral metabolism that is the most difficult to control, or the one that presents with the lowest percentages of adherence. Out of range PTH levels are reported to be twice as likely to be below K/DOQI recommended guidelines of 150-300 pg/ml than above [21], suggesting that the employed therapeutic treatment may oversuppress PTH regulation. In our study we observed that after 16 months of treatment, iPTH levels were more likely to fall within or below the recommended ranges (38%, 39%, and 23% for <150 pg/ml, 150-300 pg/ml, and >300 pg/ml respectively, $p \leq 0.001$) than above.

Missing and shortened haemodialysis sessions could potentially be another contributing factor which prevents achievement of recommended guidelines. Wald *et al.* [33] reported that for each 1% increase in frequency of abbreviated sessions, the odds of consistent control for phosphate and CaxP product decreased by 2%, while for every missed session the odds for achieving Ca, PO_4^- and CaxP recommendations is decreased by 2%, 4% and 1% respectively. These results suggest that dialysis time is a crucial ingredient for the regulation of mineral metabolism, while extended dialysis times may result in significant decreases in serum Ca, CaxP and PTH levels [34, 35]. Decreased patient-dietician ratio is another recommendation as a means to improve phosphate level control. However results on the impact of such intervention is still inconclusive [33].

Nonetheless, control of bone and mineral metabolism is a difficult task since it requires concomitant modulation of dietary intake, modifications in pharmacological interventions and modified dialysis prescription. The success of these interventions are heavily dependent on patient behavior, the level of awareness of health care providers, the quality of health care provider–patient communication [23] and most importantly on patients' compliance and adherence to prescribed treatment and dialysis regime. The last has been investigated in a group of HD and PD patients. It was estimated that 16% of the prescribed pills were omitted and this was attributed to the increased burden of patients' pharmacological intervention with orally administered agents or pill-burden. Overall compliance at the 80% level was as low as 38% and although patients did not differ in respect to serum Ca, PO_4^- and PTH, significantly higher doses of phosphate binders were prescribed to non-compliant compared to compliant patients. Moreover, patients who attained and maintained K/DOQI recommendations presented with a lower pill-load compared to non-achievers, suggesting that effective treatment options that lead to fewer pill intake may aid in achieving K/DOQI targets [21].

Recommendations for clinical practice in order to increase rate of achievement of K/DOQI guidelines include prescription of non-calcium phosphate binders, increase of vitamin D analogues and moderation in calcium carbonate administration [36]. In terms of clinical care provision it is reported that a single renal nurse practitioner

is more likely to adhere to guidelines that are multiple rotating nephrology trainees in a renal-hypertension clinic [37]. This observation was also accompanied by significant lower all-cause hospitalization 12 months after the initiation of dialysis. Despite the delimitations that the above observations may have, it is clear that clinical practice has to be accordingly modified in several aspects in order to improve health care standards and treatment outcomes of stage 5 CKD patients.

Conclusions

In conclusion, despite the above mentioned parameters, which might interfere with treatment goals raising the difficulties in attaining prescribed guidelines, there is also an increased body of data suggesting that sustaining control of bone and mineral metabolism according to K/DOQI guidelines may have positive impact on morbidity and mortality [19,24,33,38]. However our data and others, indicate that with current medication the achievement of K/DOQI guidelines for the management of bone and mineral metabolism in HD patients is very difficult in clinical practice. Moreover, the percentage of HD patients who achieve K/DOQI guidelines is alarmingly small suggesting that there is a great need to expand the available options of pharmacological treatment and standardize procedures in order to better control bone and mineral control in HD patients.

Authors' contributions

XX and XX conceived of the idea for the project and supervised the project. All authors reviewed and interpreted the statistical analyses. XX wrote the first draft of the manuscript, while all authors contributed to the final version of the manuscript. All authors read and approved of the final version of the manuscript. EC, VM, LP, GS

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Conflict of interest statement. None declared.

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