Chapter IV

Prevention and Treatment of Hyperphosphatemia

Introduction:

Derangements of mineral metabolism occur during the early stages of chronic kidney disease (CKD). Hyperphosphatemia occurs as a consequence of diminished phosphorus filtration and excretion with the progression of CKD. Decreased phosphorus excretion can initially be overcome by increased secretion of parathyroid hormone (PTH), which decreases proximal phosphate reabsorption. Hence, phosphorus levels are usually within normal range until the GFR falls below approximately 30 ml/min, or stage IV CKD according to the National Kidney Foundation. ***(National Kidney Foundation, 2003a)***.

In more advanced stages of CKD, the blunted urinary excretion of phosphorus can no longer keep place with the obligatory intestinal phosphate absorption, resulting in hyperphosphatemia. Therefore, it is not surprising that the majority of patients with ESRD have significant hyperphosphatemia ***(Coladonato, 2005)***.

Hyperphosphatemia has long been associated with progression of secondary hyperparathyroidism (SHPT) and renal osteodystrophy. However, more recent observational data have also shown a significant association of hyperphosphatemia with increased mortality among patients

who have ESRD and are on hemodialysis ***(Ganish et al., 2001)***.

Moreover, elevated serum phosphorus has been associated with an increased risk for cardiovascular mortality and hospitalization (all-cause, cardiovascular and fracture) among dialysis patients ***(Block et al., 2004)***.

Despite advanced technology and regular and efficient dialysis treatment, the prevalence of hyperphosphatemia is still high. The goal of normalization of serum phosphorus levels can only be reached by optimization of dialysis prescription in combination with individualized dietary and medical strategies ***(Kuhlmann, 2006).***

The Kidney Disease Outcomes Quality Initiative (K/DOQI) issued "Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease (dialysis patients)", in which it is recommended that the level of intact parathyroid hormone (iPTH) should be kept at 150 - 300 pg/mL, which is approximately a biointact (biPTH) of 80-160 pg/mL, the serum phosphorus (P) level at 3.5 - 5.5 mg/dL, the serum calcium (Ca) level within the normal range of laboratory values (8.4 - 9.5 mg/mL, as close to the lower limit as possible) and EBCT scores below 52. In developing these guidelines, the K/DOQI apparently considered the recently established fact that control of Ca, P and PTH influences not only the development of bone lesions but also patient prognostic factors such as arteriosclerosis, ectopic calcification, and cardiovascular complications, as well as the development of various vitamin D products and analogues and new P adsorbents. The Japanese guidelines also emphasize the control of P and Ca, rather than PTH. Therefore Phosphorus

control is a primary goal in the care of patients with end-stage renal disease ***(Raggi et al., 2001; Uemura et al., 2007)***.

Methods of Control of Hyperphoshatemia:

I. Treatment of underlying cause of renal failure.

II. Dietary Restriction:

Dietary phosphate restriction has been shown to prevent the development of SHPT early in the course of disease, as well as increase plasma calcitriol levels and inhibit parathyroid cell proliferation. Furthermore, phosphorus restriction may be instrumental in preventing progressive renal failure and soft tissue calcification. Patients with ESRD absorb approximately 50 to 60% of dietary phosphorus, and as GFR declines, urinary phosphorus excretion is inadequate to maintain normal homeostasis, resulting in a positive phosphorus balance. Vitamin D administration aggravates this problem by increasing intestinal absorption of dietary phosphorus and calcium***(Takeda,2001)***.

Aggressive dietary phosphate restriction among patients with CKD is impractical and could compromise overall nutrition, particularly protein intake. For preventing malnutrition among patients with CKD, the NKF/KDOQI guidelines recommend a minimum protein intake of 1.2 g/kg per day (approximately 800 to 1000 mg/day phosphorus). As renal function declines, a net positive balance is inevitable, and thus other therapies are required. One should be cautious because long-term consequences of protein and phosphorus restriction may lead to negative nitrogen balance ***(Coladonato, 2005)***.

III. Prevention and early treatment of SHPT:

Secondry Hyperparathyroidism (SHPT) is associated with hyperphosphatemia, hypocalcemia and increased Ca x Po_4 product. Lines of management of SHPT include; dialysis solution calcium adjustment 2-2.5 mEq/L, control of calcium and phosphorus, and use of vitamin D analogs and calcimimetics. New vitamin D analogs and calcimimetics drugs are being developed for PTH suppression. When medical therapy has failed in treatment of hyperparathyroidism, surgical parathyoidectomy or percutaneous chemical ablation of the parathyroid glands is considered. Parathyroid hormone (PTH) is the most important molecule used as the indicator of a bone and mineral metabolism including renal insufficiency patients. ***(Kato and Mitarai, 2007).***

New Vitamin D analogs:

Secondary hyperparathyroidism (SHPT) commonly deve-lops in patients with chronic kidney disease (CKD) in response to high phosphate, low calcium and low 1,25-dihydroxyvitamin D(3). High PTH levels increase the rate of bone turnover, with a net efflux of calcium and phosphate leading to vascular calcification and coronary artery disease. Treatment of secondary HPT with 1alpha,25(OH)(2)D(3) and calcium-based phosphate binders often produces hypercalcemia and over-suppression of PTH, resulting in adynamic bone that cannot buffer excess calcium and phosphate, which increases the risk of vascular calcification. It is essential, then, to reduce PTH levels to a range that supports normal bone turnover and minimizes ectopic calcification. Vitamin D analogs that inhibit PTH gene transcription and parathyroid hyperplasia, and that have less calcemic activity than 1alpha,25(OH)(2)D(3,) have

provided a greater safety margin for the treatment of secondry HPT, as well as enhancing the survival of CKD patients. efforts to develop even more selective analogs continue. Parathyroid glands express both 25-hydroxylase and 1alpha-hydroxylase and may be capable of activating prohormones or prodrugs to suppress PTH and parathyroid growth by an autocrine mechanism. Moreover, the introduction of non-calcium-based phosphate binders (sevelamer and lanthanum carbonate) and cinacalcet (an allosteric activator of the calcium receptor that reduces PTH and the serum calcium x phosphate product) may reduce the risk of hypercalcemia with vitamin D therapy. Combining these agents with higher doses of vitamin D compounds may achieve greater suppression of PTH and possibly enhance survival in patients with chronic kidney disease ***(Brown2007)***.

New vitamin D analogs effectively suppress PTH while, having significantly less impact on serum calcium and phosphorus levels. Two such analogs have been approved, 19-Nor-1,25 dihydroxyvitamin D2 (Paricalcitol or Zemplar) and 1-alpha hydroxyvitamin D2 (doxercalciferol)***).*** 1-alpha hydroxyvitamin D2 has been shown to effectively decrease PTH with a decreased incidence of hypercalcemia and hyperphosphatemia ***(Block and Port,2000).*** .

Maxacalcitol also is a vitamin D analog, which is administered intravenously for secondary hyperparathyroidism in dialysis patients ***(Mochizuki et al., 2007).*** ED-71, a new active vitamin D3 analog, increases bone mineral density in osteoporotic subjects and chronic kidney disease patients ***(Matsumoto and Kubodera, 2007)***.

Vitamin D therapy for patients with chronic kidney disease has until recently comprised alfacalcidol or calcitriol, both of

which effectively attenuate secondary hyperparathyroidism. It is likely that these in turn have adverse effects on cardiovascular and survival outcomes by promoting soft tissue and vascular calcification. These drawbacks have fuelled a search for vitamin D compounds with a wider therapeutic window. Experimentally, some of these have exhibited remarkable dissociation between their ability to suppress parathyroid hormone (PTH) and concomitant calcaemic actions ***(Cunningham, 2004).***

Therapy with i.v. calcitriol, that had been the mainstay of the cure of severe secondary hyperparathyroidism (SHPT) for many years, is often hindered by the occurrence of hypercalcemia, that requires discontinuation of the drug with consequent rebounding of the parathyroid hormone (PTH) oversecretion. To circumvent this shortcoming, Calcitriol-analogs with less calcemic effects with respect to calcitriol have been developed. One of these analogs, (paricalcitol) , proved to be at least as powerful as calcitriol in decreasing serum PTH, but it still remains endowed with some calcemic effect as the parent compound. Meanwhile, calcimimetics drugs targeting the calcium-sensing receptors on the parathyroid gland. Cinacalcet is a calcimimetic endowed with the unique prerogative to significantly decrease serum PTH while also decreasing serum calcium. Thus, one may attempt to speculate that calcimimetics may completely replace vitamin D derivatives from the therapeutic arena. Uremic patients in need of highly dosed vitamin D in order to both ameliorate their bone status and to preserve their general and cardiovascular health. Thus, a combination therapy with paricalcitol , which has a significant patient-survival advantage over calcitriol , and Cinacalcet seems to be more appropriate than only-one-drug based therapy for SHPT. Such a combination will hopefully result in a better control of SHPT,

avoidance of hypercalcemia and higher life expectancy for uremic patients than ever before ***(Canella and Messa, 2006).***

Paricalcitol has been shown to decrease intact PTH levels by 30% at six weeks and 60% at twelve weeks with no increase in incidence of hypercalcemia or hyperphosphatemia compared to placebo ***(Liach et al., 2000).***

Patients who were treated by paricalcitol survived more than patients who were treated by calcitriol. Doxercalciferol and paricalcitriol could maintain suppressed parathyroid hormone (PTH) with less frequent hypercalcemic accidents ***(Akiba, 2007).***

Proteinuria is a marker of cardiovascular and renal disease in patients with chronic kidney disease (CKD), and reduction in proteinuria has been associated with improved cardiovascular and renal outcomes. In randomized, placebo-controlled studies to evaluate the safety and efficacy of oral paricalcitol, reduction of proteinuria favored patients on paricalcitol, regardless of age, sex, race, diabetes mellitus, hypertension, or use of therapies to block the renin-angiotensin-aldosterone system. Paricalcitol as a potential pharmacologic means of reducing proteinuria in CKD patients warrants further investigation ***(Agarwal et al., 2005)***.

Calcimimetics:

Although not indicated for the treatment of hyperphosphatemia, calcimimetics are a new class of agents in treating secondary hyper-parathyroidism (SHPT) and may have a significance in the choice of phosphate binders , Calcimimetics suppress the secretion of parathyroid hormone

by sensitizing the parathyroid calcium receptor to serum calcium. secondary hyperparathyroidism in predialysis chronic kidney disease patients, hypercalcemic hyperparathyroidism in renal transplant recipients, primary hyperparathyroidism, and hypercalcemia associated with parathyroid carcinoma ***(Shahapuni et al., 2006)***.

The extracellular calcium-sensing receptor on the parathyroid cell surface negatively regulates secretion of parathyroid hormone (PTH). Its activation by small changes in the extracellular concentration of ionized calcium decreases PTH secretion and secondarily bone turnover. Calcium receptor is an ideal target for compounds that may be developed to modulate its activity - activating calcimimetics and inhibiting calcilytics. Calcimimetics can amplify the sensitivity of the Calcium receptor to extracellular ionized calcium ,thereby suppressing PTH levels and in turn reducing blood Ca++. The dose-dependently reduce the secretion of PTH in cultured parathyroid cells in humans. They normalize plasma PTH levels and bone remodeling. In uremic patients undergoing hemodialysis, calcimimetics reduce plasma PTH concentrations in the short (12 weeks) and long (2 years) terms. They also reduce serum levels of calcium-phosphorus product ***(Urena et al., 2005).***

Cinacalcet (Sensipar) is a first-in-class agent that binds to and allosterically modifies the calcium-sensing receptor (CSR) in the parathyroid glands, increasing its sensitivity to extracellular calcium ***(Goodman et al., 2002)***.

The CSR located on the chief cell of the parathyroid gland, is the principal regulator of PTH secretion and activation by serum calcium leads to the activation of secondary messenger pathways and a cascade of intracellular events resulting in decreased PTH secretion ***(Quarlis et al.,2003)***.

Cinacalcet is the only FDA-approved calcimimetic for use in the United States for the treatment of HPT and in the European Union. In randomized, placebo- controlled trials, cinacalcet significantly reduced PTH levels compared with placebo ***(Lindberg et al., 2003 ; Block et al., 2004)***.

The efficacy of cinacalcet HCl in treating SHPT in dialysis patients was studied in clinical trials comparing patients receiving standard SHPT therapy plus cinacalcet HCl or plus placebo. Cinacalcet HCl, dosed from 30 to 180 mg/day, significantly reduced PTH while simultaneously lowering calcium, phosphorus, and calcium-phosphorus product in each of the three studies. Respective to the National Kidney Foundation-Kidney Disease Outcomes and Quality Initiative (NKF-K/DOQI) recommended targets for bone and mineral metabolism, 41% of cinacalcet HCl-treated patients achieved both PTH and calcium-phosphorus product targets, compared with only 6% in the placebo group. Results of studies conducted in the United States also showed that cinacalcet HCl can significantly reduce or maintain reduction in PTH while simultaneously lowering calcium, phosphorus, and calcium-phosphorus product. In addition, patients taking vitamin D at baseline of these 2 trials were able to see significant mean reductions in vitamin D dose. Further assessment of cinacalcet HCl trial data has shown some important effects in SHPT patient clinical outcomes. Treatment with cinacalcet HCl has a beneficial effect on relative risks of parathyroidectomy, fracture, and hospitalization for cardiovascular complications. Nausea and vomiting occurred more often in patients taking cinacalcet HCl than in those taking a placebo. There were also transient episodes of hypocalcemia in 5% of cinacalcet HCl patients versus 1% of placebo patients. However, these episodes were rarely associated with symptoms. The

development of calcimimetics has already changed the treatment of SHPT in renal patients. Its effectiveness on the control of PTH secretion, along with simultaneous reductions in calcium, phosphorus, and calcium-phosphorus product, give this agent an advantage over traditional therapies in all levels of severity of SHPT ***(Torres et al.,2006)***.

Moreover, cinacalcet significantly reduced serum phosphorus, calcium, and by the way Ca x Po_4 product in all studies over the 26-wks study period. The exact mechanism by which cinacalcet is unclear but may be related to the attenuated release of PTH and subsequent mineralization of bone similar to that seen in the period after surgical parathyroidectomy (i.e., hungry bone syndrome). Alternatively, cinacalcet has also been shown to down regulate mRNA expression levels encoding proteins that are involved in active transcellular calcium reabsorption in the intestine ***(Van Abel et al., 2003)***.

Cinacalcet was well tolerated but did have a higher incidence of gastro-intestinal intolerance (nausea and vomiting). These symptoms were reduced when the drug was administered with food. Cinacalcet was also associated with a 5 to 8% incidence of hypocalcemia as defined by a serum calcium <7.5 mg/dl that necessitated modification of calcium-containing phosphate binders, vitamin D sterols, or both. ***(Block et al., 2004)***.

Arenas et al.,(2007) found that the combination of cinacalcet and low doses of vitamin D improved significantly the control of PTH and Ca x P_{O4} in patients with severe secondary hyperparathyroidism on chronic haemodialysis, without adverse effects and with lower doses of phosphate binders.

Cinacalcet also significantly reduced serum calcium, phosphorus, and Ca x Po_4 levels in patients received peritoneal dialysis. The most common side effects, nausea and vomiting, were usually mild to moderate in severity and transient. Once-daily oral cinacalcet was effective and safe reducing PTH, Ca x P, calcium, and phosphorus leve ***(Lindberg et al., 2005).***

cinacalcet decreases the risk of hypercalcemia and hyperphosphatemia in contrast to 1,25-dihydroxyvitamin D_3 derivatives. Compared with calcium-containing oral phosphate binder (OPB), it increases the risk of hypocalcemia and may decrease the PTH-mediated phosphaturia in predialysis patients. This justifies its combined use with calcium-containing OPB in order to prevent hypocalcemia and enhance the hypophosphatemic effect of the latter, while improving PTH suppression ***(Shahapuni et al., 2005).*** .

Treatment of persistent hyperparathyroidism in renal transplant patients resistant to calcium and vitamin D sterols is limited and often requires parathyroidectomy. Calcimimetics inhibit PTH secretion by modulating the calcium-sensing receptor in the parathyroid. Lowering of the serum calcium concentration with the calcimimetic cinacalcet has previously been demonstrated in patients with primary hyperparathyroidism or with secondary hyperparathyroidism on dialysis. Calcimimetics are a promising therapy in renal transplant patients with persistent hyperparathyroidism. ***(Kruse et al., 2005)***. Cinacalcet appears to be an effective drug for the treatment of post transplant hypercalcemia due to persistent secondary hyperparathyroidism ***(El-Amm et al., 2007)***.

Health-related quality-of-life (HRQOL) data and Kidney Disease Quality of Life instrument (KDQOL) showed that

cinacalcet led to significant reductions in the risk of parathyroidectomy, fracture, and cardiovascular hospitalization with improvements in self-reported physical function and diminished pain. ***(Canningham et al., 2005).***

The calcimimetic **AMG 073** increases the sensitivity of the parathyroid calcium-sensing receptor to extracellular calcium, thereby reducing PTH secretion. Consequently, AMG 073 may provide a novel therapy for secondary hyperparathyroidism. The calcimimetic AMG 073 decreases both PTH and calcium x phosphorus levels in hemodialysis patients with secondary hyperparathyroidism ***(Lindberg et al., 2003)***.

The calcimimetic agent **KRN 1493** lowers plasma parathyroid hormone and ionized calcium concentrations in patients with chronic renal failure on haemodialysis both on the day of haemodialysis and on the day without haemodialysis. KRN 1493 is safe and effective in suppressing PTH secretion and serum calcium concentrations in patients with secondary hyperparathyroidism ***(Ohashi et al., 2004).***

Amino **bisphosphonates**, have shown to completely inhibit soft tissue calcifications, calciphylaxis and prevent death in animal models. The first generation bisphosphonate; etidronate, inhibit bone resorption and reduces the progression of coronary artery calcifications in patients receiving long-term hemodialysis, and intravenous pamidronate has produced a rapid improvement of calciphylaxis. Cautious use of these agents in dialysis patients, as they may creating a form of adynamic bone disease ***(Negri, 2005).***

Recommendations of the NKF-K/DOQI for management of hyperparathyroidism in chronic kidney disease patients are: (i)

use of the new drugs; calcimimetics, lanthanum carbonate, sevelamer and paricalcitol; (ii) routine use of 1-1.25 mmol/L (2-2.5 mEq/L) dialysate calcium; (iii) limitation of the maximal daily dose of calcium-based oral phosphate binders to 1.5 g of elemental calcium; and (iv) use of vitamin D2 (ergocalciferol) when serum 25(OH)D level in CKD patients become less than 30 ng/mL. In addition, for the CKD patients with stage 5, the use of active vitamin D3 is recommended because a conversion to 1,25(OH)2D3, which is the most potent vitamin D, might be impossible in these patients ***(Monge et al., 2006).*** .

IV. Dialysis (Removal of excess phosphate):

●Hemodialysis:

Based on its molecular weight of 96 Da alone, Po_4 Clearly falls into the category of water-soluble low-molecular-weight uremic toxins. However due to its hydrophilic characteristics, the phosphate molecule is surrounded by an aqueous cover, which considerably increases the effective molecular weight. Phosphate is mainly distributed in the intercellular space with a slow intra-/extra-cellular solute transfer rate and with a distribution volume which is assumed to be equal to total body water. It needs to be stressed that in contrast to urea, phosphate is not freely diffusible across cell membranes and about 5% of circulating phosphate has been shown to be a component of sodium, calcium and magnesium salts. All these factors contribute to the fact that the eleimination characteristics of phosphate in HD and PD are dissimilar to those of urea and other small-molecular-weight toxins and much more similar to those of typical middle molecules ***(Bammens et al., 2003***)

Phosphate kinetics during HD:

The kinetics of intradialytic phosphate removal differ significantly from classic urea kinetics. During HD, blood urea nitrogen concentrations continuously decline and, following a short rebound period immediately after termination of the treatment, steadily return to predialysis values in relation to protein intake and endogenous urea generation during the interdialytic interval. Intradialytic plasma Pi kinetics show a characteristic 2-phase pattern (fig.1): the first phase is determined by a relatively steep decline of plasma Pi levels and lasts for about 2 – 2.5 h after start of the treatment. This is followed by the second phase, during which plasma Pi levels do not further decline till the end of the dialysis session. Within a couple of hours after termination of dialysis, plasma Pi levels rebound to almost predialysis values ***(Gotch et al., 2003)***.

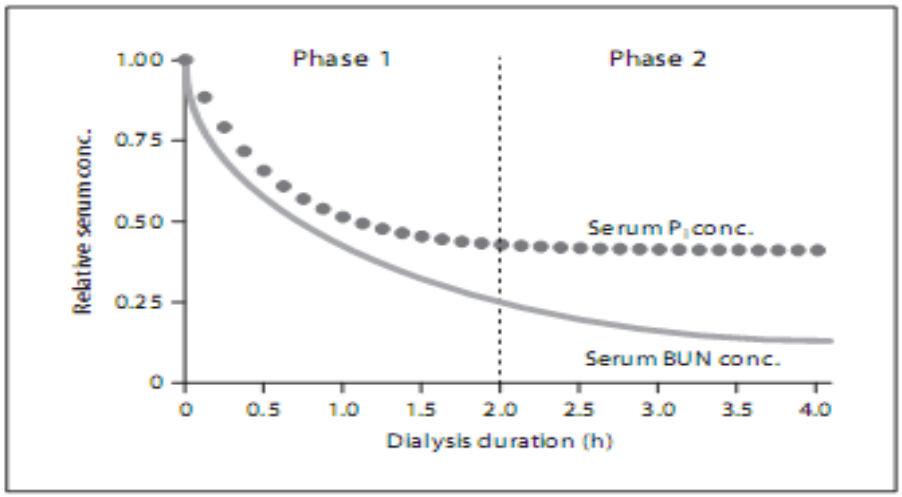

Fig. 1. Comparison of intradialytic phosphate and blood urea nitrogen (BUN) kinetics. Serum Pi concentration sharply drops during the first phase of dialysis (phase 1) and, after reduction of serum Pi to about 40% of predialysis levels, stabilizes throughout the rest of the treatment (phase 2). In contrast, BUN levels steadily decline during dialysis without reaching a plateau.

These kinetics suggest that during the first phase of dialysis predominantly the Pi available in the extracellular

plasma compartment is removed, while during the second phase Po_4 removal occurs from the intercellular space with the rate of change is plasma Pi levels determined by the rate of Pi transfer from one or more intracellular compartments to the plasma compartment ***(Spalding et al., 2002)***

The limiting factor in phosphate removal is not the phosphate flux across the dialyser, but two other main factors, the first is the rapidity of phosphate removal during the first phase and the second is the rapidity of intracellular phosphate mobilization during the second phase ***(Ayus et al., 2005).***

The phosphate reduction during hemodialysis follows a more complex behavior than other solutes of urea and creatinine. The behavior of phosphate in long (6 hours) and short session (4 h.) is nearly similar. The increase in time of hemodialysis session has no significant role in reduction of serum phosphate level and control of hyperphosphatemia in chronic renal failure patients ***(Gutzwiller et al., 2002).***

The clearance of phosphorus varies among the different modalities of dialysis. Diet approximately contains 1000 mg phosphorus/day, intestinal absorption approximately 600mg/day - 4200mg/week. Ideally, adequate dialysis in any form would remove adequate amounts of all uremic toxins, including phosphorus. Unfortunately, conventional, thrice-weekly hemodialysis (4 hours duration) removes approximately 800 mg of phosphorus each treatment (an average of only 2400 mg/week) thus approximately 1800 mg/week retained ***(Gotch et al., 2003)***.

With these characteristics of intradialytic phosphate kinetics in mind, several strategies to optimize HD Pi removal can be formulated: